

IMPACT OF THE SELECT AGENT REGULATIONS ON THE SAFETY AND SECURITY
OF BIOLOGICAL SELECT AGENTS AND TOXINS IN THE UNITED STATES

by

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(Under the Direction of Zhuo Chen and Donglan Zhang)

ABSTRACT

The use of chemical and biological warfare to terrorize individuals or opposing armies is a threat to national security. After the 2001 Anthrax attacks, Congress significantly increased the oversight of biological select agents and toxins (BSAT) by passing the Select Agent Regulations (SARs). The SARs give the federal government the authority to specify conditions that must be met by all organizations to possess, use, and transfer BSAT lawfully. The SARs were developed to protect the public from inadvertent exposure to BSAT while ensuring the safe and appropriate use of these agents for research involving the development of diagnostic tests and medical countermeasures.

The purpose of this study was to assess how the SARs have improved the safety of laboratorians and the security of BSAT in laboratories that work with BSAT. This question was answered through a quantitative analysis of the Federal Select Agent Program inspection departures from 2018-2020 and a qualitative analysis of a survey sent to registered entities.

The results of the quantitative analysis of inspection departures determined that, although not statistically significant, from 2018-2020, the average number of inspection departures decreased over time for each entity type. Throughout the study period, the study showed a

decrease in departures for all parts of the regulations. Over 75% of the departures from the study fall into the low severity category. Additionally, the entities' risk score is statistically significant when predicting the average number of departures.

Several common themes were identified from the entity survey responses, highlighting the impact of the regulations: improved biosafety, security, training, and inventory control. About 75% of respondents indicated they had the infrastructure required to support compliance; however, 85.4% indicated their entity experienced additional burdens beyond financial support, support from management, or too much responsibility placed upon one individual. Based on the entities' responses, the SARs have improved the safety and security of BSAT, training, and other areas to protect the public. Based on the inspection departures analysis and survey results, it was concluded that the SARs have improved the safety and security of BSAT through improved safety, security, training, and oversight at entities that work with BSAT.

INDEX WORDS: Select Agent Regulations (SARs), Biological Select Agents and Toxins (BSAT), inspections, biosafety, security

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B.S., Mississippi State University, 2000

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A Dissertation Submitted to the Graduate Faculty of The University of Georgia in Partial
Fulfillment of the Requirements for the Degree

DOCTOR OF PUBLIC HEALTH

ATHENS, GEORGIA

2021

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December 2021

ACKNOWLEDGEMENTS

Over the last several years, while pursuing my degree, I've become even closer to God. He is the head of my life, and none of this would have been possible without Him to lean on for guidance, support, and strength throughout this process. I believe God places people in your life for a reason, and there have been many people, including my wife, kids, friends, professors, cohort members, and colleagues, that have helped me along this journey.

I want to thank my major professor, Dr. Zhuo Chen, for guiding me through this process and being there for me at a vulnerable time in the program. He stepped in at the last minute to be my Committee Chair when faced with the loss of two committee members before my dissertation defense. I owe everything to you for stepping up and being a true leader. I would also like to thank my current and past committee members Dr. Donglan Zhang, Dr. Samuel Edwin, Dr. Brittani Harmon, and Dr. Leslie Clack. Dr. Edwin has been there from the very beginning, serving as my supervisor and committee member. Thank you for encouraging me throughout this journey and being that person that I could always lean on for support and guidance. Your wisdom and optimism have inspired and guided me as a leader and student.

Lastly, thank you to my amazing family and incredible wife. Kiesha, you have always been a blessing to me, and I continue to thank God every day for your presence and for being a wonderful and caring wife. You carried the load of the family throughout this entire journey while I juggled my responsibilities as a supervisor and student. Words can't express how much I love and appreciate your commitment to our family and me.

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CHAPTER 1

INTRODUCTION

The use of chemical and biological warfare to terrorize individuals or opposing armies dates back to early civilization (Cole, 1996; Jacobs, 2004). Prominent reports of possible biological warfare in the American continent include the distribution of blankets and handkerchiefs from smallpox-infected patients to Native Americans by the British troops in mid-17th century and the sale of clothing from yellow fever and smallpox-infected patients by Confederate soldiers to Union troops during the American Civil War (Barras & Greub, 2014). With advances in scientific knowledge and understanding of highly pathogenic bacterial and viral agents, the use of these biological agents has become a new frontier of threat used by multiple countries and armies. For example, during the early 19th century, the German Army launched a massive biological weapons campaign against the Allied Forces during World War I. However, instead of targeting humans, they concentrated on infecting livestock with *Bacillus anthracis* and *Burkholderia mallei* (Barras & Greub, 2014).

The ability to use biological agents in warfare is prohibited by the Biological and Toxin Weapon Convention (BTWC), to prevent nations from carrying out research to develop biological weapons (Roffey et al., 2002). Although the BTWC has been signed and ratified by 170 nations, it has no direct oversight mechanisms, such as on-site inspections to ensure that nations fully comply with the policies. The use of these agents of terror known as acts of bioterrorism has increased both within the nation and across the globe due to the lack of adequate oversight, such as on-site inspections.

Bioterrorism is defined as the deliberate release of viruses, bacteria, or other agents used to cause illness or death in people, animals, or plants (Jansen et al., 2014). Bioterrorism is aimed at creating terror, societal disruption, economic loss, and mass casualties. It is not a new phenomenon, and events have increased steadily since the 1980s. In 1984, 751 people became ill in Dalles, Oregon, after eating at salad bars infected with *Salmonella typhimurium* (Crow, 2014). Further investigations revealed that the Bhagwan Shree Rajneesh cult had deliberately contaminated the assorted salad bars with *Salmonella* to influence local elections (Torok, et.al., 1997). In 1995, the Aum Shinrikyo cult disseminated Sarin on five trains in Tokyo to start an apocalyptic war, resulting in 12 deaths and 1400 injured people (Jansen et al., 2014). In 1998, the law enforcement authorities also discovered that the Aum Shinrikyo cult had previously attempted to attack Tokyo with anthrax spores or botulinum toxin on at least eight different occasions from 1990–1995 (Jansen et al., 2014). Other examples include the use of Ricin by an individual in the United States to get rid of a partner and the use of *Shigella dysenteriae* in 1996 by a disgruntled hospital laboratory employee in making contaminated pastries as a gift for her colleagues (Kolavic, 1997).

In 1995, a microbiologist with a history of extremist views was arrested for obtaining *Yersinia pestis* by mail order in the United States. Concern about the ease with which disease-causing agents could be obtained in the United States led the U.S. Congress to pass the Antiterrorism and Effective Death Penalty Act of 1996 (WMDC, 2004).

The Act of 1996 directed the U.S. Department of Health and Human Services (HHS) to establish:

1. A list of biological agents and toxins (“select agents”) that pose a significant threat to public health and safety,
2. Procedures for regulating the transfer of these agents, and
3. Training requirements for entities working with these agents.

Unfortunately, acts of terrorism did not stop after the creation of the new laws. In 2001, letters containing anthrax spores were sent by post mail to U.S. senators, journalists, and media buildings, injuring over 20 people and killing five individuals (Barras & Greub, 2014). After the 2001 Anthrax attacks, Congress significantly increased the oversight of biological select agents and toxins (BSAT) by passing the *Uniting and Strengthening America by Providing Appropriate Tools Required to Intercept and Obstruct Terrorism* (USA PATRIOT), which restricted access to BSAT, and the *Public Health Security and Bioterrorism Preparedness and Response Act of 2002*, which included increased safeguards, security measures, and oversight of the possession and use of BSAT (Federal Register 2001, 2002).

The select agent regulations (SARs) give the federal government the authority to specify conditions that must be met by all individuals, private and public organizations, government agencies, and academic institutions to possess, use, and transfer BSAT lawfully. Federal oversight of BSAT is established by federal statute to decrease the risk of bioterrorism by restricting access to BSAT and decreasing the risk of accidental release through enforcement of biosafety and security standards (Morse, 2015). The enforcement of these regulations has been delegated to the Centers for Disease Control and Prevention (CDC) and Animal and Plant Health Inspection Services (APHIS) by the Secretary of HHS and the Secretary of the United States

Department of Agriculture (USDA), respectively. The Division of Select Agents and Toxins (DSAT) at CDC has been delegated the authority to implement 42 *Code of Federal Regulation* (CFR) Part 73. 42 CFR Part 73 which includes the requirements for possession, use, and transfer of BSAT that affect humans. The Division of Agricultural Select Agents and Toxins (DASAT) at APHIS has been delegated the authority for 9 CFR Part 121 and 7 CFR Part 331 (CDC, 2017), which includes the requirements for possession, use, and transfer of BSAT that affect animals and plants, respectively. Together both agencies (HHS and USDA) regulate agents that have the potential to pose a severe threat to both humans and animals.

Currently, the Federal Select Agent Program (FSAP) regulates 67 BSAT that the U.S. Government has determined to have the potential to pose a severe threat to public health, animal or plant health, or to animal or plant products (CDC, 2017). Common examples of BSAT include *Bacillus anthracis*, Ebola Virus, *Francisella tularensis*, Botulinum neurotoxin, Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV), and Marburg Virus. Out of the 67 select agents, the federal government also identified 14 Tier-1 select agents and toxins that require additional security measures (Bhattacharjee, 2011). These extra security measures are intended to safeguard Tier-1 select agents and toxins from further theft, loss, or release (CDC, 2017).

SARs enable laboratories to conduct lifesaving research on these potentially dangerous materials while increasing the assurance that it is done as safely and securely as possible. While these agents and toxins are potentially dangerous, work with BSAT provides critical scientific discoveries that have led to improved detection, prevention, diagnosis, and treatment options for diseases considered to be some of the most threatening to agriculture and public health (Lewis, Campbell, & Baskin, 2015).

The most significant danger to public health, safety, and security is the threat posed by the accidental release of BSAT and/or misuse of BSAT as weapons of mass destruction, including the impact on the economy in response to a bioterrorism event. For example, the costs associated with decontamination of buildings following the 2001 Anthrax letter attacks were approximately \$320 million (Schmitt and Zacchia, 2012). Additionally, it cost \$23 million to decontaminate one Senate office building and \$3 billion to decontaminate U.S. postal facilities, including the purchase of decontamination equipment (Federal Register, 2017). In response and in anticipation of future negative economic impact, robust safety and security requirements have been implemented in laboratories working with BSAT. These laboratories are routinely reviewed by FSAP to prevent the unauthorized access, theft, loss, or release of BSAT (Dias et al., 2007). Examples of regulatory requirements include biosafety and physical security enhancements, security risk assessments for workers with access to BSAT, training, records and inventory management, and incident response procedures.

Problem Statement

The FSAP is the only Congressionally mandated regulatory program in the U.S. that has oversight responsibilities on the possession, use, and transfer of BSAT that the government has determined to pose a severe threat to public health and safety. In 2020, 253 entities were registered with FSAP to possess, use, or transfer BSAT. One of the most severe dangers to public health and safety is the threat posed by the intentional misuse of biological agents as weapons of mass destruction against the United States population (Dias et al., 2010). While the SARs were developed to protect the public from inadvertent exposure to BSAT, the potential for intentional or unintentional release of these agents into the environment exists daily.

Policymakers and the public have become increasingly interested in the oversight of biological laboratories working with BSAT in the U.S. following reports of laboratory accidents, intentional release of dangerous pathogens (e.g., Anthrax attacks of 2001 and inadvertent release of live *Bacillus anthracis* by Department of Defense (DoD) identified in 2015), and potential acts of terrorism (Remember 9/11). In recent years, emerging infections and the risk of bioterrorist events have attracted attention from public health officials due to the capability of these types of events becoming a real public health challenge (Fauci, 2005; Morens et al., 2004). Additionally, over the past decade, scientists have criticized the government's decision to impose new and strict security measures on work involving BSAT (Methot, 2015). Most notably, a publication in the journal *Nature* underlined the negative impact regulations are likely to have on daily scientific work involving countermeasure development that may drive scientists out of this field of research (Wadman, 2009). Others (Wurtz, Grobusch, and Raoult 2014) have argued that increased regulations and additional safety and security safeguards associated with work involving BSAT have limited the number of collaborations; particularly, in the area of highly pathogenic bacteria and viruses. Since the development and implementation of SARs, several reviews assessing the FSAP were conducted by U.S. Government agencies; however, there is no systematic review or a comprehensive assessment of the impact of SARs on the regulated community and/or its impact on laboratories that work with BSAT. Information on the effectiveness of SARs from the perspective of the regulated community and laboratory operations can add tremendous value to enhancing the FSAP.

Research Question

The overarching question of the study is: how have the SARs improved the safety of laboratorians and the security of BSAT in laboratories that work with BSAT? This study will analyze data collected from a survey and FSAP inspections conducted from January 2018 through March 2020. A quantitative and qualitative analysis will assess the outcomes from 2018-2020 and identify any positive or negative trends.

Infectious biological agents and toxins have a history of being researched and investigated as potentially offensive weapons for the military. Additionally, research is needed to develop vaccines and novel therapeutics, as well as improved diagnostics. Working with highly pathogenic organisms requires precautions that ensure the public's safety and the environment (Wurtz, Grobusch, & Raoult, 2014). These pathogens can be disseminated by poor and unsafe laboratory practices, laboratory accidents, inadvertent or intentional release. The purpose of this study is to assess the impact of the SARs on laboratories that work with BSAT through a review of inspections conducted during 2018-2020 and a survey administered to registered entities. Additional inquiries for consideration include:

- Qualitative Analysis:
 - Since the implementation of the regulations, what improvements have entities seen at their facilities?
 - Do laboratories have the appropriate infrastructure to support compliance with the SARs?
- Quantitative Analysis
 - What types of laboratories have the least number of low, moderate, or severe departures?

- From 2018-2020, what are the differences between the number and types of safety and security deficiencies by entity type?
- What are the types of regulatory deficiencies observed at laboratories that work with BSAT?

Hypothesis

It is hypothesized that the SARs improved the safety of workers, the public, and the security of BSAT, through increased training, BSAT accountability, and enhanced biosafety and security practices, and decreased inspection departures.

CHAPTER 2

LITERATURE REVIEW

Deadly diseases and other biological weapons were recognized for their potential impact on people as early as the 14th century BC. During that time, the Hittes sent rams infected with Tularemia to their enemies (Barras and Greub, 2014). In the Middle Ages (1346), during the siege of Caffa, the attacking army experienced an epidemic of bubonic plague when the Mongols threw bodies of plague-infected victims over the walls of Caffa. The use of cadavers to infect a population remains a landmark in the history of biological warfare (Wheelis, 2002). During the succeeding centuries, Smallpox became a popular and effective biological weapon. It was introduced in the American continent by the European colonizers and used several times to infect Native Americans during the Conquest of the West (Barras and Greub, 2014). The foundation of microbiology at the end of the 19th century by Louis Pasteur and Robert Koch defined the modern era of using biological agents to infect people. Modern microbiological procedures developed by Louis Pasteur and Robert Koch gave individuals the ability to systematically isolate and produce biological agents on a large scale and control the dissemination. For example, some nations involved in World War I developed secret programs such as the infection of animal feed with *Bacillus anthracis* or *Burkholderia mallei* to infect the enemy.

In 1984, the Rajneesh cult, a religious group, intentionally contaminated salad bars with *Salmonella typhimurium* in restaurants throughout Dalles, Oregon. The contamination resulted in 751 cases, 45 of whom had to be hospitalized (Carus, 2001). The events leading up to the development of federal regulations restricting access to dangerous human pathogens began in

May 1995. Larry Wayne Harris, who had microbiology training and ties to the white supremacist group Aryan Nations, ordered three vials of *Yersinia pestis* (causative agent of bubonic plague) from the American Type Culture Collection in an attempt to harm (Carus, 2002; Tucker, 2000). After his conviction and other bioterrorism incidents, a proposal was developed by a special government committee and presented on March 6, 1996, at a hearing of the Senate Judiciary Committee convened to examine concerns arising from threats of bioterrorism (Guillemin, 2011; Morse, 2015). The proposed framework was subsequently incorporated into the *Antiterrorism and Effective Death Penalty Act of 1996* (Public Law 104-132) and signed into law on April 24, 1996. Section 511 of this law directed the HHS Secretary, along with the CDC, to promulgate regulations to establish and maintain a list of BSAT that have the potential to pose a severe threat to public health and safety (Morse, 2015). This list subsequently became known as the Select Agent List (Morse, 2015). Additionally, these regulations required for the first time those shipping or receiving BSAT to register with the CDC (CDC, 2017).

After the anthrax attacks of 2001, the U.S. Government recognized the growing threat posed by deadly pathogens as potential weapons of mass destruction and controls to access BSAT was strengthened in the U.S. On October 26, 2001, President George W. Bush signed Public Law 107-56 entitled "Uniting and Strengthening America by Providing Appropriate Tools Required to Intercept and Obstruct Terrorism" (Morse, 2015). The USA PATRIOT Act has provisions for: a) enhancing domestic security against terrorism, b) enhancing surveillance procedures, c) international money laundering abatement and anti-terrorist financing, d) protecting the border, e) removing obstacles to investigating terrorism, f) providing for victims of terrorism, public safety officers, and their families, g) increased information sharing for critical infrastructure protection, h) strengthening the criminal laws against terrorism, and i)

improved intelligence (Government Publishing Office, 2001). Additionally, Congress passed the *Public Health Security and Bioterrorism Preparedness and Response Act of 2002* and the *Agricultural Bioterrorism Protection Act of 2002* (Government Publishing Office, 2002, 2002). These Acts expanded the authority of the federal government to regulate the possession, use, or transfer of BSAT that have the potential to pose a severe threat to public health and safety, to animal health, or to plant health (CDC, 2017). Shortly after, the United States Department of Agriculture (USDA) /Animal and Plant Health Inspection Service (APHIS)/ Division of Agriculture (DASAT) and the Department of Health and Human Services (DHHS) / CDC/ Division of Select Agents and Toxins (DSAT) established the FSAP to coordinate the development and implementation of SARs. The FSAP is responsible for carrying out the provisions of the USA PATRIOT Act, the *Public Health Security and Bioterrorism Preparedness Act*, and *Agriculture Bioterrorism Protection Act* through three SARs (42 CFR Part 73, 9 CFR Part 121, and 7 CFR Part 331) (CDC, 2017). CDC is responsible for enforcing 42 CFR Part 73 (human health), while APHIS is responsible for enforcing 7 CFR Part 331 (plant health) and 9 CFR Part 121 (animal health) (CDC, 2017). FSAP promotes laboratory safety and security through registering laboratories, conducting on-site inspections, and providing guidance to the regulated community (CDC, 2017). FSAP also approves transfers of BSAT, investigates reports of theft, loss, or release, and receives reports of BSAT identified by diagnostic laboratories (Blaine, 2012).

Changes in how scientists conduct research with BSAT have occurred not only in the United States but internationally as well. Change has been influenced by several terrorist events, which have increased international awareness of the threat of bioterrorism. Examples of acts of bioterrorism include the 1993 anthrax attack in Kameido, Tokyo (Danzig et al., 2011); the 1995

release of the nerve agent sarin in the subway system of Tokyo (Danzig et al., 2011); the 1995 bombing of the Murrah Federal Building in Oklahoma City (Smoak and Geiling, 2004); the September 11 terrorist attacks in the United States (Smoak and Geiling, 2004); and the 2001 anthrax attacks in the U.S. (Cole, 2003).

An in-depth review of the literature returned five journal articles that are somewhat relevant to this study's topic and questions. However, none of the identified articles focused on the safety and security of research at laboratories registered with the FSAP. Bjork and Sosin (2017) characterized departures from regulatory requirements noted during FSAP inspections. This study focused on the characterization of the FSAP inspection departures identified at registered laboratories from 2014-2015. Regulatory departures from FSAP inspections were grouped into biosafety, security, and other observation categories and assigned a risk level and score reflecting perceived severity. The highest proportion of biosafety observations involved equipment and facilities, and the highest proportion of security observations involved security access restrictions. Additionally, the highest proportion of higher-risk observations for biosafety were biocontainment issues and for security were BSAT inventory discrepancies. This study also showed that when compared with announced inspections, unannounced inspections had proportionally more upper-risk level observations. The current study will contribute to the literature by focusing on a different FSAP inspection timeframe (2018-2020) and adding additional factors, such as training, incident response, and input from subject matter experts.

Henkel, Miller, and Weyant (2012) reported on select agent theft, loss, and release reports in the United States (2004-2010). In this study, a total of seven hundred and twenty-seven reports were received by the DSAT. The results demonstrated that the FSAP had successfully increased compliance of registered and non-registered laboratories, including resolving potential

laboratory-acquired infections, loss, and release reports to ensure safety and security is sustained in U.S. laboratories (Henkel, Miller, & Weyant, 2012). The current study contributes to the literature and addresses a gap in research by focusing on a more recent timeframe and including additional factors such as biosafety and security regulatory departures identified during inspections.

The SARs became effective in 2003, which resulted in publications related to the impact of SARs on research and collaborations. However, the focus on data received from FSAP inspections of registered laboratories limited the availability of research articles to assess the effectiveness of the SARs on overall safety and security at the regulated entities. Additionally, since FSAP collects and maintains the data to support the regulatory requirements, there is limited published literature to determine the impact or effectiveness of the regulations. The literature review confirms the importance of the current study topic and its potential contribution to the research literature in the area of BSAT.

Impact of the SARs

Although regulations are enforced to ensure work involving BSAT is conducted as safely and securely as possible, they can present some unique challenges and controversies. While the goals of most regulatory programs possess public support, in practice, regulation usually comes down to detailed rules and strict record-keeping that can be burdensome and costly to those who must comply with them. This includes large corporations, small businesses, non-profit organizations, state and local governments, and universities. While policies and procedures involving the safety and security of BSAT benefit Americans, the costs associated with regulatory programs are much less transparent. Following the Anthrax attacks in 2001, biosafety laboratories evolved to incorporate work involving BSAT. The regulations demanded more

stringency on training staff, maintaining containment facilities, inventory management and accountability, background checks for individuals with access to BSAT, reporting of theft, loss or releases of BSAT, and approvals for the transfer of BSAT. The review of the literature shows how spending and a regulatory program may significantly impact an organization.

Many of the proposed negative impacts of the SARs are based on anecdotal evidence (Morse, 2015). To date, there has been little documentation of any unintended consequences of the SARs. Casadevall and Relman (2010) suggested that many collections of microorganisms were destroyed when the SARs were first implemented in the United States. The authors also suggested that the regulations "mitigate risk by imposing a strict regulatory environment on laboratories working with select agents" (Casadevall and Relman, 2010). Researchers believe that several limitations impact an organization when it pertains to complying with regulations (Wurtz, Grobusch, & Raoult, 2014). These limitations have negatively impacted the number of collaborations, the size of research projects, and scientific research on microorganisms (Wurtz, Grobusch, & Raoult, 2014). Due to the SARs, there is currently a monitoring program in place that can help to foster sustained biosafety and security in U.S. laboratories, which is a positive outcome for the program. The FSAP, through inspection, ensures that the staff accessing BSAT receive adequate training to work safely in the containment laboratories and ensure that the entities working with Tier-1 select agents have an occupational health provider to address occupational exposures involving select agents. As science expands and techniques become more modernized, it is even more important to collaborate on projects with domestic and foreign partners. Extensive oversight and regulations can prevent that from occurring at times.

The increase in laws concerning BSAT has had significant consequences, as the costs of ongoing safety and security exceed the funds received by institutions through grants or contracts

to cover the costs of operations, facilities, and maintenance (Wurtz, Grobusch, & Raoult, 2014). Without continued funding to support research, regulated institutions must be prepared and willing to commit funds to meet the additional financial burden. In 2006, the Stimson Center conducted a study that concluded that select agent researchers' main complaints were the time and costs of security upgrades and procedures, managing inventory of samples, and barriers to international collaboration (Fischer, 2006). In a separate survey, 93.4% of investigators responded that these agents should be regulated and that the security risk assessment (background checks) for individuals was the most effective component of the SARs (Sutton, 2009). Dias et al. (2010) conducted a literature review of research articles between 1992 and 2007 in the United States to determine whether negative consequences of regulations on BSAT could be detected. After 2002, the number of publications concerning *Bacillus anthracis* and the Ebola virus, two select agents, increased.

Wurtz, Grobusch, and Raoult (2014) summarizes the impacts of the increase in biosafety and security regulations. Among many reports on biosafety in the literature, only a few presented information regarding the effectiveness of the SARs. Additionally, there have been no criteria or reports for judging their effectiveness. The SARs balance the need to regulate access to the most dangerous pathogens and minimize regulatory burdens on basic biological research. The study concluded that only a few presented data regarding the effectiveness and impact of regulations among many reports on biosafety.

Inspections of regulated entities are the primary tool used by the FSAP to determine compliance with the SARs. Bjork and Sosin (2017) conducted a review and characterization of departures identified during a select agent inspection. The study's purpose was to examine inspection departures from 2014-2015 to increase transparency regarding security and biosafety

risk and conditions at FSAP-regulated entities and identify areas for programmatic improvement. It is believed that providing more transparency allows for a better understanding of the risk associated with BSAT (Bjork and Sosin, 2017). The study described the impact and relative risk of regulatory departures from 2014 through 2015 and identified several areas of variation that can inform the further study and programmatic attention. Their initial analysis identified factors that differentiated risk associated with inspection findings and allowed consideration to apply inspection resources differently by entity type, inspection type, and biological select agent and toxin possession status. The study further shows that the impact of regulations and inspection may differ based on the type of inspection (announced or unannounced), entity type, size of the entity, and the number of days on-site by the inspectors. For example, a laboratory with multiple research projects, several registered laboratories, and hundreds of scientists on their registration may require more government oversight, experience more severe departures, and require more funding to meet regulatory requirements. Additionally, the type of impact experienced by a high containment research laboratory may differ from a small public health laboratory that does not possess BSAT. The BSAT regulations attempt to minimize the regulatory burden on biological research and balance the need for regulating access to dangerous pathogens for small or large high-risk laboratories.

Regulatory oversight is necessary, and a healthy organizational culture significantly increases safety and security in the laboratory (Franz, 2015). Franz critiques the journal article *Transfer of BSAT: 2010-2013* as the article attempts to address whether the publication is the “Perfect Record or Wrong Metric” (Franz, 2015). Franz concludes that the information published regarding agent transfers did not help evaluate the efficacy or efficiency of SARs (Franz, 2015). SARs can impact a facility negatively and positively. An organization can be negatively

impacted by funds spent or stringent paperwork or records requirements. Positive impacts include safety and security lapses prevented, exposures prevented, thefts or losses prevented, and environments protected. Franz (2015) asks, "What was the impact, positive and negative, on research? Did it make the work and the nation safer or more secure?" These are two questions that have often gone unanswered, which this study will attempt to address.

Franz (2015) argues that unless we can demonstrate a measurable reduction in laboratory accidents or nefarious intent that justifies the costly oversight, we should be assured that we are not causing additional harm to research and the organizations regulated (Franz, 2015). Based on comments from the scientific field, most people believe that transfer approvals do happen quickly; however, researchers experience different outcomes when it comes to inspections (Franz, 2015). Based on the article, select agent program inspections are costly and time-consuming to scientists and institutions (Franz, 2015). Additionally, organizations routinely experience multiple separate inspections each year, with each inspection involving 3-15 government inspectors over 3-4 days. The United States government addresses this issue with Executive Order 13546, which has resulted in joint inspections and the elimination of duplicative inspections (Federal Register, 2010). Franz (2015) identifies the negative impact of the SARs, countering the positive comments about transfers in Shelby et al. (2015). It is noted that the article by Franz was published in 2015. Thus, based on published data from the FSAP annual inspection timeliness report, the program has made significant improvements in inspections, including conducting joint inspections to reduce the time spent at facilities. Also, the transition to the electronic Federal Select Agent Program (eFSAP) information system now allows most programmatic transactions to occur *via* a highly secure, 2-way, 24/7 web-based portal. The literature lacks a study that shows the impact of inspections on organizations since the 2015

article published by Franz. The remaining question is, how many safety or security incidents have been avoided because of the program? This study will identify the trends in inspection departures, their severity, and whether safety and security incidents were avoided due to the findings from 2018-2020.

One of the critical parts of the SARs is the requirement of all entities to immediately report any theft, loss, or release (TLR) of BSAT to FSAP (42 CFR § 73.19). This requirement applies to entities that are required to register with the FSAP and undergo inspections as well as to those exempted from the regulations. TLR reporting requirements for all entities possessing or working with BSAT are found in 42 CFR § 73.19 (Notification of theft, loss, or release). The regulation specifically states, “Upon discovery of the theft or loss of a select agent or toxin, an individual or entity must immediately notify CDC or APHIS and appropriate Federal, State, or local law enforcement agencies” (CDC, 2017). Thefts or losses must be reported to FSAP even if the select agent or toxin is subsequently recovered (CDC, 2017). An entity must report a release of a select agent or toxin causing occupational exposure or release of a select agent or toxin outside of primary containment to FSAP (CDC, 2017). Henkel, Miller, and Weyant (2012), published a review of the TLR reports received by FSAP during 2004-2010. After monitoring over 300 registered entities each year between 2004-2010, the key findings from the study included: a) no reports of a theft of BSAT between 2004-2010; b) out of more than 3400 shipments, there was only one instance in which a select agent was lost during the shipment; c) 11 laboratory-acquired infections during the reporting period; d) no fatalities that resulted from any of these infections; and e) no reported secondary transmission cases to other humans.

The Henkel, Miller, and Weyant (2012) article provides positive and negative impacts of the SARs. The requirement to report the theft, loss, or release of BSAT immediately and submit

an APHIS/CDC Form 3, Report of Theft, Loss, or Release of BSAT, within seven calendar days can be seen as burdensome for some entities. However, there are many positive aspects of this part of the SARs. One of the most severe dangers to public health and safety addressed by the SARs is the threat posed by the intentional misuse of BSAT as weapons of mass destruction. To prevent such misuses, security and reporting requirements have been enforced in laboratories and are routinely reviewed by FSAP to prevent the theft, loss, or release of BSAT. Henkel, Miller, and Weyant (2012) shows positive outcomes (e.g., program improvements) of reports of the theft, loss, or release of BSAT. However, the study fails to identify positive or negative outcomes related to inspection findings and ways to improve a program based on established guidelines or best practices. This study seeks to address this gap in the literature.

Biosafety

Biosafety is defined as the application of safety precautions that reduce a laboratorian's risk of exposure to a potentially infectious microbe and limit contamination of the work environment and, ultimately, the community (CDC, 2020). Laboratory biosafety (42 CFR 73.12) is one of the key components of the SARs. If successfully implemented, safety in the laboratory can save lives, reduce laboratory-acquired infections, and reduce the potential threat of microorganisms being released into the environment. The literature search resulted in hundreds of articles on working safely in the laboratory. However, none focus primarily on safety in the laboratory as a result of the SARs. Over the years, the research community has adjusted to the SARs and made continual improvements to facilities, equipment, and procedures in response to safety incidents (Franz, 2015). Scientists have long understood safety risks and dealt with them appropriately. However, the SARs require them to continually train and always be conscious of the risk of working with dangerous bioterrorism agents. While Franz (2015) discusses how

scientists have worked safely in the laboratory for many years, even before the SARs, it does not discuss the impact the select agent regulations have had on the safety of BSAT. Franz further states that the regulations implemented over 15 years ago due to security risks or bioterrorism events have become a bureaucratic approach to oversight of laboratory safety by the government. Lastly, Franz believes that it is time that we revisit the implementation of the SARs and consider the impacts on scientific institutions, the public, and national security (Franz, 2015). This study considers the impact of the SARs, including assessing the factors that affect biosafety in the laboratory.

Henkel, Miller, and Weyant (2012) provides information on the theft, loss, and release reports (APHIS/CDC Form 3) from 2004-2010. Focusing primarily on biosafety, the release reports (minus thefts and losses) can provide insight into reports of releases from the study's timeframe (2004-2010). The 2017 Federal Select Agent guidance document (APHIS/CDC Guidance for Reporting Potential Theft, Loss Release, or Occupational Exposure, 2015) defines a release as a “discharge of a select agent or toxin outside the primary containment barrier due to a failure in the containment system, an accidental spill, occupational exposure, or a theft” (CDC, 2017). Information contained in an APHIS/CDC Form 3, submitted by regulated entities to CDC, was used in the analysis. Examples of releases or occupational exposures (laboratory-acquired infections) may include reasonably anticipated eye, skin, mucous membrane, or parenteral contact with potentially infectious materials that may result from performing work in the laboratory (Henkel, Miller, & Weyant, 2012). During the study period, of the 727 reports received, 88 (12%) were loss reports (each loss was investigated by the FBI and determined to have no criminal nexus), and 639 (88%) were release reports (Henkel, Miller, & Weyant, 2012).

Additionally, there were no theft reports within the study's timeframe. There were 11 laboratory-acquired infections or occupational exposures that resulted from the incidents described in the 639 release reports received between 2004-2010. While these reports demonstrate significant biosafety concerns, further investigations showed no fatalities associated with any of the laboratory-acquired infections (LAIs), nor were there any confirmed instances of secondary infection to any other person through an infected laboratory worker (Henkel, Miller, & Weyant, 2012). All 11 LAIs resulted from either unrecognized or unreported exposures, presumably through the aerosol release of the BSAT (Kaye, 2005). Occupational exposures represent an event in which the worker exposed to the BSAT may be at risk for developing a laboratory-acquired infection. According to the study, this type of release can be minimized through proper use of personal protective equipment, training, and improved engineering controls for sharp instruments such as needles. It should be noted that before the SARs there was no reporting system at any level of government that monitored the number of laboratory workers and the types of exposures associated with their occupation (Sewell, 1995).

Initial analysis of the information included in the study provided insights that may improve biosafety practices in laboratories working with BSAT under differing conditions. The findings in the study are subject to a few limitations. For example, in the early years of the program, there was very little encouragement for exempt entities to report TLRs. Therefore, the number of reports received by the CDC is likely an underestimate of the actual number of releases and was never reported (Henkel, Miller, & Weyant, 2012). While the study by Henkel, Miller, and Weyant (2012) was sufficient to monitor TLR reports from 2004-2010, more studies are needed to assess more recent data, including how inspection-related activities and departures play a part in laboratory safety. Instead of reviewing TLR reports by entities, this study focuses

on inspection departures, including those related to biosafety, to provide more recent information regarding laboratory safety and risk.

Laboratory safety and risk of exposures are critical components to eliminate the potential for laboratory-acquired infections or releases of BSAT into the environment. A release, whether an occupational exposure or release into the environment, can result in exposures to individuals outside the laboratory and create the potential for an epidemic or significant public health issues (Olle-Goig & Canela-Soler, 1987). While there are hundreds of manuscripts that focus on working safely in the laboratory, there are very few that associate work with BSAT and the negative or positive impact of the SARs. This study identifies trends in inspection findings related to biosafety work with BSAT, and it will provide guidance and best practices of how to improve programs for entities that work with these dangerous pathogens.

Biosecurity

Biosecurity refers to procedures implemented to keep diseases and the pathogens that carry them away from animals and people (APHIS, 2020). This also includes measures taken to ensure the security of biological agents in laboratories. It is recognized that security risks cannot be eliminated but can be reduced while some threats are more likely to occur than others (Gaudioso & Salerno, 2004; Royes, 2002). Additionally, since 2009, the federal government has taken measures to strengthen laboratory biosecurity through executive orders to protect against theft, misuse, or diversion to unlawful activity (Federal Register, 2009). The SARs were developed and implemented to prevent bioterrorism attacks by using required biosecurity measures for working with BSAT. In Wurtz, Grobusch, and Raoult (2014), evidence was provided on the negative impact of laws regarding biosecurity and bioterrorism in fighting diseases. The increase in laws concerning BSAT laboratories has had significant consequences.

The costs of ongoing security exceed the funds received by institutions to cover the costs of facilities and operations. Based on the study, some laboratories withdrew from research areas due to funding, which will produce a gap in the health network (Wurtz, Grobusch, & Raoult, 2014). This study analyzes the impact on research due to the financial burden of implementing security procedures for work with BSAT. However, it does not account for the impact (positive and negative) of the SARs related to inspection findings. This study addresses this gap in the literature.

In addition to release reports, Henkel, Miller, and Weyant (2012), focused on theft and loss reports of BSAT. Based on the regulations, security procedures are required to be implemented in laboratories. They are routinely reviewed by CDC to prevent the theft or loss of BSAT, including accountability of inventory and conducting security risk assessments for workers with access to BSAT through background checks by the FBI. It is also noted that an individual who will have access to BSAT must undergo a security risk assessment performed by the FBI's Criminal Justice Information Services Division. These personnel security requirements help prevent access to BSAT by bioterrorists or others likely to misuse them (Higgins et al., 2013). During the study period (2004-2010), there were no thefts of BSAT reported to CDC, and of the 727 reports received, only 88 (12%) were loss reports. The remaining were related to release reports (88%). The final disposition of BSAT described in the 88 loss reports was reconciled in all but one report. Additionally, approximately 70% (62 of 88) of all loss reports were submitted between 2007 and 2010 (Henkel, Miller, & Weyant, 2012). Ninety-two percent of the loss reports from regulated and exempt entities were associated with laboratory biocontainment facilities instead of animal facilities. Sixty-eight percent of these events involved BSL-3 laboratories at registered facilities. Nearly two-thirds (65.9%) of all loss reports

were inventory discrepancies. Other losses were categorized as shipping/transport errors (18%) and discarded samples (14 %). Lastly, there was only one loss report submitted by an exempt entity.

The data provided through the reporting system could help identify specific combinations of agents and activities for which security risk assessments can be focused. Monitoring BSAT associated events through theft and loss reports may provide a broader understanding of the incidence of such events and inform biosecurity guidance. While the study by Henkel, Miller, and Weyant (2012) was sufficient to monitor TLR reports from 2004-2010 for thefts and losses, more studies are needed to assess more recent data, including how inspection-related activities and departures play a part in laboratory security. In place of reviewing TLR reports by entities, this study focuses on inspection departures, including those related to biosecurity, to provide more recent information regarding laboratory security and risk mitigation strategies.

In Franz (2015), the author collected comments from entities registered with the FSAP regarding biosecurity regulations. Franz stated that "While the inventory requirements for "agent accountability" put in place as part of surety programs after September 11 and the anthrax letter mailings of 2001 have been modified somewhat, they are still onerous" (Franz 2015). During the review, one lab reported having to hire two full-time staff to track the vials of inventory (Franz, 2015). This was likely something that was done for entities with thousands or millions of vials of BSAT inventory. Additionally, investigators routinely discarded samples from animals infected with select agents before a thorough analysis is done to get the vials from the records or eliminate the potential for administrative loss of the vials. As stated in the publication, a laboratory performing multiple studies and working with many microorganisms, creates many sources, such as tissue culture flasks, infected animal organs, and discarded pipette tips to obtain

BSAT (Franz, 2015). “Therefore, a knowledgeable insider with malicious intent likely would not steal an accountable vial” (Franz, 2015). Instead, they might sample the intrinsically unaccountable sources (Franz, 2015). Current SARs require insider threat awareness training and suitability programs for staff working with Tier-1 agents to enhance biosecurity. However, no information is provided about how these participants were chosen and whether the comments accounted for each type of registered entity. Additionally, this review was conducted before 2015. This study addresses the gap in the literature and includes entities that can provide a more recent account (2018-2020) of the impact of the regulations on their facility by type of entity.

FSAP Inspections

Inspections are considered one of the most important methods to enforce regulations and ensure regulatory compliance (OECD, 2014). The FSAP allows laboratories to conduct lifesaving research on potentially dangerous pathogens while ensuring it is done as safely and securely as possible. Inspections, which are critical components of the FSAP's oversight, are conducted to ensure compliance with the SARs. FSAP, through on-site inspection, ensures appropriate measures are in place at each registered entity to prevent unauthorized access to, theft or loss of, or unintended exposure to or release of BSAT. Ensuring compliance ultimately leads to safer laboratories, reduced laboratory infections, and public health protections.

Although inspections serve a meaningful purpose for the FSAP, some scientists may see it as an extra burden (Franz, 2015). Bjork and Sosin (2017) studied departures from regulatory requirements identified during FSAP inspections to increase transparency with the public and regulated entities regarding biosafety and security risk at FSAP registered entities and identify areas for programmatic improvements for FSAP. Regulatory departures from inspections led by CDC (2014-15) were grouped into "biosafety," "security," and "other" observation categories

and assigned a risk level and score reflecting perceived severity (Bjork and Sosin, 2017). Data were obtained from the National Select Agent Registry (NSAR), a national database maintained by FSAP, and was transferred to a Microsoft Access relational database. The variables included in the study based on entity registered with FSAP were:

- Academic
- Commercial
- Federal Government,
- Non-federal government
- Private

The six inspection types conducted by FSAP and included in the study were:

- Renewals
- Verification
- Maximum containment
- New entity
- New space
- Compliance

Renewal, verification, and maximum containment inspections were the most routine types of laboratory spaces approved for the possession, use, or transfer of BSAT (Bjork and Sosin, 2017). Additionally, departures from inspection report narratives were assessed by an 8-person team of CDC scientists with laboratory research or inspection backgrounds who were not involved in the inspections reviewed. The review resulted in regulatory departures being classified into three main observation categories: 1) Biosafety, 2) Security, and 3) Other. Lastly, each observation (departure) was assigned to 1 of 3 risk levels of increasing severity. "Risk"

reflects the relative probability of an adverse biological select agent and toxin outcome (e.g., theft, loss, or unintended exposure) and the consequence of that adverse outcome should it occur (Bjork and Sosin, 2017). The risk levels were weighted to reflect their nonlinear relative risk as follows: level 1 (1 point), level 2 (2 points), and level 3 (4 points). Inspection risk was defined as the sum of assigned points for the observations associated with each inspection” (Bjork and Sosin, 2017).

A total of 230 FSAP-registered entities were involved in the 324 inspections meeting the study criteria. This resulted in a mean of 1.4 inspections/entity during the 2-year study period and 5,061 regulatory departures categorized into 3,280 observations (Bjork and Sosin 2017). A combined total of 2,267 biosafety and security observations were classified across all 296 routine inspections. To calculate an overall risk score for each inspection, risk levels were weighted to reflect their nonlinear relative risk as follows: level 1 (1 point), level 2 (2 points), and level 3 (4 points). Inspection risk was defined as the sum of assigned points for the observations associated with each inspection. By entity type, commercial entities had the highest median combined (i.e., biosafety plus security) observation frequency and the highest median risk per inspection (9 observations/ inspection; inspection risk: 17, (Bjork and Sosin, 2017). Commercial entities were followed by private (7 observations/inspection; inspection risk: 13), academic (6 observations/inspection; inspection risk: 10), federal government (6 observations/inspection; inspection risk: 10), and non–federal government (5 observations/inspection; inspection risk: 8) (Bjork and Sosin, 2017). A combined 74% of biosafety observations were attributed to equipment and facility (28%), BSAT containment (24%), and safety (22%) issues. A combined 81% of security observations were attributed to restricted access (33%), inventory records (29%), or plans and procedures (19%) issues. The security categories with the highest percentage of

observations scored above risk level 1 were inventory discrepancy (79%) and security operations (77%) (Bjork and Sosin, 2017).

When analyzing biosafety and security observations, commercial and private entities had the highest, and non-federal government entities had the lowest observation frequency per inspection and risk per inspection. This indicates that inspection duration and frequency might be better weighted by entity type than applied equally across all registered entities. Non-possessors of BSAT also had substantially fewer observations and lower risk than entities that possessed BSAT. "Given the absence of BSAT in storage or use, inspections of non-possessing entities do not allow for direct observation and review of select biological agent and toxin work or security procedures, so these inspections likely offer less opportunity for departure findings than inspections of active facilities" (Bjork and Sosin, 2017). Additionally, the study concluded that further consideration should be given to increasing the frequency of unannounced inspections, allowing inspectors to observe daily routine operations that pose a security or biosafety risk. This could result in improved security and biosafety by increasing the specificity and impact of post-inspection remediation efforts. The study provided evidence that balancing resources according to entity risk may strengthen FSAP oversight. Additionally, varying inspection methods by select agent possession and entity type and conducting more unannounced inspections may be beneficial (Bjork and Sosin, 2017).

This study was the first risk-based review of the FSAP inspection findings. However, additional analytic techniques may further refine the understanding of risk characteristics based on inspection findings. Additional analyses will also help understand how risk discovered during inspections relates to the reported biological select agent and toxin loss or release incidents at FSAP-regulated entities. Additionally, the study mainly focused on biosafety and security-related

departures. Biosafety and security requirements are the key components when protecting public health. However, other critical components of the SARs should be included in an analysis of inspection departures. Other risk components that are not included in previous studies but are included in this study are 1) incident response (42 CFR 73.14), 2) training (42 CFR 73.15), and 3) records (42 CFR 73.17). Lastly, the study included a review of CDC inspection reports from 2014-2015. This study includes data collected from recent (2018-2020) inspection reports created by DSAT and DASAT.

The FSAP has gone through multiple program improvements over the last few years, and this study demonstrates how those improvements have negatively or positively impacted the public and regulated entities. In an article by Franz (2015), he stated that “the greatest negative impact on research progress described to me appears to be the arbitrary requirements placed on labs by inspectors—some of whom have relatively little relevant experience—without a proper risk assessment or a means to appeal.” Franz also stated that he heard many examples of costly facility modifications and procedures that resulted in months or years of delays from inspectors' results. Some believe that what was implemented 15 to 20 years ago due to potential security risks has become a bureaucratic approach to overseeing laboratory safety by the government (Franz, 2015). A remaining question that has not been answered is how many safety or security incidents were avoided because of the SARs and inspections. Additionally, none of the researched articles provide information about what inspections or the SARs did to prevent potential exposures and protect public health, animals, and plants. The study provides answers to some of these questions and addresses gaps in the current published literature.

CHAPTER 3

METHODOLOGY (INSPECTION REPORT DEPARTURES)

A mixed-methods design was used for this study: a combination of quantitative and qualitative analyses. Through an analysis of FSAP inspection departures and survey results, this research study aims to determine how the SARs improved laboratories' safety and security that work with BSAT. The quantitative analysis includes a review of the inspection reports from 2018-2020 (Chapter 3). The qualitative analysis includes a survey administered to entities registered with the FSAP (Chapter 4). Qualitative research typically involves purposeful sampling to enhance understanding of an information rich case or situation (Patton, 2009). However, quantitative research involves probability sampling to permit statistical inferences based on the results (e.g., inspection departures) (Sandelowski, 2000).

Quantitative analysis is defined as objectively collecting and analyzing numerical data to control variables of interest, describe, or predict outcomes (McLeod, 2019). The goals of quantitative research are to test the casual relationship between the established variables (independent and dependent), make predictions, and generalize results across wider populations. Conducting a quantitative and qualitative analysis of the data enabled the opportunity to assess the regulations' outcomes from the regulator (FSAP) and the registered entities' perspectives, including identifying positive or negative trends from a review of inspection departures and survey results. In this study, I relied on information received from the respective entities registered with FSAP.

The methods described below assess the impact of the SARs on laboratories that work with BSAT by analyzing data collected from FSAP inspections conducted from January 2018 through March 2020. A quantitative analysis was conducted to identify any positive or negative trends in the regulatory inspection departures observed during on-site inspections by inspectors. The FSAP currently uses a secure electronic information system to collect, store, analyze, and build inspection reports from departures from the regulations or nationally recognized standards identified during inspections. Data were extracted from the electronic Federal Select Agent Program portal (eFSAP) to conduct the quantitative analysis. FSAP (DSAT and DASAT) inspections with a start date of January 1, 2018, through March 31, 2020, were included in the study. Data describing laboratory characteristics and research activities for each entity was excluded from the analysis. Inspection reports include inspector-written narratives describing each finding that was deemed a departure from regulatory requirements. For the study, an inspection departure is defined as a deviation from an accepted standard of practice or part of the SARs. The variables included in the analysis are: 1) entity type; 2) year of inspection; 3) the number of inspection departures; 4) entity risk score; and 5) severity of inspection departures. It is hypothesized that the data will show that the SARs improved the safety of workers, the public, and the security of BSAT, through decreased inspection departures from 2018-2020.

Study Criteria

To be included in the analysis, entities must: 1) be registered with the FSAP; 2) have been inspected between January 1, 2018-March 31, 2020; 3) have experienced an announced or unannounced inspection within the study timeframe; 4) be defined as a federal, state, commercial, private, or academic facility; and 5) have received a verification or renewal

inspection. Entities that do not meet any of the inclusionary criteria listed above were excluded from the analysis.

Entity Type

The five entity types included in the analysis are:

- 1) Academic: a university, college, or other institution of higher learning
- 2) Commercial: a for-profit company
- 3) Federal government: an entity that is part of an agency of the federal government
- 4) Non-federal government: an entity that is part of an agency of a state or local government (excluding academic entities)
- 5) Private: a privately owned, nonprofit entity whose principal purpose is charitable or benevolent

For this study, private and commercial entities were combined due to their similarities and the low number of registered private and commercial entities in the program. This part of the analysis aims to answer the question: 1) Did inspection departures during 2018-2020 increase or decrease by entity type? 2) Comparing entity types, which entities had the most and least number of departures? Additional information on the statistical analysis related to the entity type is listed below.

Inspection Year

Inspections have been conducted by the FSAP since 2003 to ensure entity compliance with the SARs. FSAP conducts inspections throughout the year for entities registered with the program. For this part of the study, the inspection reports' data were analyzed from January 1, 2018 – March 31, 2020. Some entities may experience three inspections within that timeframe, while others only experience one or two. The total number of entities inspected each year, and

the total number of departures observed each year by entity type were included in the analysis. Inspections conducted between April – December 2020 were not included in this analysis as the FSAP started conducting remote inspections due to travel limitations after the start of the COVID-19 pandemic. In addition, this part of the analysis aims to answer the question: 1) How many inspection departures were observed by year of inspection? 2) Did inspection departures increase or decrease by year of inspection and entity type? Additional information on the statistical analysis related to the year of inspection is listed below.

Inspection Type

The FSAP conducts announced and unannounced inspections at registered entities annually to ensure compliance with the SARs. On-site inspections ensure appropriate measures are in place at each registered entity to prevent unauthorized access to, theft or loss of, or unintended exposure to or release of BSAT. Compliance with the regulations leads to safer laboratories, reduced laboratory-acquired infections, decreased regulatory departures, and enhanced public health protections.

Announced inspections are defined as site visits where entities are given prior notice before inspectors arrive at the facility to inspect. Unannounced inspections are defined as site visits conducted without prior notice to the entity. For this study, both inspection types are included in the analysis to identify trends in inspection departures based on the type of inspection.

The FSAP conducts several inspection types, including renewals, verifications, compliance, new entity registration, and amendments (changes) to registration. The inspection report data analysis only included entity renewal and verification inspections, two of the most common types of inspections conducted by FSAP annually.

- **Renewal:** review, typically conducted every three years, of the entire entity program, including all registered spaces and documents, to renew an existing entity's registration. It is one of the most comprehensive inspections.
- **Verification:** an intermediate review of entity program, including assessing responses to previous inspection departures, conducted within 12 to 18 months of a renewal inspection.

SARs

FSAP regulates the possession, use, and transfer of 67 BSAT that have been determined by the U.S. Government to pose a severe threat to public health, animal or plant health, or to animal or plant products. The analysis of inspection results from 2018-2020 includes a review of the regulations 42 CFR Part 73, 9 CFR Part 121, and 7 CFR Part 331. Each time a part of the regulation is cited, it is included in the total number of departures by part of the regulations. This part of the analysis aims to answer the following question: 1) Which part of the regulations was cited the most by entity type (2018-2020)? Additional information on the statistical analysis related to regulations is listed below.

Severity of Inspection Departures

Each categorized inspection departure is assigned to 1 of 3 risk levels of increasing perceived severity (low, moderate, serious). "Risk" in this context reflects the relative probability of an adverse biological select agent and toxin outcome (e.g., theft, loss, or unintended exposure) and the consequence of that adverse outcome should it occur. A severity risk score is assigned immediately following the classification of a departure to a part of the regulations. Parameters for each risk level were established in advance in consultation with FSAP leadership and inspectors. Departures may include low-risk findings and findings that may

lead to an immediate stoppage of some or all entity activities. The severity level of departures from the SARs are communicated through the inspection report.

Serious severity departures (a score of 3) are an immediate threat to human, plant, or animal health, animal or plant products, and/or security of BSAT and those that indicate a need for systemic improvements. Required corrective action may include ceasing work or addressing departures within a shortened period. Moderate severity departures (a score of 2) are those that have the potential to be a threat to human, plant, or animal health, animal or plant products, and/or security of BSAT. If not corrected, such departures will likely impact the safety of humans, animals, and/or plants, animal or plant products, and/or security of BSAT and increase the risk of more serious departures. Low severity departures (a score of 1) are unlikely to pose an immediate threat to human, plant, or animal health, animal or plant products, and/or security of BSAT. However, they are not consistent with safe and secure standards of practice. If not corrected, such departures degrade the culture of safety and security. Repetition of departures may be considered more serious and lead to enforcement actions. The total risk scores were calculated by entity type for each year to analyze inspection risk by inspection departure.

Entity Risk Score

The FSAP assigns a risk score to all registered entities to assist in evaluating their complexity and risk level. The overall score is the total of parts of the entity's registration, focusing on areas of entity size, BSAT on registration, possession status, and work practices. The entity risk score can range from 20-200 based on the scoring system defined by FSAP. For this study, the following scoring system was used: 0-59 (Low Risk Entity); 60-99 (Moderate Risk Entity); 100 and above (High Risk Entity).

Data Collection & Analysis

Data Collection

Data was collected, stored, analyzed, and reported through the eFSAP information system. The eFSAP information system is a real-time two-way portal that maintains information on all registered and exempt entities that possess, use, or transfer BSAT. The eFSAP is a Federal Information Processing Standards (FIPS) 199 high rated platform with multiple module-like applications supporting the programmatic requirements for FSAP. The eFSAP system architecture is an on-premises Customer Relationship Management (CRM) solution consisting of Microsoft Dynamics, SharePoint, Modern AP, PowerBI, SSRS, and Team Foundation Services (TFS). External users access the system via the CDC's Secure Access Management System (SAMS). Internal users access the system via Active Directory. The system has the capability and accuracy needed to conduct a reliable analysis of inspection departures. The system is a national select agent database of regulated entities for the FSAP program that includes the names and locations of registered individuals and entities, the listed agents and toxins such individuals or entities possess, use, or transfer, and the characterization of such agents and toxins.

Entity inspection reports are written and stored in the eFSAP information system. For the analysis, entity information, and inspection report, data was collected, analyzed, and extracted from the eFSAP information system. There were rare occasions where a laboratory would be inspected more than one time in a year. This occurs very infrequently, and these occurrences were not be removed over the three years examined.

There were also occasions where there is only one inspection in the three years for a specific entity. Information extracted from inspection reports in eFSAP included: 1) Name of the entity; 2) dates of inspection; 3) type of entity; 4) type of inspection (announced and unannounced; 5) list of inspection departures; 6) severity of inspection departures; 7) Part of regulation.

Data Analysis

An exploratory statistical analysis was conducted using descriptive statistics to identify any significant correlations between the independent and dependent variables in the inspection results from 2018-2020. The data was analyzed to identify increases and decreases in inspection departures from 2018-2020 based on the entity type. A descriptive statistical analysis was conducted to review the number of overall departures by year and entity type. The descriptive analysis results identified the means, and sum of inspection departures by year and entity type. Descriptive statistics were then conducted surrounding the primary variables of interest, including the total number of departures, departure severity, entity type, and inspection year. The trends of the data over time were then analyzed by conducting linear regressions with the following outcomes: number of departures per inspection, the average number of departures per inspection, and average departure severity per inspection. Linear regression is a standard analysis used to model the relationship between variables (Beck, 2017).

A chi-square analysis was conducted to determine the significance of all independent variables as predictors of the number of departures per inspection. A chi-square test is commonly used to evaluate any associations between dependent and independent variables (Rana & Singhal, 2015). The independent variables used in each analysis were inspection date, entity risk score, and entity type. These variables also represented the controlling variables. The dependent variables included the number of inspection departures and inspection departure severity. For all

statistical analyses in this study, a $p\text{-value} < 0.05$ was considered statistically significant. The analysis was conducted using Microsoft Excel version 16.47 and R Studio software version 1.4.1106 (R Core Team, 2017).

Ethical considerations included drawing attention to specific entities. While the inspection database includes every entity's name, registered laboratories, registered agents, work objectives, and staff names, none of the entity-specific information was included in the study. The laboratory inspection by entity type was the focus of the research and not entity-specific information. Institutional Review Board (IRB) approval (IRB ID: PROJECT00002688) was obtained from the University of Georgia on October 16, 2020.

Results

Exploratory Analysis

A total of 392 inspections were conducted across the study period, at 215 different entities, falling into four different entity types: academic, commercial/private, federal government, and state government facilities. One hundred seventy-three inspections were conducted in 2018, 182 in 2019, and 37 January – March 31, 2020 (Table 2). One hundred eighty-six of the inspections conducted were unannounced, while 206 inspections were announced. Table 3 gives the frequencies and percentages of risk categories and inspection warnings (announced or unannounced) by entity type. Most government entities (both state and federal) inspected during the study period fall within the low-risk category, while most academic and commercial or private entities fall within the moderate-risk category. While there are more academic entities in the moderate-risk category (63.31%), the federal government entities have the highest proportion of high-risk facilities (33.85%).

A total of 1921 individual regulatory departures were identified across the study period adding up to 2410 in the severity score. Table 4 gives frequencies and percentages of departures and sums and percentages of severity scores by entity type, inspection year, inspection type, and inspection warning level. Academic entities had the most significant number of departures as well as the highest severity score sum. This can be attributed to the fact that there were 138 total inspections for academic entities, 109 for state government, 79 for private/commercial, and 66 for federal government entities during the study period (Table 2). Most departures occurred in entities with a moderate risk designation. The preponderance of inspections occurred as renewal and verification inspections, with renewals accounting for 57.83% of the inspection departures during the study period. The number of departures for announced inspections occurred slightly more often than unannounced inspections. The difference in the number of departures can be attributed to the increased number of announced inspections (206) compared to unannounced inspections (186). The precipitous drop in the total number of departures in 2020 is primarily due to the truncated study period resulting from the COVID-19 pandemic.

Figure 1 illustrates the sections of the SARs that were identified as regulatory departures during the inspections. The three most common regulatory sections cited were: Section 12: Biosafety (N = 797), Section 15: Training (N = 280), Section 11: Security (N = 262). To examine the differences more closely, Figure 2(a) describes the departures of the SARs according to the severity score assigned to each departure. Of the three most sections of the regulations where departures were observed, training and biosafety departures were more likely to be categorized as moderate severity than security violations. Departures in Section 3: HHS BSAT; Section 4: Overlap BSAT; Section 16: Transfers; and Section 19: Notification of theft, loss, or release had the highest proportions of the most severe violations (Figures 2(a) and 2(b)).

Table 5 describes the average number of departures per year for the top three sections of the regulations with the most departures: Section 12: Biosafety, Section 15: Training, and Section 11: Security. During the study period, the average number of inspection departures decreased from all three sections during 2018-2020. The most significant decrease in the average number of departures by regulatory section was seen in Biosafety, with an average of 2.03 in 2019 and 1.43 in 2020. The second-largest decrease in the average number of departures was seen in the Training Regulations, going from 0.94 in 2018 to 0.56 in 2019.

Figure 3 describes the average number of departures by entity type and year. For the overall average number of departures, the federal government slightly increased from 6.2 in 2018 to 6.6 in 2019 and dropped significantly in 2020 to 3.4. The average number of departures for all other entity types either decreased or remained the same throughout the study period. The state government experienced the highest decrease in the average number of departures going from 5.1 in 2018 to 3.3 in 2019 and 2.6 in 2020.

Table 6 describes the average number of departures identified and severity for each departure, divided across the entity types. For each year, there was a decrease in the average number of departures for each entity type. In addition, most entity types had similar distributions of departure severities, but federal government facilities had a larger proportion of moderate departures. This may be attributed to the fact that the federal government laboratories were more complex and conducted higher risk activities in their high and maximum containment laboratories.

Table 7 characterizes the data slightly differently, examining the departure severity by entity type and the inspection year. The proportions listed are column proportions representing the distribution of frequency and severity of departures within each entity type. Nearly half of all

severe departures identified during the study period were identified in federal government facilities. Only a third of all moderate departures identified during the study period were identified in academic facilities. There was a slight increase in moderate and severe departures from 2018 to 2019, with approximately half of all moderate and severe departures reported in 2019. Overall, there was a decrease in low severity departures from 2018 to 2019, although nine more inspections were conducted in 2019.

The final component of the exploratory analysis of the inspection data focused on assessing whether any of the characteristic variables of the entities or inspections were reliable predictors of the number of departures identified in a given inspection. Table 8 describes the results of the univariate tests to determine which of the independent variables in the model were predictive of the number of departures per inspection. Entity Risk Score is the only statistically significant predictor of the number of departures, but inspection year suggests some marginal significance. Next, risk ratios and corresponding 95% confidence intervals were calculated for each category of the independent variables in the Poisson model (Table 9). Entity Risk Score was again significant, suggesting that for each 10-unit increase in the entity risk score, the number of departures per inspection increases by a factor of 1.029 ($p = 0.0075$).

Temporal Effects

The primary objective of the study was to examine the trend of departures over time. Due to the truncated characteristics of the data for inspections in 2020, the remaining analysis examined the data as a function of days and months rather than by year. Figure 4 plots the total number of departures per inspection as a function of time throughout the study period, separately by the entity types. To minimize the variance in the slope coefficient, the x-axis represents the inspection date in the form of the number of days since the beginning of the study. While there

seems to be an overall slight downward trend, there is insufficient evidence to identify a statistical decrease in the frequency of departures over time in this study. Therefore, this analysis also considered the average number of departures per inspection over time for each entity type, as illustrated by Figures 5 – 8. This analysis reduced some of the noise present in the data. However, again, there is no statistically significant evidence to identify a decrease in the average number of departures per inspection over time in any facility type.

Figure 9 illustrates the final analysis of the impact of the regulations over time by examining the average severity of the departures identified during an inspection over time, according to each entity type. Similar to Figure 4, the x-axis represents the inspection date in the form of the number of days since the beginning of the study to minimize the noise in the slope coefficients. This analysis also reveals no statistically significant difference in departures over time. However, it is curious to note that there is a trend towards a slight increase in the average severity score in commercial or private entities over time, in contrast to the other entity types, which have a slight decrease in the average severity score over time. While this is likely due to the noise in the data, it warrants further analysis to better discern the trueness of this effect.

Conclusion

This study examined the impact of the SARs on the safety and security of BSAT from January 2018 to March 2020. A total of 392 inspections were conducted over the study period at 215 different entities. It also conducted an exploratory and temporal analysis of the departures to determine any significant characteristics associated with the frequency of regulation violations.

The preponderance of the departures fell within four regulatory sections: Biosafety (Section 12), Training (Section 15), Security (Section 11), and Records (Section 17). Throughout the study period, the study showed a decrease in departures for these four critical areas: safety,

training, security, and records. Over 75% of the departures from the study fall into the low severity category. Based on the FSAP definition for low severity departures, over 75% of the departures from the study are unlikely to pose an immediate threat to human, plant, or animal health, animal or plant products, and/or security of BSAT. Most entity types had similar distributions of departure severities, but federal government facilities had a larger proportion of moderate departures. This suggests that the federal government facilities may require additional assistance or oversight in complying with the SARs. Overall, the data shows a slight downward trend in the average number of inspection departures across all entities. However, there is no statistically significant evidence to identify a decrease in the average number of departures per inspection over time in any facility type.

The entity risk score showed statistical significance when predicting the average number of departures. This suggests that entities with a higher risk score of moderate or high may result in more departures and require more oversight to ensure the safety and security of BSAT at these facilities. Overall, based on the analysis, each assessment showed decreased inspection departures and severity scores for biosafety, security, and training. However, most did not result in statistical significance based on entity type, year of inspection, or type of inspection. More importantly, throughout the study period, there were no reports or findings of theft, illness, or deaths related to entity possession and use of BSAT.

When considering the longitudinal analysis of the regulation departures, no statistically significant effect was detected. The study period covers 27 months, nearly 20 years after the implementation of the regulations. The most significant impact of the regulations likely occurred when the regulations were first implemented in the early 2000s. It would be expected that the impact would dwindle over time as more entities become compliant with the regulations. Further

research incorporating data immediately before and after the implementation of the regulations may better elucidate the impact of these regulations. Moreover, by lengthening the study period to be more representative of the time period of the regulations, the long-term impacts may be better identified. The truncated nature of the data from 2020 due to the COVID-19 pandemic also likely impairs the significance of the regulations over time. Instead of a full twelve months of inspection data, the researchers were forced to halt all inspections in early March. Once the inspections resume following the COVID-19 pandemic, a similar analysis should be conducted for multiple, total years of inspections. An oversight program solely based on facility reporting and inspections has limitations by the willingness of the entity to report problems and the ability of regulatory inspections to uncover deficiencies in good laboratory practice during a point-in-time visit. Therefore, FSAP should focus its efforts on where the risk of exposures, safety, and security of BSAT is most significant.

Table 1: Parts of the SARs

Parts of the SARs (42 CFR 73, 9 CFR 121, 7 CFR 331)	
Section 3: HHS BSAT	Section 12: Biosafety
Section 4: Overlap BSAT	Section 13: Restricted Experiments
Section 5: Exemptions for BSAT	Section 14: Incident Response
Section 6: Exemptions for Overlap BSAT	Section 15: Training
Section 7: Registration and related security risk assessments	Section 16: Transfers
Section 8: Denial, revocation, or suspension of registration	Section 17: Records
Section 9: Responsible Official	Section 18: Inspections
Section 10: Restricting access to BSAT	Section 19: Notification of Theft, Loss, or Release
Section 11: Security	Section 20: Civil Money Penalties

Table 2: Number of Inspections by Entity Type, Year, and Inspection Warning

Entity Type	Inspection Year			Inspection Warning	
	2018	2019	2020	Announced	Unannounced
Academic (N = 138)	59 (42.75%)	64 (46.38%)	15 (10.87%)	74 (53.62%)	64 (46.38%)
Commercial / Private (N = 79)	29 (36.70%)	43 (54.43%)	7 (8.86%)	36 (45.56%)	43 (54.43%)
Federal Government (N = 66)	33 (50.00%)	28 (42.42%)	5 (7.58%)	42 (63.64%)	24 (36.36%)
State Government (N = 109)	52 (47.70%)	47 (43.12%)	10 (9.17%)	54 (49.54%)	55 (50.46%)
Total	173	182	37		

Table 3: Frequencies (percentages) of risk categories by entity type

Entity Type	Entity Risk Category		
	Low	Moderate	High
Academic (N = 138)	24 (17.39%)	87 (63.04%)	27 (19.57%)
Commercial / Private (N = 79)	23 (29.11%)	47 (59.49%)	9 (11.39%)
Federal Government (N = 66)	27 (40.90%)	16 (24.25%)	23 (34.85%)
State Government (N = 109)	78 (71.56%)	31 (28.44%)	0 (0.00)

Table 4: Frequencies and percentages of departures and sums and percentages of severity scores by entity type, inspection year, and inspection type and inspection warning level

	Number of Departures (N = 1921)	Severity Score Sum (N = 2410)
Entity Type		
Academic	653 (33.99%)	798 (33.11%)
Commercial / Private	412 (21.45%)	515 (21.37%)
Federal Government	408 (21.24%)	584 (24.23%)
State Government	448 (23.32%)	513 (21.29%)
Inspection Year		
2018	935 (48.67%)	1143 (47.43%)
2019	849 (44.20%)	1091 (45.27%)
2020	137 (7.13%)	176 (7.30%)
Inspection Type		
Renewal	1111 (57.83%)	1403 (58.21%)
Verification	810 (42.17%)	1007 (42.20%)
Inspection Warning		
Announced	1080 (56.22%)	1341 (55.64%)
Unannounced	841 (43.78%)	1069 (44.36%)

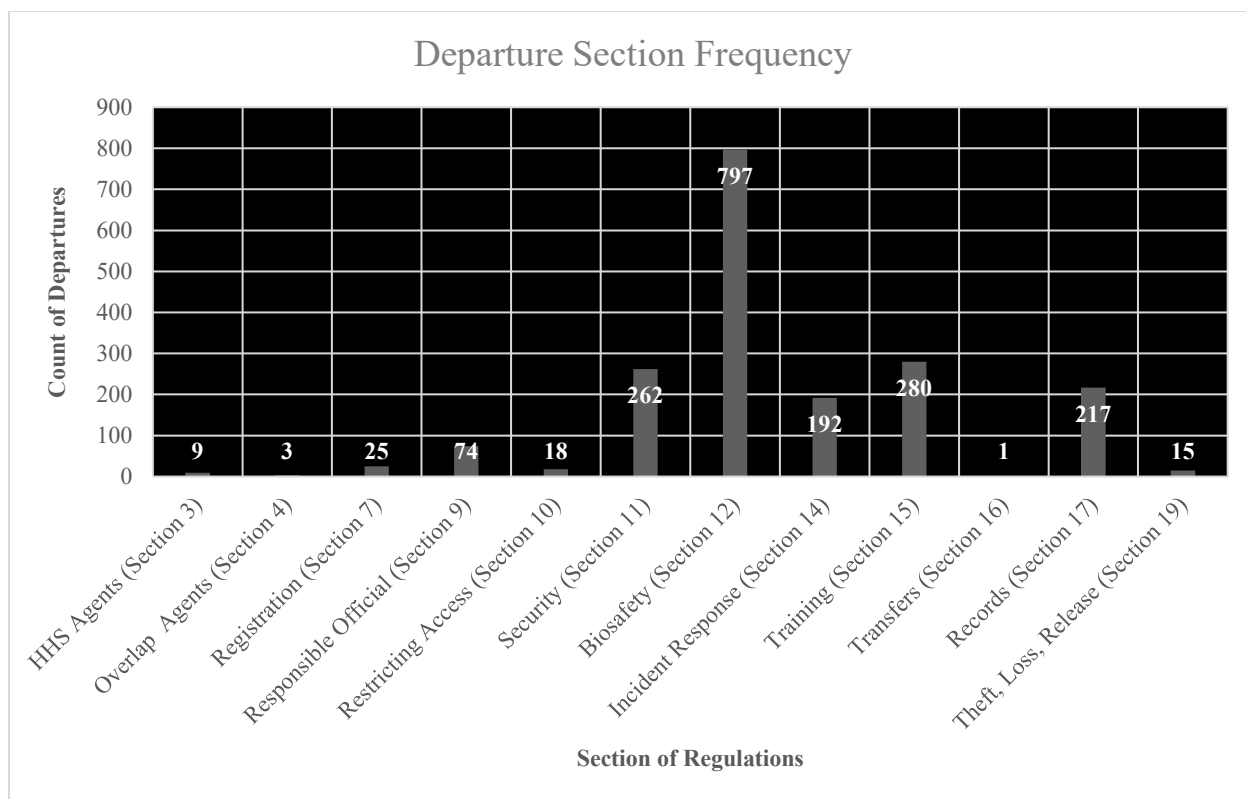


Figure 1: Frequency of departures identified in each section of the regulation

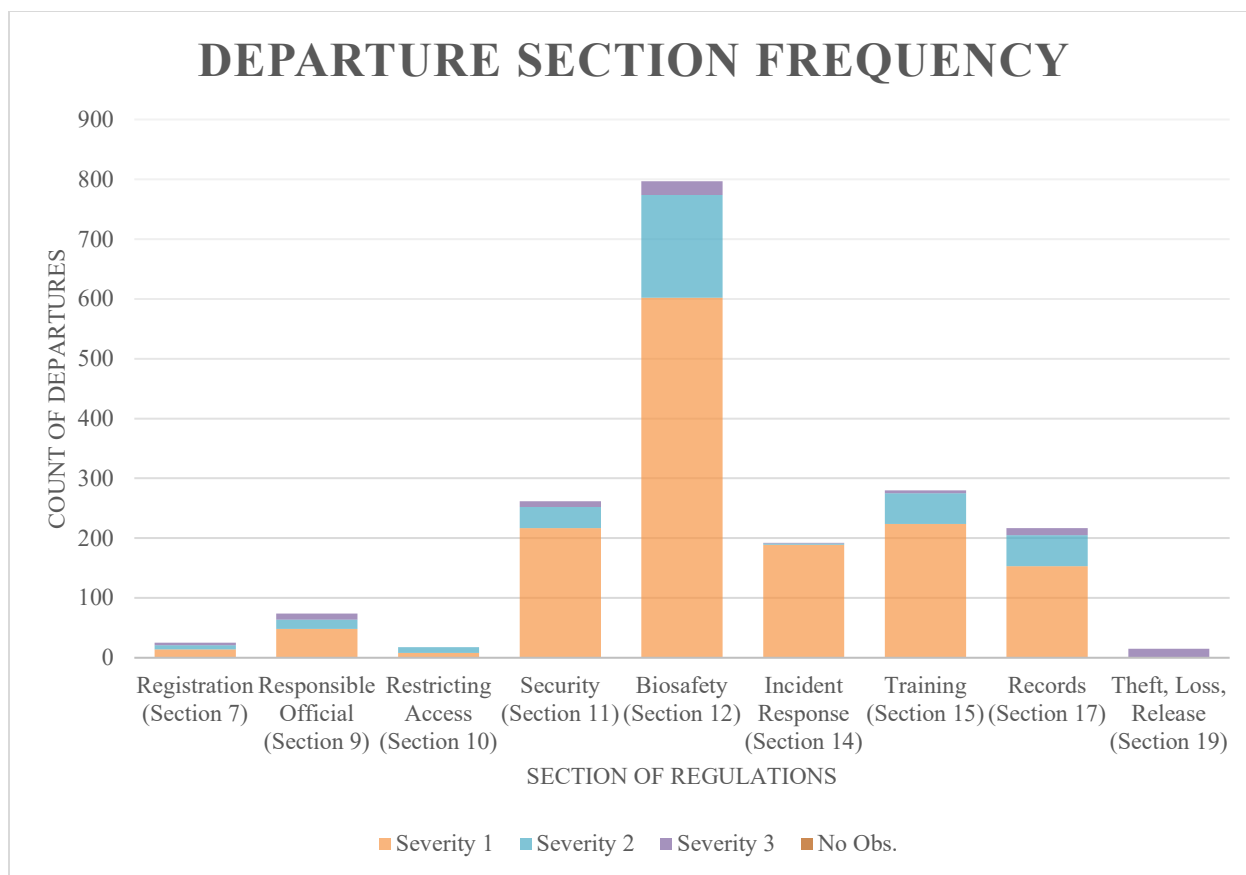


Figure 2(a): Frequency of departures identified in each section of the regulation, categorized by severity score of each departure 1=Low; 2=Moderate; 3=Severe

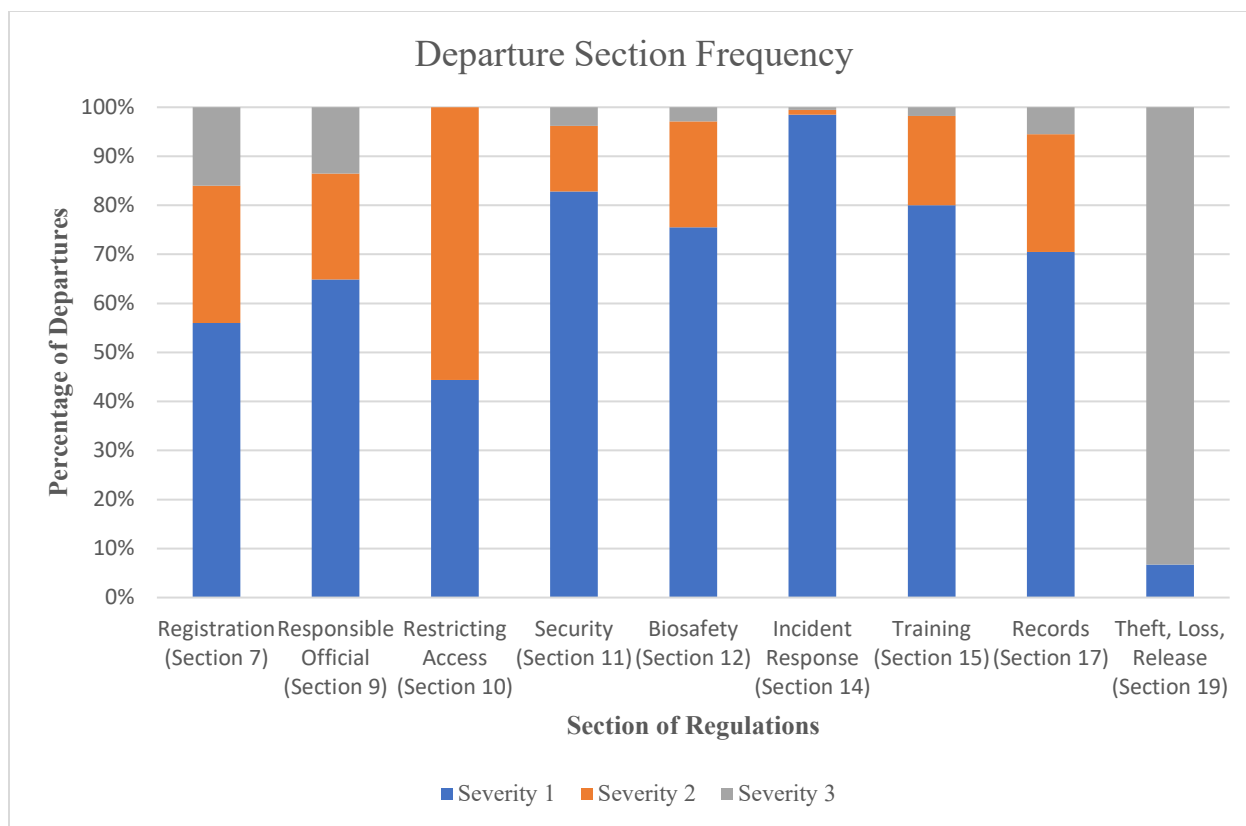


Figure 2(b): Percent departures identified in each section of the regulation, categorized by severity score of each departure

Table 5: Average number of Departures per year for Biosafety, Training, and Security

	Biosafety Average Average (total)	Training Average (total)	Security Average (total)
2018	2.17 (375)	0.94 (163)	0.70 (121)
2019	2.03 (369)	0.56 (102)	0.70 (127)
2020	1.43 (53)	0.41 (15)	0.41 (14)

2018=173 inspections; 2019=182 inspections; 2020=37 inspections

Table 6: Averages of departures and severity of departures by entity type and year

	Entity Type				
	Academic (N = 653)	Commercial / Private (N = 412)	State Government (N = 448)	Federal Government (N = 408)	Total (N = 1921)
Average Departures					
2018	5.2 (N=307)	5.4 (N=158)	5.1 (N=265)	6.2 (N=205)	5.4 (N=935)
2019	4.4 (N=280)	5.3 (N=226)	3.3 (N=157)	6.4 (N=186)	4.7 (N=849)
2020	4.4 (N=66)	4 (N=28)	2.6 (N=26)	3.4 (N=17)	3.7 (N=137)
Departure Severity Level					
Low	505 (77.34%)	318 (77.18%)	369 (82.37%)	264 (64.71%)	1456 (75.79%)
Moderate	115 (17.61%)	73 (17.72%)	63 (14.06%)	95 (23.28%)	346 (18.01%)
Severe	21 (3.21%)	19 (4.61%)	6 (1.34%)	45 (11.03%)	91 (4.74%)
None Observed	12 (1.84%)	2 (0.49%)	10 (2.23%)	4 (0.98%)	28 (1.46%)

Table 7: Frequencies of departures cross-tabulated by severity level and entity type, and cross-tabulated by severity level and inspection year

	Severity Level				
	Low (N = 1456)	Moderate (N = 346)	Severe (N = 91)	None Observed (N = 28)	Total (N = 1921)
Entity Type					
Academic	505 (34.68%)	115 (33.24%)	21 (23.08%)	12 (42.86%)	653 (33.99%)
Commercial / Private	318 (21.84%)	73 (21.10%)	19 (20.88%)	2 (7.14%)	412 (21.45%)
Federal Government	264 (18.13%)	95 (27.46%)	45 (49.45%)	4 (14.29%)	408 (21.24%)
State Government	369 (25.34%)	63 (18.21%)	6 (6.59%)	10 (35.71%)	448 (23.32%)
Year					
2018	742 (50.96%)	145 (41.91%)	37 (40.66%)	11 (39.29%)	935 (48.67%)
2019	618 (42.45%)	170 (49.13%)	48 (52.75%)	13 (46.43%)	849 (44.20%)
2020	96 (6.59%)	31 (8.96%)	6 (6.59%)	4 (14.29%)	137 (7.13%)

Table 8: Significance of all independent variables as predictors of number of departures per inspection

Variable	DF	Chi – Square	P-value
Entity Type	3	1.40	0.7065
Entity Risk Score	1	7.16	0.0075
Inspection Category	3	2.07	0.5575
Inspection Warning	1	1.79	0.1809
Year	2	4.68	0.0965

****DF=degrees of freedom**

Table 9: Risk ratios and 95% confidence intervals for number of departures per inspection

	Relative Risk	95% Confidence Interval	P-value
Entity Type			
Academic	ref	Ref	Ref
Commercial / Private	0.9018	0.7088 – 1.1473	0.4001
State Government	0.9622	0.7862 – 1.1777	0.7090
Federal Government	1.0662	0.8600 – 1.0048	0.5589
Entity Risk Score	1.0029	1.0009 – 1.0048	0.0037
Inspection Category			
Renewal	ref	Ref	Ref
Verification	0.9735	0.8253 – 1.1482	0.7495
Inspection Warning			
Announced	ref	Ref	Ref
Unannounced	0.8954	0.7644 – 1.0489	0.1711
Inspection Year			
2018	ref	Ref	ref
2019	0.8799	0.7233 - 1.0706	0.2011
2020	0.7148	0.5257 - 0.9720	0.0322

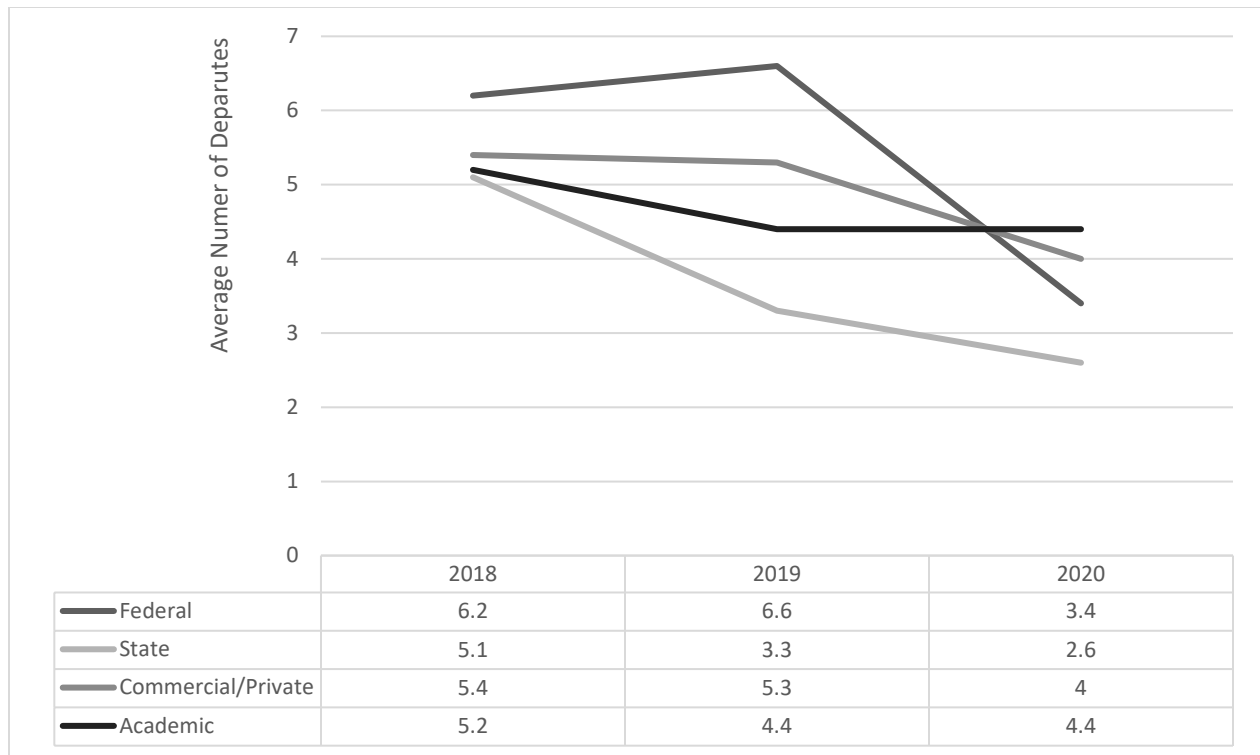


Figure 3: Average Number of Departures by Entity Type and Year

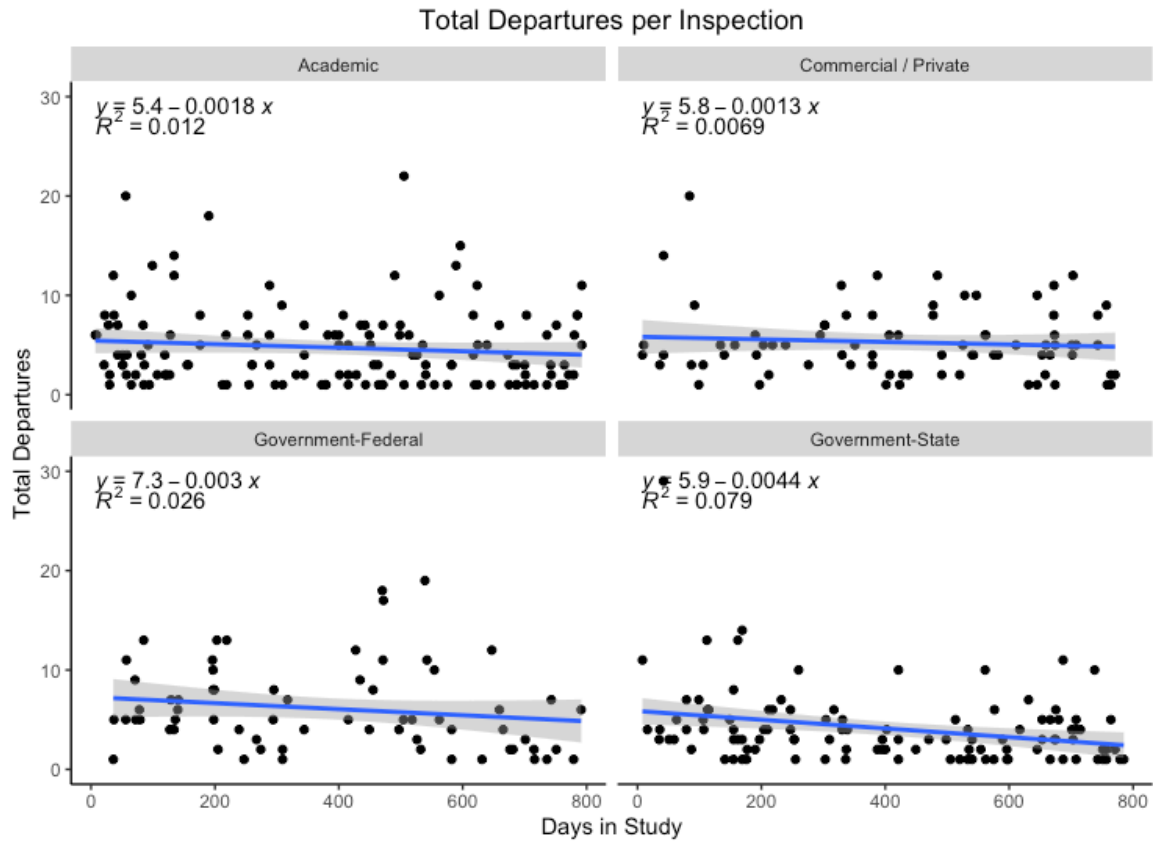


Figure 4: Total number of departures per inspection over time, divided by facility types

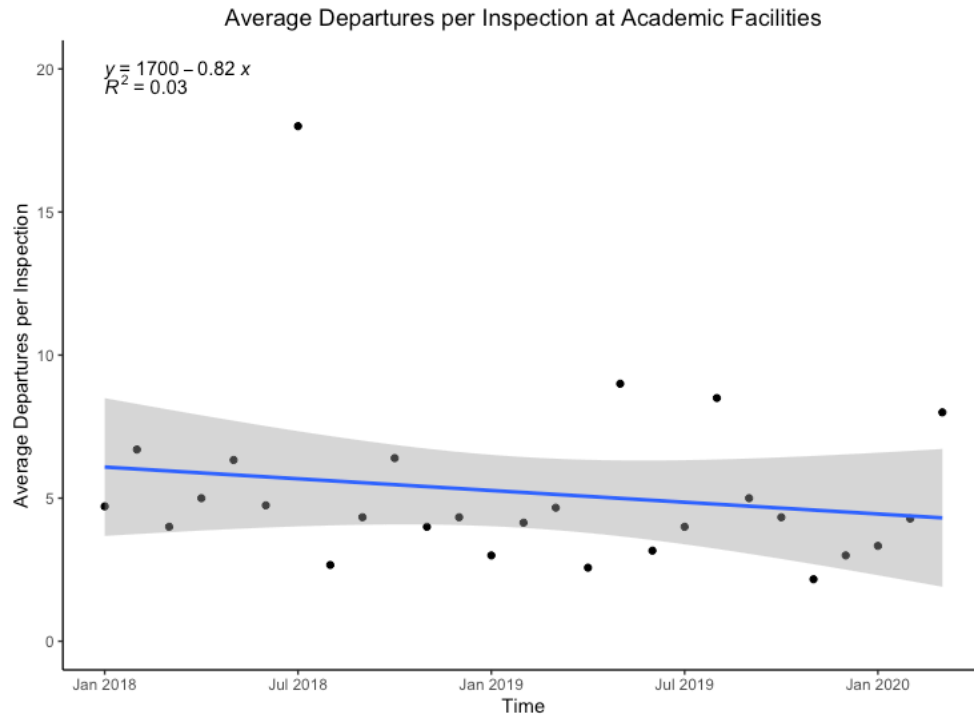


Figure 5: Average number of departures per inspection at academic entities over time

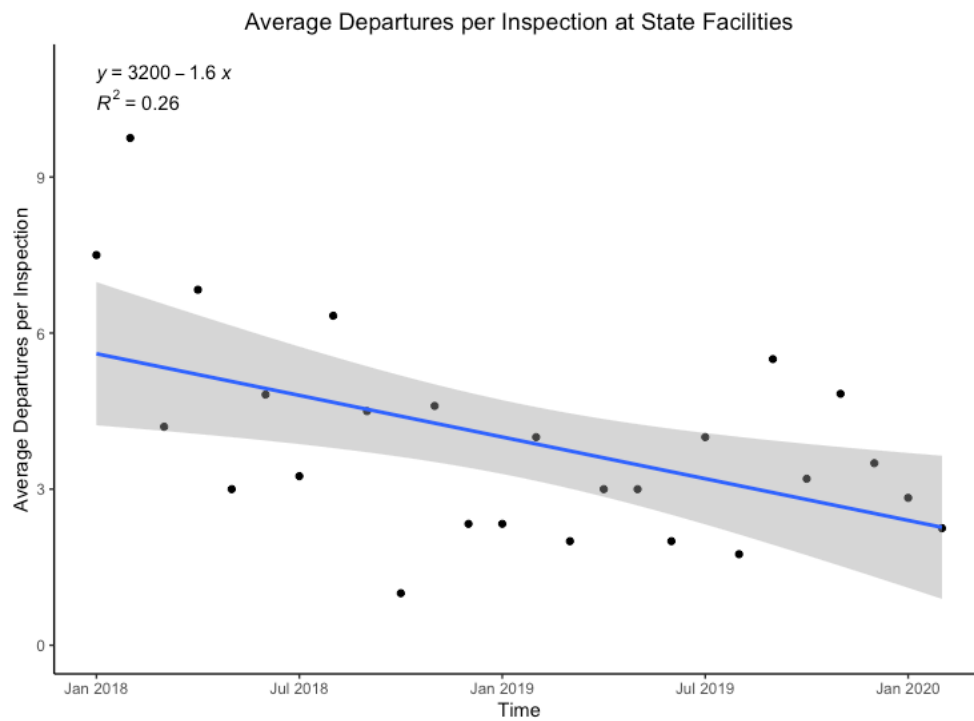


Figure 6: Average number of departures per inspection at state entities over time

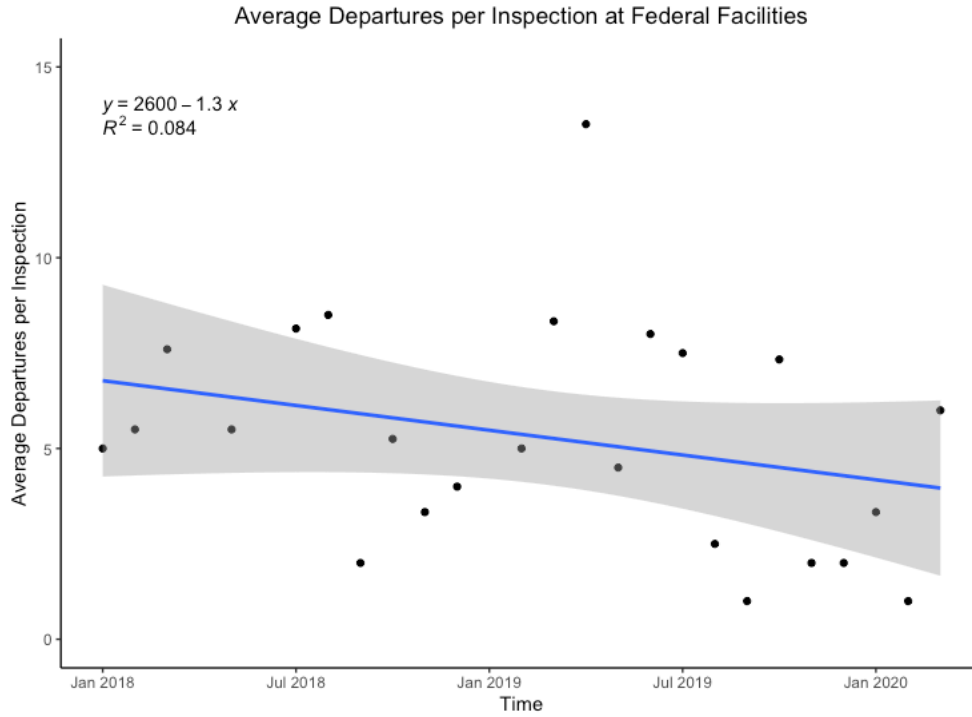


Figure 7: Average number of departures per inspection at federal entities over time

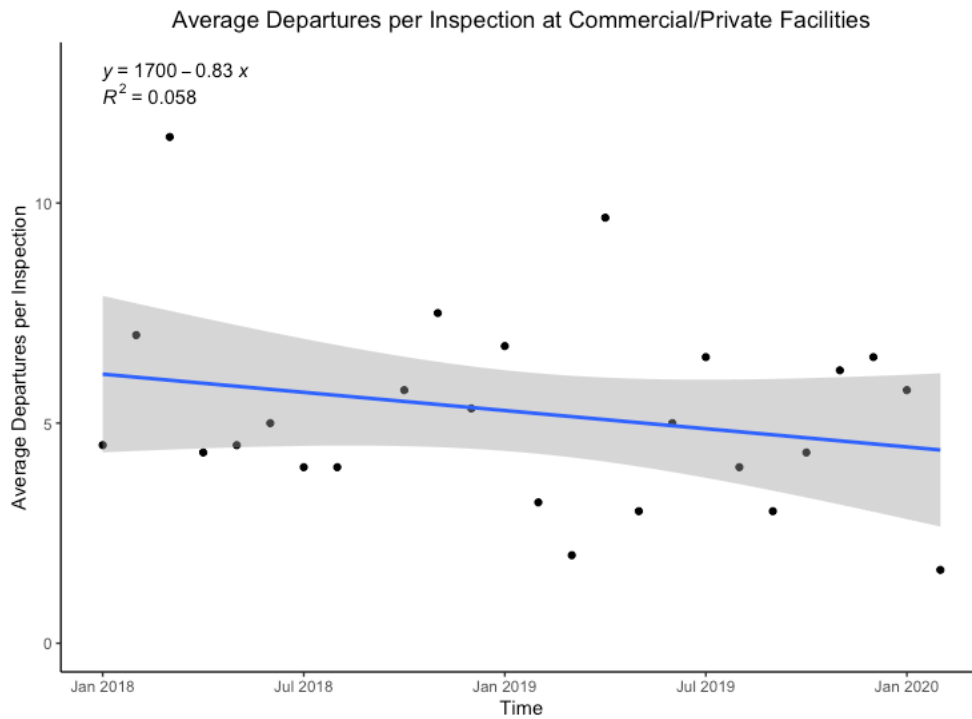


Figure 8: Average number of departures per inspection at commercial/private entities over time

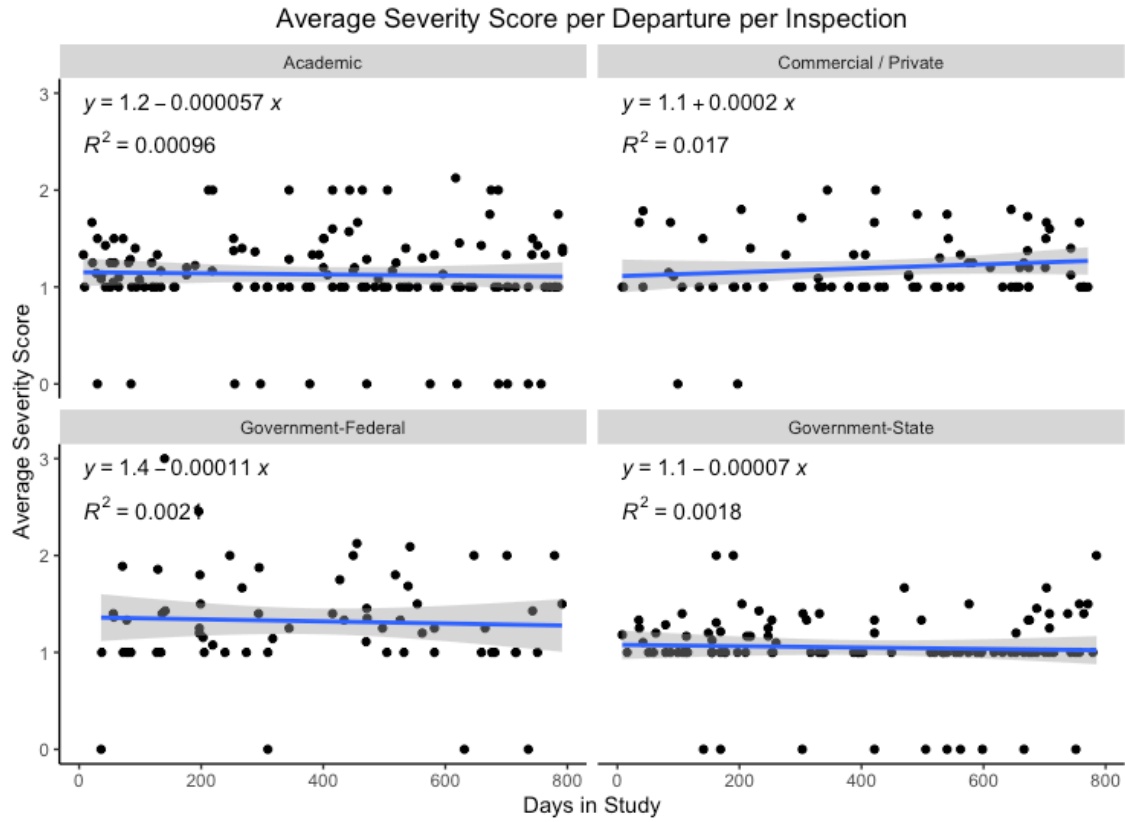


Figure 9: Average severity of departures identified per inspection over time, by facility type

CHAPTER 4

METHODOLOGY (FSAP SURVEY)

The FSAP survey consisted of quantitative and qualitative analysis for this part of the research study. This was made possible by using a combination of closed-end question (e.g., yes or no) and open-ended questions. Creswell (2017) defined qualitative research as an “approach for exploring and understanding the meaning individuals or groups attribute to a social or human problem.” An important aspect of qualitative studies is that it shapes policymakers’ opinions whose actions affect people’s health and well-being (Polit and Beck, 2010). Through an analysis of survey results, this part of the study seeks to determine if the SARs have improved the safety and security of laboratories that work with BSAT (2018-2020) from the registered entities' perspective.

The survey was sent to the Responsible Officials for each registered entity. The study utilized questions adapted by the Federal Select Agent Program to be administered to over 200 entities registered with the program. The survey consisted of multiple-choice and open-ended questions that were administered online via a Qualtrics system. Institutional Review Board (IRB) approval (IRB ID: PROJECT00002688) was obtained from the University of Georgia on October 16, 2020 before starting the study. The research question being studied is: Through an analysis of survey results, how have the SARs improved the safety and security of laboratories that work with BSAT (2018-2020)?

Registered entities that received an inspection from 2018-2020 were invited to participate in the survey. Participation in the survey was voluntary. An entity could refuse to take part or

stop at any time without penalty. A decision to refuse or withdraw did not affect their work or registration with the FSAP. Additionally, a decision to participate did not impact an entity's registration with the FSAP. All entities received the same questions while utilizing the same process without influence from the FSAP.

The survey consisted of 10-12 questions that took approximately 10-15 minutes to complete. Individuals who consented to participate in the study were given a link to the survey via email. The information collected remains confidential, and all submissions were received through the electronic system. There were no codes or personal identifiers linked to survey responses. The survey was accessible for two weeks with built-in reminders to the participants and all responses were anonymous. It is noted that this research involves the transmission of data over the Internet. Therefore, every reasonable effort was taken to ensure the effective use of available technology; however, confidentiality during online communication cannot be guaranteed. It is hypothesized that the data will show that the SARs improved the safety of workers, the public, and the security of BSAT, through increased training, BSAT accountability, and enhanced biosafety and security practices.

Study Criteria

To be participants in the survey analysis, entities must: 1) be registered with the FSAP; 2) have been inspected January 1, 2018-March 31, 2020; 3) have experienced an announced or unannounced inspection within the study timeframe; 4) be defined as federal, state, commercial, private, or academic facility; and 5) have received a verification or renewal inspection.

Data Collection & Analysis

Data Collection

The collected survey data were descriptively analyzed, and results were depicted in frequency distribution tables and figures. The Qualtrics system was used to administer the survey, collect the responses, and analyze the results. The study analyzed data collected from the survey (questionnaire) and FSAP inspections conducted from January 2018 through March 2020 to determine the impact of the SARs on registered entities.

Data Analysis

A bivariate statistical analysis will be conducted to identify any significant correlations between the survey results' independent and dependent variables. The data will be analyzed to identify a trend analysis by entity type and a causation/correlation between the independent and dependent variables established in the survey questions.

The analysis will determine if the implementation of the SARs by registered entities (independent variable) results in:

- enhanced biosafety and security practices,
- trained staff,
- less laboratory incidents,
- improved record-keeping

Results

To better understand the impact and compliance with the SARs, a survey was distributed to all entities registered in the program as of March 2021. The survey received 136 responses, 85 (62.5%) of which were fully completed, with all questions answered. At the time of the survey, there were 242 entities registered with the program, which suggests an overall response rate of

56.2% and a complete response rate of 35.1%. Table 12 lists the number and proportion of entity types that responded to the survey. State government and academic facilities represented the highest number of respondents that completed the survey at 40.2% and 39.1%, respectively. Federal and commercial/private entities each responded at 12.4%. It should be noted that only 97 of 136 answered this question regarding the entity type.

When asked what improvements have been seen since the implementation of the regulations, 80.8% of respondents (N=78) indicated biosafety and security (Table 13). Other improvements indicated by respondents include record keeping/documentation, oversight, training, and inventory control (Table 13). If improvements were seen at institutions, a total of 61 of 85 respondents (71.8%) stated they implemented similar improvements for non-BSAT/BSAT used at their facility (Figure 10). When asked if incidents involving BSAT or non-BSAT had changed since the implementation of the regulations, 23.7% of respondents indicated incidents decreased (Figure 11). Nearly half of the 136 respondents did not answer the question, but of those that answered, 67.1% indicated the frequency of incidents has approximately remained the same following the implementation of SARs.

To address the cost of compliance with the regulations, respondents were asked if their entity had the infrastructure to support compliance with the regulations (Figure 12). Of those who answered the question (N=83), 74.70% indicated they did have the infrastructure required to ensure compliance with the regulations. However, 19.3% indicated that their entity did not have the infrastructure due to lack of financial support, support from management, and too much responsibility placed upon one individual. Additionally, 85.4% (N=82) of the respondents indicated that they experienced additional burden and time to ensure compliance with the

regulations (Figure 13). Types of additional burden included: cost, time-consuming, increased documentation, lack of resources, and too many regulations.

When asked if they believe the benefits of strengthened safeguards against the unintentional or deliberate release of a select agent or toxin significantly exceed the regulations' compliance costs, of those who answered the questions (N =73), 50.7% affirmed this belief, while 49.3% indicated the cost of compliance exceeded the benefit of strengthened safeguards (Figure 14). When asked how the regulations have impacted their organization, 50% of the respondents (N=64) provided a positive response, while 34% provided a negative response (Table 14(a)). Positive themes included: improved biosafety and security, inventory control, improved awareness/compliance, oversight, and training. Negative themes by the respondents included: cost, time-consuming, negative impact on research, documentation, and too much burden (Table 14(b)).

Conclusion

Several common themes were identified from the entity responses, highlighting the impact of the regulations: improved biosafety, security, training, and inventory control. When asked what improvements have been seen since implementing the regulations, 80.8% of respondents indicated biosafety and security. Additionally, out of those that experienced improvements, 72% of entities that responded implemented the same provisions for work with non-BSAT. This suggests that not only has the SARs improved the safety and security of BSAT, but it has also positively impacted work with non-BSAT.

Nearly three-quarters of respondents indicated they had the infrastructure required to support compliance; however, 85.4% indicated their entity experienced additional burdens beyond financial support, support from management, or too much responsibility placed upon one

individual. Additional types of burden included the cost associated with adhering to the regulations, time commitment, and documentation/record keeping requirements.

When publishing the Final Rule for the SARs, the federal government is required to conduct a regulatory impact analysis. In the analysis conducted in 2005, the FSAP agreed that the required documentation of mitigation measures such as biosafety, security, incident response, and information security, may require additional time of personnel (Federal Register, 2005). One additional cost is related to information security which is required by the SARs. It is estimated that costs related to information security, such as software updates, could total approximately \$2 million per year for all registered entities, or about \$5,500 per entity (Federal Register, 2005). However, most entities already use equivalent information security for their systems. Therefore, it should be noted that many of these costs are already currently created by entities in their normal job responsibilities or practices.

Although most entities agree that the regulations have improved the safety and security of BSAT, the additional burden that comes with it should not be overlooked, which is the purpose of the regulatory impact analysis. The benefits of strengthened safeguards against the deliberate or unintentional release of BSAT greatly exceed the compliance costs of the regulations. For example, the October 2001 anthrax attacks caused five fatalities and 17 illnesses (Federal Register, 2017). Additionally, this event resulted in two billion dollars in lost revenue for the Postal Service (Federal Register, 2017). It cost \$23 million to decontaminate one Senate office building and \$3 billion to decontaminate postal facilities and purchase decontamination equipment (Federal Register, 2017). Deliberate introduction greatly increases the probability of a select agent causing devastating impacts to the economy, disruptions to society, and diminished trust in research institutions.

When asked if they believe the benefits of strengthened safeguards against the unintentional or deliberate release of BSAT significantly exceeded the regulations' compliance cost, only 51% of the respondents answered yes to this question. Considering the number of deaths and costs associated with the Anthrax Attacks of 2001, one would expect the affirmative response to this question would be higher. The SARs were created to safeguard Americans from exposure and death from dangerous pathogens, such as BSAT. Although laboratory incidents regarding BSAT remained the same, there have been no reports of theft, illness, or death related to BSAT.

Based on the entity's responses, the SARs have been shown to improve the safety and security of BSAT, training, and other areas to protect the public. Plus, when asked how the regulations impacted their organization, over 65% of the respondents provided a positive or neutral response. However, future entity surveys may be necessary to determine the true efficacy of the regulations. Future studies should encompass the entire relevant study period, including periods before and after implementing the SARs. Each survey question resulted in many responses, with several entities deciding not to answer specific questions. This inconsistency in the number of entity responses prevents the study from making any generalized statements based on entity types.

Additionally, over 75% of the responses came from academic and state entities. This percentage is higher than the number of entities registered with FSAP, with academic and state facilities accounting for over 60% of the entities registered with the program (CDC, 2021). Although these two entity types represent most FSAP registered entities, additional responses from federal and commercial/private entities are needed to conduct a true assessment.

In addition, a more in-depth qualitative research study could determine a true cost/benefit analysis for each entity complying with these regulations. Lastly, a third party should administer any future surveys to mitigate entity concerns of potential repercussions and increase the response rate.

Table 10: FSAP survey questions

FSAP Survey	
Question	Response
What type of organization is your laboratory?	a. Federal b. State c. Private/Commercial d. Academic
Since the implementation of the SARs, what improvements have you seen at your entity?	Open-ended question
If improvements were observed, did your entity implement similar provisions for work with non-BSAT?	a. Yes b. No c. N/A; Only work with BSAT d. If so, what provisions were implemented?
If your entity implemented similar provisions for non-BSAT, what improvements have you seen at your entity?	Open-ended question
Since the inception of the SARs, incidents involving BSAT have	a. Increased b. Decreased c. Remained the same
Since the inception of the SARs, incidents involving non-BSAT have	a. Increased b. Decreased c. Remained the same
Does your entity have the appropriate infrastructure to support compliance with the SARs?	a. Yes b. No, not enough financial support c. No, not enough support from management d. No, too much responsibility for one person e. other
Did your entity experience any additional burden and time to become compliant with the SARs?	a. Yes b. No c. If yes, please state how
Do you believe the benefits of strengthened safeguards against the unintentional or deliberate release of a select agent or toxin significantly exceed the regulations' compliance costs?	a. Yes b. No
In your opinion, how have the SARs impacted your organization?	Open-ended question

Table 11: Independent and dependent variables

Independent Variable	Dependent Variables
Implementation of SARs	Enhanced biosafety practices
	Enhanced security practices
	Enhanced training
	Reduced laboratory incidents
	Enhanced record-keeping

Table 12: Frequencies and percentages of survey respondents by entity type

N=97	Academic	Commercial / Private	Federal Government	State Government
Count	34	12	12	39
Proportion	35.1%	12.4%	12.4%	40.2%

Table 13: Top Responses for improvements seen at entities since implementation of the regulations (Question 2)

	Security	Biosafety	Record Keeping	Training	Oversight	Inventory Control
Count	36	27	10	8	8	5
Proportion of entities	46.2%	34.6%	12.8%	10.3%	10.3%	6.4%

*Some entities provided more than one response

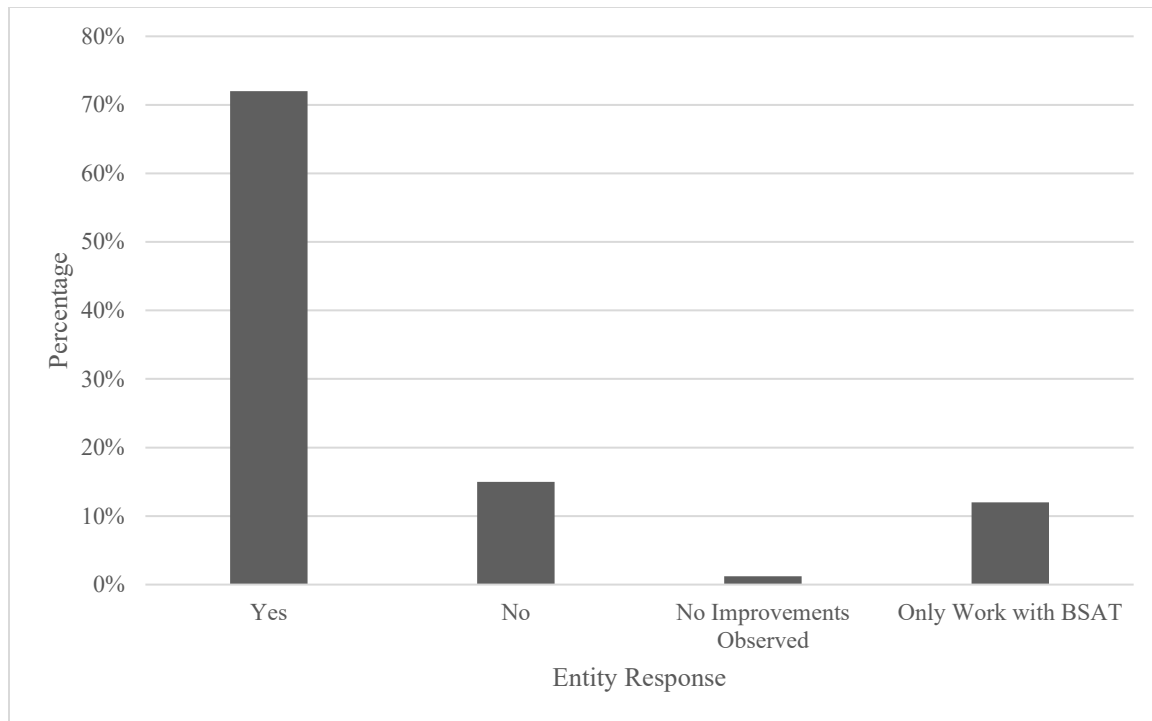


Figure 10: If improvements were observed, did your entity implement similar provisions for work with non-BSAT (Question 3)

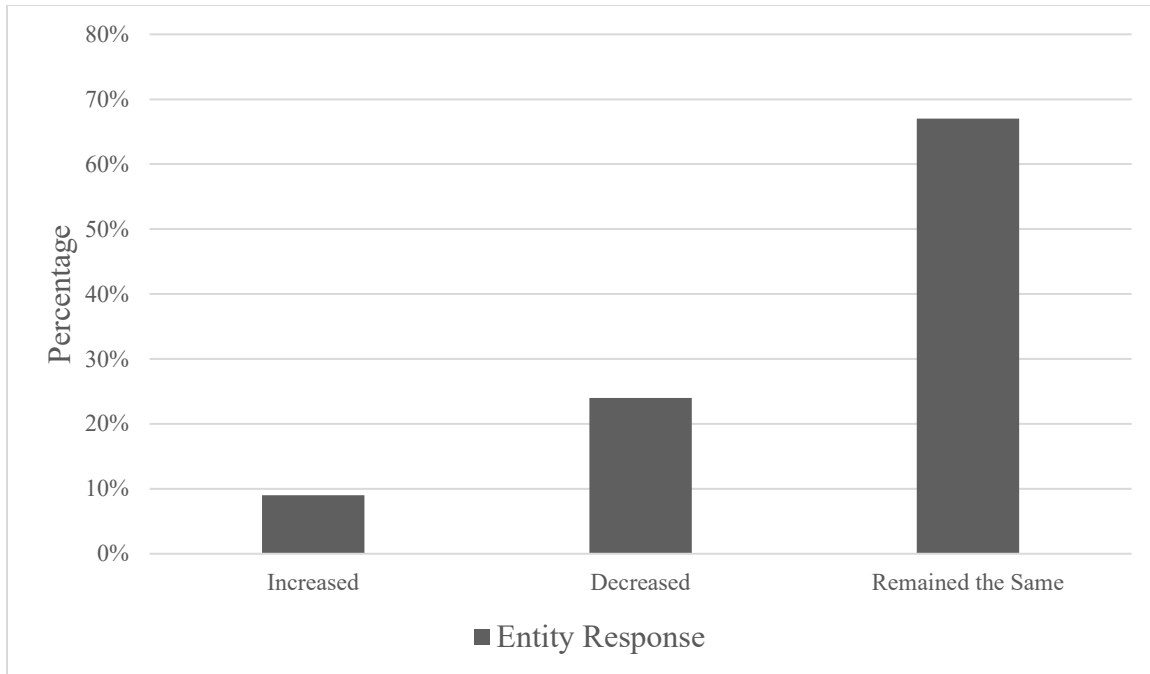


Figure 11: Since the inception of the regulations, incidents involving BSAT have (Question 5)

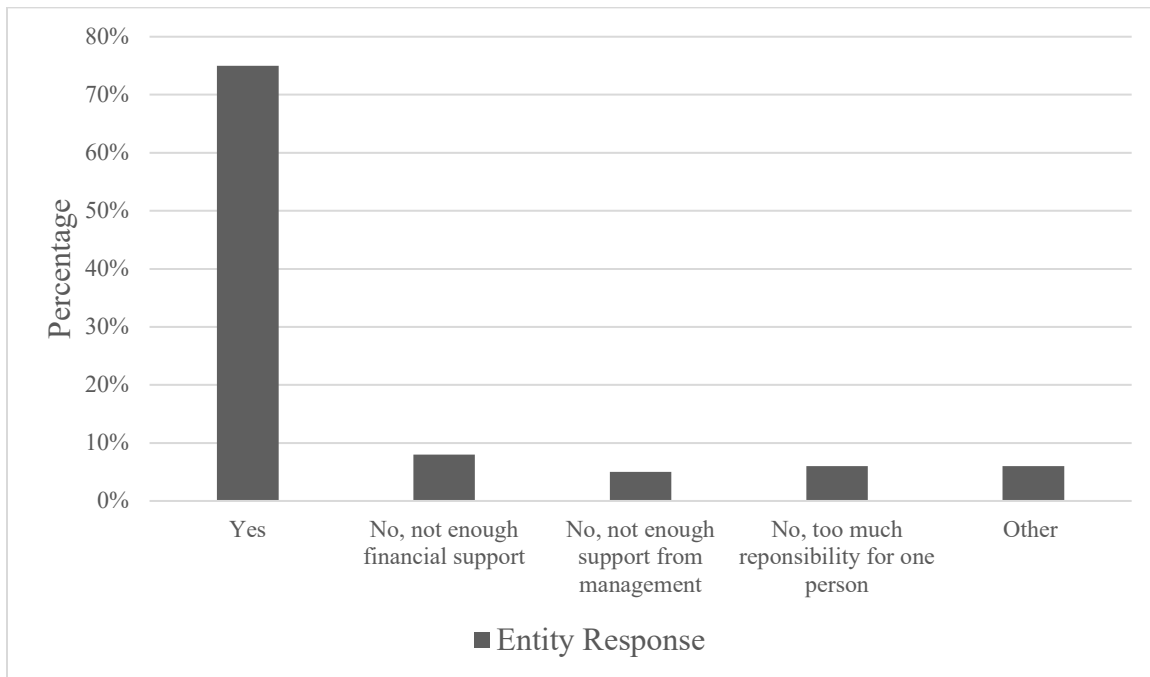


Figure 12: Does your entity have the infrastructure to support compliance with the SARs (Question 6)

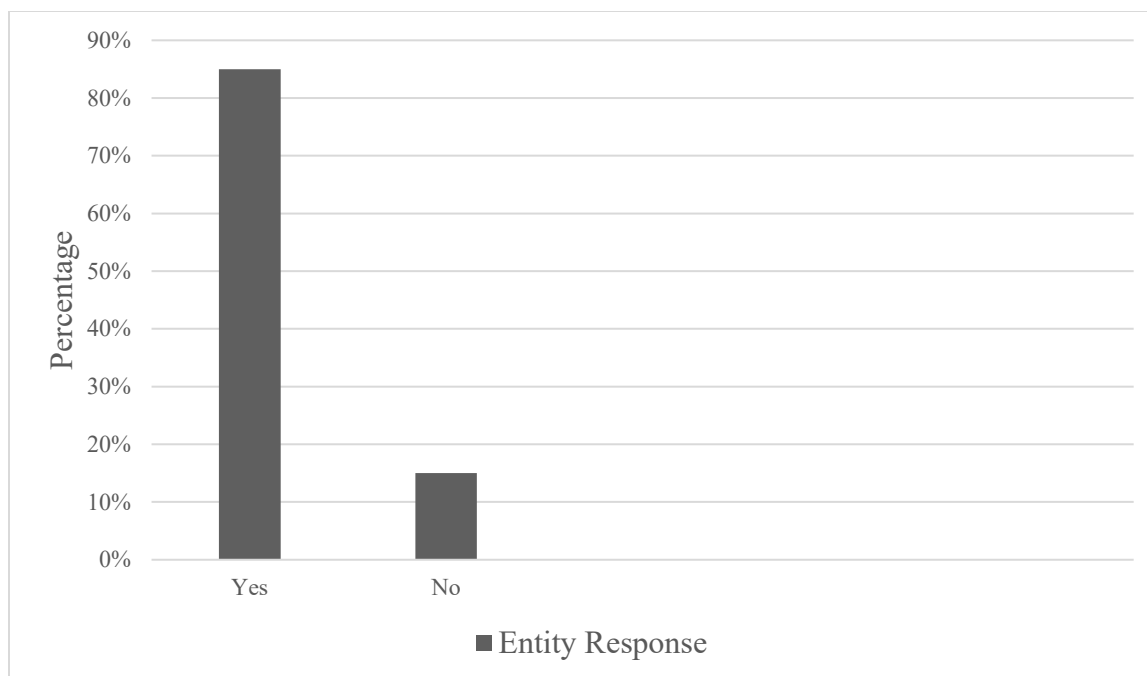


Figure 13: Did your entity experience any additional burden and time to become compliant with the SARs (Question 7)

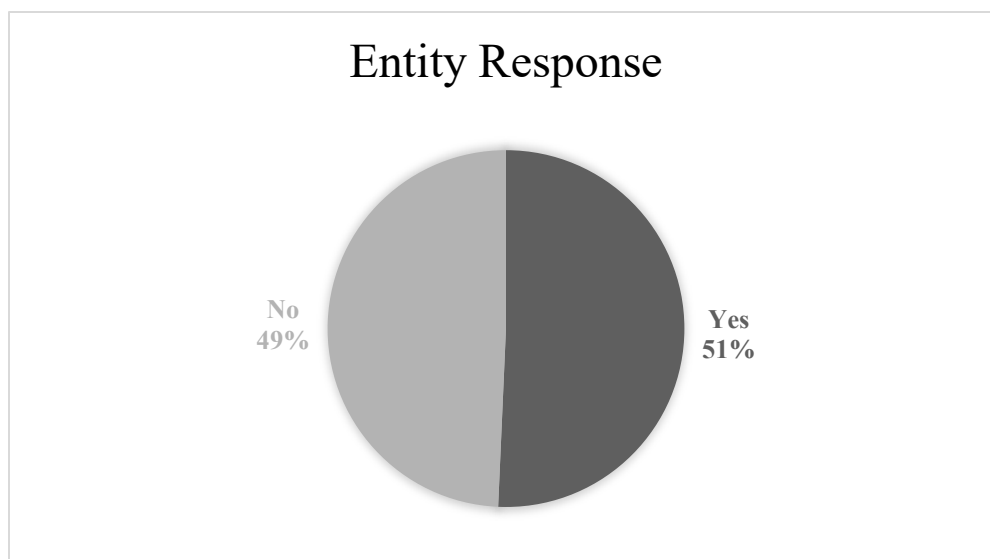


Figure 14: Do you believe the benefits of strengthened safeguards against the unintentional or deliberate release of a select agent or toxin significantly exceed the regulations' compliance cost (Question 10)

Table 14(a): In your opinion, how have the SARs impacted your organization (Question 11)

	Positive Response	Negative Response	Neutral Response	Total Responses
Count	32	22	10	64
Proportion	50.0%	34.4%	15.6%	100%

Table 14(b): In your opinion, how have the SARs impacted your organization (Question 11)

Common Types of Positive Impact	Common Types of Negative Impact
Improved Biosafety	Increased Cost
Improved Security	Increased Burden
Better Oversight/Management	Increased Paperwork/Record keeping
Inventory Control	Impact on Research
Training	Time-consuming
Increased Awareness/compliance	

CHAPTER 5

DISCUSSION AND RECOMMENDATIONS

Inspection Departures

The primary purpose of this study was to show how the SARs continue to improve public safety and security of BSAT by reviewing inspection departures and survey results from registered entities. The inspection departure results provide an understanding of the compliance to SARs by the registered entities and the risk associated with this work and considerations to improve the safety and security of BSAT by entity type and risk score. The inspection departure results showed a steady decrease in the average inspection departures for the study period across all entity types and sections of the regulations. The decrease in departures included the four major sections that resulted in the most departures during the study period: biosafety, security, training, and records. It should be noted that biosafety and security are two critical core components of the SARs in ensuring the safe and secure possession and use of BSAT. Additionally, there were no reports of theft, illness, or death resulting from exposure to BSAT during the study period. Although not statistically significant, this suggests that the regulations continue to improve public safety and security of BSAT based on the inspection departures for the study period.

In the last few years, the FSAP has transitioned from a heavily paper based regulatory program to electronic paper-less regulatory program with significant increase in program effectiveness and efficiency. This is a web portal based, high secure, 24/7, 2-way communication system with real-time program data and capable of all programmatic transactions

from entity registration, amendment processing, ability to receive reports of theft, loss or release of BSAT, transfer approvals, and reports of identification of BSAT. Going forward, the FSAP can mine data from the inspection module of the eFSAP information system to better analyze the effectiveness of the FSAP.

The FSAP had to cease routine in-person onsite inspections on March 31, 2020, due to high community spread of SARS-CoV-2 infections and the COVID-19 pandemic, hence the study end date. The FSAP's role in ensuring public health and safety from pathogens that pose a severe threat to public health and safety is a critical part of the mission. A vital part of performing this critical function is the onsite inspections conducted at public health laboratories and research institutes across the country. In the face of agency-wide travel restrictions and COVID-19 pandemic-related safety concerns, the FSAP developed and implemented innovative processes to conduct oversight by remote and hybrid inspections of select agent registered entities for the remainder of the 2020 calendar year.

Briefly, remote inspections were developed and implemented beginning April 2020 to ensure continuity of operations. The FSAP considerations during the COVID-19 pandemic included: a) safety of registered entity staff and the FSAP inspection staff; b) widespread travel restrictions nation-wide; c) increased demand for work involving SARS-CoV-2 (non-select agent); and d) registered entity and the FSAP staff availability while in remote work status. Remote inspections allowed the registered entity staff to provide inspection documents/records for review and assessment to the FSAP inspectors via the electronic Federal Select Agent Program (eFSAP) information system.

The hybrid inspections are defined as any combination of remote and on-site program review. These inspections are used by the FSAP to maximize resources and limit size of

inspection teams and on-site presence. The hybrid inspections are geared toward allowing comprehensive review of inspection records in-house and more focused inspection of on-site operations. During traditional inspections, a significant portion of inspector time was dedicated to conducting record reviews at the entity. Incorporation of remote reviews of the inspection documents significantly reduces burden on the entities, allows inspectors to fully review all documents in-house and better prepare for the on-site inspections.

The remote and hybrid inspections have allowed FSAP to continue to implement highly effective oversight mechanisms and assure the health and safety of the public even during the COVID-19 pandemic. Implementation of this new process allowed for greater conservation of government resources over that of a traditional inspection model by deploying a smaller number of inspectors to oversee laboratory operations without the time-consuming burden of document review at the regulated entity. The efforts of the FSAP have demonstrated the long-term viability of the remote and hybrid inspection processes for select agent laboratory oversight nationwide, with expectations that the majority of select agent inspections will be handled through the remote and hybrid inspections in 2021 and beyond. We will continue to monitor the inspection departure numbers and perform additional analysis to support FSAP's efforts in improving the safety and security of BSAT while reducing entity burden with this new innovative approach.

Entity Risk Score

The study described the entity risk score, its relation to increased inspection departures and the relative risk of regulatory departures identified during 2018-2020. There are several areas of variation that warrants further study and programmatic attention. This initial analysis has identified factors that differentiate risk associated with inspection findings and allows

consideration to apply inspection resources differently by entity type and entity risk score. The increased number of inspection departures for moderate and high-risk entities, such as academic and federal entities, appears different from low-risk entities and may warrant changes to the oversight process. Further consideration is warranted to increasing the frequency of inspections for moderate and high complex entities due to their risk and ensure a continuous decrease in inspection departures. With focused onsite inspection, inspectors are more likely to observe routine day-to-day operations that pose biosafety or security risk. This could improve security and biosafety by increasing the specificity and impact of post-inspection remediation efforts recommended by inspectors to improve the entity's program. Additionally, it could help the FSAP to prioritize and customize its guidance, training, and outreach efforts to support entity compliance. Assessing factors associated with biosafety and security risk in greater detail may allow for more efficient use of program resources to identify and mitigate biosafety and security risks.

Entity Survey

The primary purpose of administering the survey to registered entities was to identify how the SARs have improved the public's safety and security of BSAT from the entity's perspective. Based on the entity's input and survey results, the SARs have improved the safety, security, training, and oversight of registered entities. Additionally, entities believe that oversight and management have improved the safety and security of BSAT. Although most respondents provided positive responses, there were negative responses from the entities that warrant further review and analysis. In many instances, increased burden (e.g., reporting requirements, time commitment, and background checks), and recordkeeping was mentioned by the entities. This suggests that although the SARs have improved the safety and security of BSAT, there is an

additional administrative burden that comes along with complying with the regulations that should not be overlooked. For those reasons, entities may decide not to conduct work with BSAT due to the burden associated with the regulations. Although there is an additional administrative burden, some foreign governments have been successful in reducing the burden by working collaboratively with the public to come up with successful solutions for everyone (Effers et al., 2007; Hampton, 2015). The United States government should consider the same practices when assessing and reducing entity burden.

During the study period, there were no reports of theft, illness, or death associated with BSAT. However, as identified in the survey results, 49% of the respondents do not believe that the benefits of strengthened safeguards against the unintentional or deliberate release of a select agent or toxin significantly exceed the regulations' compliance cost. One of the objectives of the SARs are to create a means of ensuring enhanced oversight in the transfer, storage, and use of BSAT, including requiring entities to develop and implement effective means of biosafety, information security, and physical security. The overall benefits are reduced likelihood of the accidental or intentional release of a select agent or toxin and the avoidance of costs associated with such a release to the public health and the environment. Further considerations are needed to explore how to reduce entity cost through a cost-benefit analysis while ensuring the safety and security of America's citizens and the environment. The FSAP may consider reviewing the existing regulations to focus primarily on work practices that could result in a significant threat to public health (moderate to severe departures) rather than paperwork and plan statements (low departures).

The survey resulted in mixed findings for each question, which may have negatively impacted the survey results. There were 136 responses received from the survey, but there were

instances where nearly 50% of the participants decided not to answer all the questions. Additionally, most respondents were from academic and state facilities, preventing any generalized statements of the conclusion. Although academic and state laboratories make up majority of the entities registered with FSAP, federal and commercial/private entities accounted for only 12% of the responses to the survey, respectively. According to the FSAP, federal and commercial/private laboratories account for 16% and 23% of the registered laboratories, respectively (CDC, 2019). The lack of entity responses to some questions suggests the entities may not feel comfortable providing information about their organization, considering that government regulators administered the survey even though the survey was completely anonymous without entity identifiers. Further considerations should be given to conducting a survey or focus group discussions led by a third party to provide more specificity and equity across all types of entities registered with the FSAP.

The most significant danger to public health, safety, and security is the threat posed by the accidental release of BSAT and misuse of BSAT as weapons of mass destruction, including the impact on the economy in response to a bioterrorism event. Although the regulations were developed to solve problems and address public health issues, they can present unique challenges for entities working with BSAT. While the goals of most regulatory programs have public support, regulations usually come down to detailed rules and record keeping (i.e., paperwork) that can be burdensome and costly to those who must comply with them. Thus, while policies provide benefits to Americans, the costs associated with regulatory programs are sometimes less transparent. Following the September 11 attacks in 2001, biosafety in laboratories evolved, and the regulations demanded more stringency to protect the public through increased safety and security at these facilities. Additionally, since 2001 and the Amerithrax anthrax letters, America

has had a significant focus on biosafety and security (Nordmann, 2010). Globally, biosecurity has also been the main topic in security discussions, mainly through the mechanisms of the Biological and Toxin Weapons Convention and World Health Organization (Nordmann, 2010).

Recommendations

This is the first policy impact analysis that has been conducted on entities and the SARs after implementation. Based on the inspection departures and survey results, the regulations have improved the safety and security of BSAT through improved biosafety practices, security posture, staff training, and oversight at entities that work with BSAT. The following are recommendations to further enhance the regulatory oversight and safety and security at registered facilities:

1. Conduct inspections based on the entity's risk by using a risk management and oversight approach. Increasing oversight at entities defined as moderate to high risk based on their risk level could improve security and biosafety by increasing the specificity and impact of post-inspection remediation efforts recommended by inspectors. Moderate to high-risk entities are the most complex that typically conducts high-risk work that pose a significant threat to public health.
2. Conduct a cost-benefit analysis to determine the true cost and benefit of enforcing the regulations and an entity's compliance with the regulations, regulating all high-containment laboratories in the United States. According to government issued documents, the United States currently does not have an account of all high (BSL-3/ABSL-3) and maximum (BSL-4/ABSL-4) containment laboratories, increasing the risks of accidental or intentional release of pathogens into the public or environment (GAO, 2009; USDA, 2009).

3. Conduct a focus group or survey with equal representation from all entity types registered with the program to explore the burden created by the regulations and identify areas of improvement. This should be done through a third-party organization using a qualitative approach to learn more about the entities. Qualitative research gives the researcher the ability to situate themselves in the personal experience of participants (Johnson & Christensen, 2017).
4. Assess the impact of the regulations and the safety and security of BSAT, pre-pandemic versus post-pandemic. Due to the COVID-19 pandemic, the FSAP had to make many changes in its inspection procedures, including enforcing the regulations remotely by reducing onsite inspections. Remote and hybrid inspections and oversight may save government funds and reduce entity burden while protecting public health.

The work of a modern research facility engaged in work involving BSAT can be wide-ranging and complex. An oversight program solely based on facility reporting and inspections has limitations by the willingness of the entity to report problems and the ability of regulatory inspections to uncover deficiencies in good laboratory practice during a point-in-time visit. Therefore, it would be prudent for the FSAP to focus its efforts on where the risk of exposures, safety, and security of BSAT is most significant.

The United States government and FSAP have been implementing changes since 2009 to strengthen laboratory biosecurity, better understand risk at regulated entities, and strengthen risk-based oversight (NSC, 2009; CDC, 2017). Additionally, the FSAP has gone through many program reviews by external federal advisory panels and oversight committees to address some of the issues identified in this study. For example, a 2014 report by the Federal Expert Security

Advisory Panel identified needs and gaps, and made recommendations to optimize biosafety, biosecurity, oversight, and inventory management and control of BSAT (FESAP, 2014).

Secondly, the Fast-Track Action Committee issued a report with recommendations for improving the SARs through stakeholder engagements with the public (FTAC, 2015). The FSAP successfully developed and implemented these recommendations and other program improvement initiatives over the last few years (CDC, 2020). The results of this study and the recommendations from these oversight committees should help further our understanding to develop optimal regulations and oversight of this critical work involving BSAT.

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APPENDIX A
FSAP INSPECTION PROCESS

A. INTRODUCTION

A.1 Purpose

This document describes the process to prepare for and perform inspections for the Federal Select Agent Program. It covers the Centers for Disease Control and Prevention (CDC), Division of Select Agents and Toxins (DSAT) led entities that are registered or seeking registration under the provisions of 42 Code of Federal Regulations (CFR) Part 73 and USDA, Division of Agricultural Select Agents and Toxins (DASAT) led entities that are registered or seeking registration under the provisions of 7 CFR Part 331 and 9 CFR Part 121.

A.2 Site Visit – Performed by the Inspection Team as Coordinated by the Lead Inspector

A.2.1 Routine (Not Compliance) Inspections – Announced and Unannounced

a. Tour the facility.

1) Renewals or Verifications: Tour all registered laboratories, storage rooms, HVAC-related areas serving the registered space, security-related areas, shipping and receiving, specialized areas (e.g., effluent decontamination systems, incinerators, etc.).

i. Observe biosafety practices (ask questions during tour).

1. Note safety features in place – record in notebook. If the laboratory rooms are being actively used, and the entity procedures are that no paper may be removed from the laboratories, every effort must be made to take notes during the walkthrough. Notes can be taken on special coated paper which

is then sprayed with disinfectant prior to removal, or notes may be faxed out of the laboratory. Note: An agreement with the entity as to how notes will be handled must be reached with the entity before entering active labs.

2. Smoke test ABSL-2, BSL-3, ABSL-3 and BSL-3Ag doors for directional airflow, biosafety cabinets and fume hoods for proper functioning, and other equipment as needed.

ii. Observe security practices and ask questions during tour

1. For Tier 1 registered areas, observe for the presence of a minimum of three security barriers and an intrusion detection system.

2. Note security features in place. Record in notebook.

2) New space: same as above as it relates to the new space only.

b. Conduct a spot check of inventory held in long-term storage – check approximately 10% of tubes/vials/containers of each agent in each storage unit and compare with the inventory log to confirm accuracy of inventory. Factors to consider in determining the quantity of inventory to check include:

- the overall amount.
- knowledge of the entity's performance during past inventory audits.
- the apparent organization of the inventory as it is checked.

For very large inventory collections, inspectors must use their discretion in the percent of tubes/vials/containers to select for the inventory audit. **Note:**

Inspectors must not handle or otherwise have access to inventory; inspectors

must compare the inventory record to the inventory containers which are pulled from storage and manipulated for viewing by registered entity personnel.

1) Verify that all elements required under Section 17(a)(1) for agents and (a)(3) for toxins are captured on the inventory record:

a) If animals or plants are present, ensure records are compliant with all elements of Section 17(a)(2).

2) Compare select agents acquired from APHIS/CDC Form 2 and APHIS/CDC Form 4 records with inventory records.

3) For new space: inventory will not be available to conduct an audit.

a) Check that the above written procedures have been addressed in the security plan.

b) Consideration may be given to conducting an inventory audit of old space prior to the move of the agents to the new space.

c. Review documents.

1) Plans: Security, Incident Response, and Biosafety:

a) Review for:

1. Content

2. Annual plan review

3. Plan review after drills and exercises and after any incident, and plan revision if necessary

2) Chemical hygiene plan (if applicable):

a) Review for:

1. Content

2. Annual plan review

- 3) Training: biosafety/biocontainment, security (insider threat briefings, if applicable), incident response, select agent or toxin specific training, and training on personnel suitability for employees with access to Tier 1 agents or toxins:
 - a) Verify training prior to individuals having access to select agents
 - b) Verify visitor training
 - c) Verify annual refresher training
 - d) Review curriculum used for training
 - e) Verify means of confirming understanding of training
- 4) Drills and exercises
 - a) Review documentation of how they tested each plan (security, incident response, and biosafety/biocontainment), problems identified, and corrective action taken, participant list
 - b) Review for annual performance
- 5) Entity Annual Inspection by Responsible Official
 - a) Review that inspections covered all sections of 42 CFR Part 73, 7 CFR § 331.18, and 9 CFR § 121.18 depending on the agents possessed. See SOP JOINT.29 for additional information. Review that corrective action was taken for problems identified
 - b) Review for annual performance
- 6) Occupational Health Program

- a) Check enrollment dates for personnel with access to SARS-CoV or Tier 1 select agents and toxins
- 7) Electronic and manual area access records, as appropriate (dates to be selected by the inspector)
- 8) Intra-entity transfer records, if applicable
- 9) Verify that observations from past inspections have been resolved.
- 10) Procedures to verify accuracy of records.
 - a) Area access records
 - b) Inventory records
- 11) Annual BSC/fume hood certification documents:
 - a) Class II Type A1 BSC – Certification may require a cabinet integrity test, depending on the cabinet's design, if the cabinet is new, has been moved, or if panels have been removed for maintenance.
 - b) Class II Type B1 or B2 BSC – Certification must include a test of the internal cabinet supply fan interlock; the internal supply fan must shut off if failure exhaust airflow occurs. Alternatively, the BSC can served by redundant exhaust fans or has a documented airflow monitor alarm test in lieu of the interlock.
 - c) Class III BSCs – Certification must include a cabinet integrity test if the cabinet is new, has been moved, or if panels have been removed for maintenance. Certification must include testing of negative pressure/ventilation rate and testing of all alarms and interlocks which are present.

12) BSL3/ABSL-3/BSL-3Ag facility verification if applicable. See **Appendix**

I.3.

13) BSL-3/ABSL-3 HVAC verification (new space, and renewal if applicable)

- a) HVAC verification test results must be requested from the entity if instructed to do so by the Facility Specialist.
- b) Any HVAC testing results must be brought back from the site visit for review by the Facility Specialist.

14) Tapes from camera recordings (as applicable or available)

- a) Is the intended information captured, per entity security plan?
- b) Observe tapes of workers entering and working in the laboratory (e.g., PPE, practices, etc.)

15) Any other pertinent select agent documents or other records (IBC and IACUC minutes, Medical Surveillance records, etc.)

d. Conduct interviews. **Note:** Some examples of information which can be gained from interviews include: personnel who are unfamiliar with biosafety and security procedures, laboratorians describing unregistered current select agent or toxin work, or an RO who lacks the authority needed to ensure compliance with the regulations.

- 1) Interview RO and AROs.
- 2) Interview PIs, selected laboratorians and support staff.
- 3) Typically, interviews are conducted on a one-on-one basis.
- 4) The BSL-3/ABSL-3 HVAC system major changes/problems questions must be asked of the facility personnel, if applicable.

A.3 Out-briefings – Performed by the Inspection Team as Coordinated by the LI

A.3.1 Routine Inspections – Announced or Unannounced

See **Appendix I.1**

- a. Prior to the out-briefing meeting, request that your team be allowed to have some time alone to review and organize the observations.
 - 1) Discuss the observations with the team members and resolve any questions or differences among team members.
 - 2) Organize the observations into broad categories (e.g., biosafety, security, etc.)
 - 3) If possible, select some outstanding positive observations that were identified during the inspection.
 - 4) Order the negative observations by category and severity.
- b. Begin the out-brief meeting by thanking the entity for their cooperation during the inspection.
- c. Remind the entity that the mission of FSAP is to ensure the safety and security of all select agents and toxins.
- d. Briefly discuss the eFSAP inspection module interface, and prior to presenting the observations, give brief overview/description of inspection report components (i.e., observations, concerns, RFIs, etc.), and the
- e. Emphasize that the topics discussed during the out-brief meeting are observations that will be brought to FSAP management for final approval.
- f. Present the observations in the order of importance, from greatest to least. Identify any repeat deficiencies. Minor observations do not have to be

mentioned. Be specific about the observations so that the RO and staff are clear about the deficiency which could be cited in the inspection report.

- g. Inform the RO that all inspection findings will be released in the eFSAP inspection module within 30 business days, and that responses will be required within 30 business days of release. Do not negotiate or argue with the entity about any observations but do provide any clarification needed. If there are controversial issues, state that their concerns will be brought back to management for further consideration.
- h. Do not recommend a product or service of a particular brand or establishment.
- i. Allow the entity to ask questions but do not make any statements that could be misconstrued as waiving regulatory requirements or approving variances from the standards.
- j. Record in your notes any significant conversations with the RO, ARO(s), or PI(s) which you feel may be of concern and need to be relayed to FSAP management. In most instances it is not necessary to quote entity officials verbatim. If it becomes necessary to do so, then record the exact statement in quotation marks in your notebook along with the name of the individual, the date and time the statement was made.
- k. In conclusion, thank the entity again for their hospitality and cooperation.

B. POST-INSPECTION

B.1 Internal Debriefings

- a. Internal debriefings help to ensure consistency between teams and offer an opportunity to determine if the observations found during the inspection

warrant further action. Additional Subject Matter Experts (e.g., Security Specialist, Facility Specialist, Biosafety Manager, Associate Director of Science, or Associate Director of Policy) may be solicited for the internal debrief.

- b. Internal debriefings with the inspection team, PO/FM, all TLs, and OBC/UD will be conducted, within ten business days if possible. This timeline begins the first Monday after the last day of inspection. If Monday is a holiday, the next applicable working day will be the start date of the 10 days.
- c. The LI schedules the meeting, prepares the debrief report, and must be prepared to discuss inspection findings similar to the debriefing session for the entity.

B.2 Internal Review and Release of Inspection Findings

- a. Upon completion of physical inspection of the entity and within performance metrics timeline, LI conducts debrief of inspection findings. See Appendix I.5, Part 2 for details.

LI and TL/Approver/FM send all inspection findings through internal review. See Appendix I.5, Part 2h and Appendix I.6, Inspection Finding Review Process for details.
- b. Final releaser provides inspection findings to the entity. See Appendix I.5, Part 2i and Appendix I.6 for details.

I.7 BSL-4 Inspection Documents

General Documents Review:

- 1. Biosafety Plans for BSL4

2. Occupational Health Plan
3. Security Plan
4. Incident Response Plan
5. Floorplans for lab suites and HEPA deck
6. List of SOPs developed
7. Training Records
8. Lab Access Records
9. Irradiator chain of custody documents
10. Irradiator kill curve data
11. Validation data
 - a. BSL4 specimens that are removed from containment for nucleic acid, protein, fluorescence, immunofluorescence, histopathology, and immunohistopathology analysis. SOPs will need to be supplied for all methods listed.
 - b. Autoclave parameters utilized for carcass cycles. Validation data will need to be provided using surrogate carcasses (i.e., turkey, Cornish game hen, etc.) that would mimic tissue density of the largest animal model intended to be decontaminated. Validation data will need to be provided for all carcass cycles used (small rodents, NHPs, etc.).
 - c. Gross decontamination parameters used for room decontaminations.
12. All laboratory incident reports

- a. Summary/SOP that explains how staff are to report incidents, how they are assessed for further action including potential reporting to the CDC as a Form 3, and by whom

13. Inventory records

14. BSL4 drills and exercises reports

15. IBC/IACUC minutes

Facilities Documents Review:

1. BSL4 Daily checklists

2. HEPA certs on all housings, BSCs, necropsy/backdraft tables, animal caging

3. Spore test data on EDS

4. Spore test data on autoclaves

5. Autoclave validation data for animal carcass run cycle times (see above)

6. EDS cook cycle data

7. Pressure decay tests

8. Maintenance / Decontamination records for Pall filters

9. Breathing air quality data

10. Daily (shift) inspection / maintenance records

11. Preventative maintenance schedule and records

12. BAS critical alarm definitions

13. BAS alarm notification scheme

14. BAS facility power re-start sequence

15. BAS calibration records

16. Generator load testing, backup power reliability testing, etc. -- schedules and associated containment data
17. Fan failure tests and associated containment data
18. Autoclave vent filter change records

APPENDIX B

CODE OF FEDERAL REGULATIONS: 42 CFR PART 73

§ 71.63

writing and be submitted to the CDC official whose office issued the order, and you must submit the appeal within 2 business days after you receive the order. Your appeal must state the reasons for the appeal and show that there is a genuine and substantial issue of fact in dispute. We will issue a written response to the appeal, which shall constitute final agency action.

[68 FR 62369, Nov. 4, 2003]

§ 71.63 Suspension of entry of animals, articles, or things from designated foreign countries and places into the United States.

(a) The Director may suspend the entry into the United States of animals, articles, or things from designated foreign countries (including political subdivisions and regions thereof) or places whenever the Director determines that such an action is necessary to protect the public health and upon a finding that:

(1) There exists in a foreign country (including one or more political subdivisions and regions thereof) or place a communicable disease the introduction, transmission, or spread of which would threaten the public health of the United States; and

(2) The entry of imports from that country or place increases the risk that the communicable disease may be introduced, transmitted, or spread into the United States.

(b) The Director shall designate the foreign countries or places and the period of time or conditions under which the introduction of imports into the United States shall be suspended. The Secretary or Director will coordinate in advance with other Federal agencies that have overlapping authority in the regulation of entry of animals, articles, or other things, as may be necessary to implement and enforce this provision.

[82 FR 6978, Jan. 19, 2017]

PART 72 [RESERVED]

PART 73—SELECT AGENTS AND TOXINS

Sec.

73.0 Applicability and related requirements.

73.1 Definitions.

42 CFR Ch. I (10–1–20 Edition)

73.2 Purpose and scope.

73.3 HHS select agents and toxins.

73.4 Overlap select agents and toxins.

73.5 Exemptions for HHS select agents and toxins.

73.6 Exemptions for overlap select agents and toxins.

73.7 Registration and related security risk assessments.

73.8 Denial, revocation, or suspension of registration.

73.9 Responsible Official.

73.10 Restricting access to select agents and toxins; security risk assessments.

73.11 Security.

73.12 Biosafety.

73.13 Restricted experiments.

73.14 Incident response.

73.15 Training.

73.16 Transfers.

73.17 Records.

73.18 Inspections.

73.19 Notification of theft, loss, or release.

73.20 Administrative review.

73.21 Civil money penalties.

AUTHORITY: 42 U.S.C. 262a; sections 201–204, 221 and 231 of Title II of Public Law 107–188, 116 Stat. 637 (42 U.S.C. 262a).

SOURCE: 70 FR 13316, Mar. 18, 2005, unless otherwise noted.

§ 73.0 Applicability and related requirements.

All individuals and entities that possess SARS-CoV, Lujo virus, or Chapare virus must provide notice to CDC regarding their possession of SARS-CoV, Lujo virus, or Chapare virus on or before December 4, 2012. Currently registered individuals and entities possessing SARS-CoV, Lujo virus, or Chapare virus must meet all the requirements of this part by December 4, 2012. All previously unregistered individuals and entities possessing SARS-CoV, Lujo virus, or Chapare virus must meet all of the requirements of this part by April 3, 2013.

[77 FR 61110, Oct. 5, 2012, as amended at 77 FR 71702, Dec. 4, 2012]

§ 73.1 Definitions.

For purposes of this part:

Administrator means the Administrator, Animal and Plant Health Inspection Service, or any person authorized to act for the Administrator.

Animal and Plant Health Inspection Service (APHIS) means the Animal and Plant Health Inspection Service of the U.S. Department of Agriculture.

Attorney General means the Attorney General of the United States or any person authorized to act for the Attorney General.

Biological agent means any microorganism (including, but not limited to, bacteria, viruses, fungi, rickettsiae, or protozoa), or infectious substance, or any naturally occurring, bioengineered, or synthesized component of any such microorganism or infectious substance, capable of causing death, disease, or other biological malfunction in a human, an animal, a plant, or another living organism; deterioration of food, water, equipment, supplies, or material of any kind; or deleterious alteration of the environment.

CDC means Centers for Disease Control and Prevention of the Department of Health and Human Services.

Conotoxins means short, paralytic alpha conotoxins containing the following amino acid sequence $X_1CCX_2PACGX_3X_4X_5X_6CX_7$, whereas:

- (1) C = Cysteine residues are all present as disulfides, with the 1st and 3rd Cysteine, and the 2nd and 4th Cysteine forming specific disulfide bridges;
- (2) The consensus sequence includes known toxins α -MI and α -GI (shown above) as well as α -GIA, AcI.1a, α -CnIA, α -CnIB;
- (3) X_1 = any amino acid(s) or Des-X;
- (4) X_2 = Asparagine or Histidine;
- (5) P = Proline;
- (6) A = Alanine;
- (7) G = Glycine;
- (8) X_3 = Arginine or Lysine;
- (9) X_4 = Asparagine, Histidine, Lysine, Arginine, Tyrosine, Phenylalanine or Tryptophan;
- (10) X_5 = Tyrosine, Phenylalanine, or Tryptophan;
- (11) X_6 = Serine, Threonine, Glutamate, Aspartate, Glutamine, or Asparagine;
- (12) X_7 = Any amino acid(s) or Des X; and
- (13) "Des X" = "an amino acid does not have to be present at this position." For example if a peptide sequence were XCCHPA then the related peptide CCHPA would be designated as Des-X.

Diagnosis means the analysis of specimens for the purpose of identifying or confirming the presence or characteristics of a select agent or toxin provided that such analysis is directly related to protecting the public health or safety, animal health or animal products, or plant health or plant products.

Entity means any government agency (Federal, State, or local), academic institution, corporation, company, part-

nership, society, association, firm, sole proprietorship, or other legal entity.

HHS means the Department of Health and Human Services.

HHS Secretary means the Secretary of the Department of Health and Human Services or his or her designee, unless otherwise specified.

HHS select agent and/or toxin means a biological agent or toxin included in §73.3.

Information security means protecting information and information systems from unauthorized access, use, disclosure, disruption, modification, or destruction in order to provide—

(1) Integrity, which means guarding against improper information modification or destruction, and includes ensuring information authenticity;

(2) Confidentiality, which means preserving authorized restrictions on access and disclosure, including means for protecting personal privacy and proprietary information; and

(3) Availability, which means ensuring timely and reliable access to and use of information.

Occupational exposure means any reasonably anticipated skin, eye, mucous membrane, parenteral contact, or respiratory aerosol exposure to select agents or toxins that may result from the performance of an employee's duties.

Overlap select agent and/or toxin means a biological agent or toxin listed in §73.4 and 9 CFR part 121.4.

Principal investigator means the one individual who is designated by the entity to direct a project or program and who is responsible to the entity for the scientific and technical direction of that project or program.

Proficiency testing means the process of determining the competency of an individual or laboratory to perform a specified test or procedure.

Recombinant nucleic acids means:

(1) Molecules that are constructed by joining nucleic acid molecules and that can replicate in a living cell or

(2) Molecules that result from the replication of those described in paragraph (1) of this definition.

Responsible Official means the individual designated by an entity with the

authority and control to ensure compliance with the regulations in this part.

Security barrier means a physical structure that is designed to prevent entry by unauthorized persons.

Select agent and/or toxin means unless otherwise specified, all of the biological agents or toxins listed in §§ 73.3 and 73.4.

Specimen means samples of material from humans, animals, plants or the environment or isolates or cultures from such samples for the diagnosis, verification, or proficiency testing.

State means any of the several States of the United States, the Commonwealth of the Northern Mariana Islands, the Commonwealth of Puerto Rico, the District of Columbia, Guam, the Virgin Islands of the United States, or any other territory or possession of the United States.

Synthetic nucleic acids means:

(1) Molecules that are chemically or by other means synthesized or amplified, including those that are chemically or otherwise modified but can base pair with naturally occurring nucleic acid molecules (*i.e.*, synthetic nucleic acids) or

(2) Molecules that result from the replication of those described in paragraph (1) of this definition.

Toxin means the toxic material or product of plants, animals, microorganisms (including, but not limited to, bacteria, viruses, fungi, rickettsiae, or protozoa), or infectious substances, or a recombinant or synthesized molecule, whatever their origin and method of production, and includes any poisonous substance or biological product that may be engineered as a result of biotechnology, produced by a living organism; or any poisonous isomer or biological product, homolog, or derivative of such a substance.

United States means all of the States.

USDA means the United States Department of Agriculture.

Validated inactivation procedure means a procedure, whose efficacy is confirmed by data generated from a viability testing protocol, to render a select agent non-viable but allows the select agent to retain characteristics of interest for future use; or to render any nucleic acids that can produce infectious

forms of any select agent virus non-infectious for future use.

Viability testing protocol means a protocol to confirm the validated inactivation procedure by demonstrating the material is free of all viable select agent.

Verification means the demonstration of obtaining established performance (*e.g.*, accuracy, precision, and the analytical sensitivity and specificity) specifications for any procedure used for diagnosis.

[70 FR 13316, Mar. 18, 2005, as amended at 77 FR 61110, Oct. 5, 2012; 82 FR 6290, Jan. 19, 2017]

§ 73.2 Purpose and scope.

This part implements the provisions of the Public Health Security and Biodefense Preparedness and Response Act of 2002 setting forth the requirements for possession, use, and transfer of select agents and toxins. The biological agents and toxins listed in this part have the potential to pose a severe threat to public health and safety, to animal health, or to animal products. Overlap select agents and toxins are subject to regulation by both CDC and APHIS.

§ 73.3 HHS select agents and toxins.

(a) Except for exclusions under paragraphs (d) and (e) of this section, the HHS Secretary has determined that the biological agents and toxins listed in this section have the potential to pose a severe threat to public health and safety. The select agents and toxins marked with an asterisk (*) are designated as Tier 1 select agents and toxins and are subject to additional requirements as listed in this part.

(b) HHS select agents and toxins:

Abrin

Bacillus cereus Biovar *anthracis**

Botulinum neurotoxins*

Botulinum neurotoxin producing species of

*Clostridium**

Conotoxins (Short, paralytic alpha conotoxins containing the following amino acid sequence X₁CCX₂PACGX₃X₄X₅X₆CX₇)¹

¹C = Cysteine residues are all present as disulfides, with the 1st and 3rd Cysteine, and the 2nd and 4th Cysteine forming specific disulfide bridges; The consensus sequence includes known toxins α-MI and α-GI (shown above) as well as α-GIA, Ac1.1a, α-CnIA, α-

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Coriella burnetii
 Crimean-Congo hemorrhagic fever virus
 Diacetoxyscirpenol
 Eastern equine encephalitis virus
 Ebola virus*
*Francisella tularensis**
 Lassa fever virus
 Lujo virus
 Marburg virus*
 Monkeypox virus
 Reconstructed replication competent forms of the 1918 pandemic influenza virus containing any portion of the coding regions of all eight gene segments (Reconstructed 1918 influenza virus)
 Ricin
Rickettsia prowazekii
 SARS coronavirus (SARS-CoV)
 Saxitoxin
 South American hemorrhagic fever viruses:
 Chapare
 Guanarito
 Junin
 Machupo
 Sabia
 Staphylococcal enterotoxins (subtypes A-E)
 T-2 toxin
 Tetradotoxin
 Tick-borne encephalitis virus
 Far Eastern subtype
 Siberian subtype
 Kyasanur Forest disease virus
 Omsk hemorrhagic fever virus
 Variola major virus (Smallpox virus)*
 Variola minor virus (Alastrim)*
*Yersinia pestis**

(c) Genetic Elements, Recombinant and/or Synthetic Nucleic Acids, and Recombinant and/or Synthetic Organisms:

(1) Nucleic acids that can produce infectious forms of any of the select agent viruses listed in paragraph (b) of this section.

(2) Recombinant and/or Synthetic nucleic acids that encode for the toxic form(s) of any of the toxins listed in paragraph (b) of this section if the nucleic acids:

CnIB; X1 = any amino acid(s) or Des-X; X2 = Asparagine or Histidine; P = Proline; A = Alanine; G = Glycine; X3 = Arginine or Lysine; X4 = Asparagine, Histidine, Lysine, Arginine, Tyrosine, Phenylalanine or Tryptophan; X5 = Tyrosine, Phenylalanine, or Tryptophan; X6 = Serine, Threonine, Glutamate, Aspartate, Glutamine, or Asparagine; X7 = Any amino acid(s) or Des X and; "Des X" = "an amino acid does not have to be present at this position." For example if a peptide sequence were XCCHPA then the related peptide CCHPA would be designated as Des-X.

(i) Can be expressed *in vivo* or *in vitro*, or

(ii) Are in a vector or recombinant host genome and can be expressed *in vivo* or *in vitro*.

(3) HHS select agents and toxins listed in paragraph (b) of this section that have been genetically modified.

(d) HHS select agents or toxins that meet any of the following criteria are excluded from the requirements of this part:

(1) Any HHS select agent or toxin that is in its naturally occurring environment provided the select agent or toxin has not been intentionally introduced, cultivated, collected, or otherwise extracted from its natural source.

(2) Non-viable HHS select agents or nontoxic HHS toxins.

(3) A select agent or toxin that has been subjected to decontamination or a destruction procedure when intended for waste disposal.

(4) A select agent or regulated nucleic acids that can produce infectious forms of any select agent virus that has been subjected to a validated inactivation procedure that is confirmed through a viability testing protocol. Surrogate strains that are known to possess equivalent properties with respect to inactivation can be used to validate an inactivation procedure; however, if there are known strain-to-strain variations in the resistance of a select agent to an inactivation procedure, then an inactivation procedure validated on a lesser resistant strain must also be validated on the more resistant strains.

(5) Material containing a select agent that is subjected to a procedure that removes all viable select agent cells, spores, or virus particles if the material is subjected to a viability testing protocol to ensure that the removal method has rendered the material free of all viable select agent.

(6) A select agent or regulated nucleic acids that can produce infectious forms of any select agent virus not subjected to a validated inactivation procedure or material containing a select agent not subjected to a procedure that removes all viable select agent cells, spores, or virus particles if the material is determined by the HHS Secretary to be effectively inactivated or

effectively removed. To apply for a determination an individual or entity must submit a written request and supporting scientific information to CDC. A written decision granting or denying the request will be issued.

(7) Except as required in § 73.16(l), the aggregate amount of the toxin under the control of a principal investigator, treating physician or veterinarian, or commercial manufacturer or distributor does not, at any time, exceed the following amounts: 1000 mg of Abrin; 1 mg of Botulinum neurotoxins; 100 mg of Conotoxins (Short, paralytic alpha conotoxins containing the following amino acid sequence X₁CCX₂PACGX₃X₄X₅X₆CX₇); 10,000 mg of Diacetoxyscirpenol; 1000 mg of Ricin; 500 mg of Saxitoxin; 100 mg of Staphylococcal enterotoxins (subtypes A–E); 10,000 mg of T-2 toxin; or 500 mg of Tetrodotoxin. Provided that,

(i) The toxin is transferred only after the transferor uses due diligence and documents the identification of the recipient and the legitimate need (*e.g.*, prophylactic, protective, bona fide research, or other peaceful purpose) claimed by the recipient to use such toxin. Information to be documented includes, but is not limited to, the recipient identity information, including the recipient's name, institution name, address, telephone number and email address; name of the toxin and the total amount transferred; and the legitimate need claimed by the recipient. Notwithstanding the provisions of paragraph (d) of this section, the HHS Secretary retains the authority to, without prior notification, inspect and copy or request the submission of the due diligence documentation to the CDC.

(ii) Reports to CDC if they detect a known or suspected violation of Federal law or become aware of suspicious activity related to a toxin listed in this part.

(8) An animal inoculated with or exposed to an HHS select toxin.

(9) An HHS select toxin identified in an original food sample or clinical sample.

(10) For those laboratories that are not exempt under § 73.5(a) and § 73.6(a), Botulinum neurotoxin that is produced as a byproduct in the study of Botu-

linum neurotoxin producing species of *Clostridium* so long as the toxin has not been intentionally cultivated, collected, purified, or otherwise extracted, and the material containing the toxin is rendered non-toxic and disposed of within 30 days of the initiation of the culture.

(11) Waste generated during the delivery of patient care by health care professionals from a patient diagnosed with an illness or condition associated with a select agent, where that waste is decontaminated or transferred for destruction by complying with state and Federal regulations within seven calendar days of the conclusion of patient care.

(12) Any South American genotypes of Eastern Equine Encephalitis Virus and any West African Clade of Monkeypox virus provided that the individual or entity can identify that the agent is within the exclusion category.

(e) An attenuated strain of a select agent or a select toxin modified to be less potent or toxic may be excluded from the requirements of this part based upon a determination by the HHS Secretary that the attenuated strain or modified toxin does not pose a severe threat to public health and safety.

(1) To apply for exclusion, an individual or entity must submit a written request and supporting scientific information. A written decision granting or denying the request will be issued. An exclusion will be effective upon notification to the applicant. Exclusions will be listed on the National Select Agent Registry Web site at <http://www.selectagents.gov/>.

(2) If an excluded attenuated strain or modified toxin is subjected to any manipulation that restores or enhances its virulence or toxic activity, the resulting select agent or toxin will be subject to the requirements of this part.

(3) An individual or entity may make a written request to the HHS Secretary for reconsideration of a decision denying an application for the exclusion of an attenuated strain of a select agent or a select toxin modified to be less potent or toxic. The written request for reconsideration must state the facts

and reasoning upon which the individual or entity relies to show the decision was incorrect. The HHS Secretary will grant or deny the request for reconsideration as promptly as circumstances allow and will state, in writing, the reasons for the decision.

(f) Any HHS select agent or toxin seized by a Federal law enforcement agency will be excluded from the requirements of this part during the period between seizure of the select agent or toxin and the transfer or destruction of such agent or toxin provided that:

(1) As soon as practicable, the Federal law enforcement agency transfers the seized select agent or toxin to an entity eligible to receive such agent or toxin or destroys the agent or toxin by a recognized sterilization or inactivation process.

(2) The Federal law enforcement agency safeguards and secures the seized select agent or toxin against theft, loss, or release, and reports any theft, loss, or release of such agent or toxin, and

(3) The Federal law enforcement agency reports the seizure of the select agent or toxin to CDC or APHIS.

(i) The seizure of *Bacillus cereus* Biovar *anthracis*, Botulinum neurotoxins, Botulinum neurotoxin producing species of *Clostridium*, Ebola viruses, *Francisella tularensis*, Marburg virus, Variola major virus (Smallpox virus), Variola minor (Alastrim), or *Yersinia pestis* must be reported within 24 hours by telephone, facsimile, or e-mail. This report must be followed by submission of APHIS/CDC Form 4 within seven calendar days after seizure of the select agent or toxin.

(ii) For all other HHS select agents or toxins, APHIS/CDC Form 4 must be submitted within seven calendar days after seizure of the agent or toxin.

(iii) A copy of APHIS/CDC Form 4 must be maintained for three years.

(4) The Federal law enforcement agency reports the final disposition of the select agent or toxin by submission of APHIS/CDC Form 4. A copy of the

completed form must be maintained for three years.

[70 FR 13316, Mar. 18, 2005, as amended at 70 FR 61049, Oct. 20, 2005; 73 FR 61365, Oct. 16, 2008; 73 FR 64554, Oct. 30, 2008; 77 FR 61110, Oct. 5, 2012; 79 FR 26861, May 12, 2014; 81 FR 63143, Sept. 14, 2016; 82 FR 6290, Jan. 19, 2017]

§ 73.4 Overlap select agents and toxins.

(a) Except for exclusions under paragraphs (d) and (e) of this section, the HHS Secretary has determined that the biological agents and toxins listed in this section have the potential to pose a severe threat to public health and safety, to animal health, or to animal products. The select agents and toxins marked with an asterisk (*) are designated as Tier 1 select agents and toxins and are subject to additional requirements as listed in this part.

(b) Overlap select agents and toxins:

*Bacillus anthracis**
Bacillus anthracis Pasteur strain
Brucella abortus
Brucella melitensis
Brucella suis
*Burkholderia mallei**
*Burkholderia pseudomallei**
Hendra virus
Nipah virus
Rift Valley fever virus
Venezuelan equine encephalitis virus

(c) Genetic Elements, Recombinant and/or Synthetic Nucleic Acids, and Recombinant and/or Synthetic Organisms:

(1) Nucleic acids that can produce infectious forms of any of the overlap select agent viruses listed in paragraph (b) of this section.

(2) Recombinant and/or synthetic nucleic acids that encode for the toxic form(s) of any overlap toxins listed in paragraph (b) of this section if the nucleic acids:

(i) Can be expressed *in vivo* or *in vitro*, or

(ii) Are in a vector or recombinant host genome and can be expressed *in vivo* or *in vitro*.

(3) Overlap select agents and toxins listed in paragraph (b) of this section that have been genetically modified.

(d) Overlap select agents or toxins that meet any of the following criteria are excluded from the requirements of this part:

(1) Any overlap select agent or toxin that is in its naturally occurring environment provided that the select agent or toxin has not been intentionally introduced, cultivated, collected, or otherwise extracted from its natural source.

(2) Non-viable overlap select agents or nontoxic overlap toxins.

(3) A select agent or toxin that has been subjected to decontamination or a destruction procedure when intended for waste disposal.

(4) A select agent or regulated nucleic acids that can produce infectious forms of any select agent virus that has been subjected to a validated inactivation procedure that is confirmed through a viability testing protocol. Surrogate strains that are known to possess equivalent properties with respect to inactivation can be used to validate an inactivation procedure; however, if there are known strain-to-strain variations in the resistance of a select agent to an inactivation procedure, then an inactivation procedure validated on a lesser resistant strain must also be validated on the more resistant strains.

(5) Material containing a select agent that is subjected to a procedure that removes all viable select agent cells, spores, or virus particles if the material is subjected to a viability testing protocol to ensure that the removal method has rendered the material free of all viable select agent.

(6) A select agent or regulated nucleic acids that can produce infectious forms of any select agent virus not subjected to a validated inactivation procedure or material containing a select agent not subjected to a procedure that removes all viable select agent cells, spores, or virus particles if the material is determined by the HHS Secretary or Administrator to be effectively inactivated or effectively removed. To apply for a determination an individual or entity must submit a written request and supporting scientific information to CDC or APHIS. A written decision granting or denying the request will be issued.

(7) An overlap select toxin identified in an original food sample or clinical sample.

(8) Waste generated during the delivery of patient care by health care professionals from a patient diagnosed with an illness or condition associated with a select agent, where that waste is decontaminated or transferred for destruction by complying with state and Federal regulations within seven calendar days of the conclusion of patient care.

(9) Any subtypes of Venezuelan equine encephalitis virus except for Subtypes IAB or IC provided that the individual or entity can identify that the agent is within the exclusion category.

(e) An attenuated strain of a select agent, or a select toxin modified to be less potent or toxic, may be excluded from the requirements of this part based upon a determination by the HHS Secretary that the attenuated strain or modified toxin does not pose a severe threat to public health and safety.

(1) To apply for exclusion, an individual or entity must submit a written request and supporting scientific information. A written decision granting or denying the request will be issued. An exclusion will be effective upon notification to the applicant. Exclusions will be listed on the National Select Agent Registry Web site at <http://www.selectagents.gov/>.

(2) If an excluded attenuated strain or modified toxin is subjected to any manipulation that restores or enhances its virulence or toxic activity, the resulting select agent or toxin will be subject to the requirements of this part.

(3) An individual or entity may make a written request to the HHS Secretary or Administrator for reconsideration of a decision denying an application for the exclusion of an attenuated strain of a select agent or a select toxin modified to be less potent or toxic. The written request for reconsideration must state the facts and reasoning upon which the individual or entity relies to show the decision was incorrect. The HHS Secretary or Administrator will grant or deny the request for reconsideration as promptly as circumstances allow and will state, in writing, the reasons for the decision.

(f) Any overlap select agent or toxin seized by a Federal law enforcement agency will be excluded from the requirements of this part during the period between seizure of the select agent or toxin and the transfer or destruction of such agent or toxin provided that:

(1) As soon as practicable, the Federal law enforcement agency transfers the seized select agent or toxin to an entity eligible to receive such agent or toxin or destroys the agent or toxin by a recognized sterilization or inactivation process,

(2) The Federal law enforcement agency safeguards and secures the seized select agent or toxin against theft, loss, or release, and reports any theft, loss, or release of such agent or toxin, and

(3) The Federal law enforcement agency reports the seizure of the overlap select agent or toxin to CDC or APHIS.

(i) The seizure of *Bacillus anthracis*, *Burkholderia mallei* and *Burkholderia pseudomallei* must be reported within 24 hours by telephone, facsimile, or e-mail. This report must be followed by submission of APHIS/CDC Form 4 within seven calendar days after seizure of the overlap select agent or toxin.

(ii) For all other overlap select agents or toxins, APHIS/CDC Form 4 must be submitted within seven calendar days after seizure of the select agent or toxin.

(iii) A copy of APHIS/CDC Form 4 must be maintained for three years.

(4) The Federal law enforcement agency reports the final disposition of the overlap select agent or toxin by the submission of APHIS/CDC Form 4. A copy of the completed form must be maintained for three years.

[70 FR 13316, Mar. 18, 2005, as amended at 73 FR 61366, Oct. 16, 2008; 77 FR 61111, Oct. 5, 2012; 79 FR 26861, May 12, 2014; 82 FR 6291, Jan. 19, 2017]

§ 73.5 Exemptions for HHS select agents and toxins.

(a) Clinical or diagnostic laboratories and other entities that possess, use, or transfer a HHS select agent or toxin that is contained in a specimen presented for diagnosis or verification will be exempt from the requirements of

this part for such agent or toxin contained in the specimen, provided that:

(1) Unless directed otherwise by the HHS Secretary, within seven calendar days after identification of the select agent or toxin (except for Botulinum neurotoxin and/or *Staphylococcal* enterotoxin (Subtypes A–E)), or within 30 calendar days after identification of Botulinum neurotoxin and/or *Staphylococcal* enterotoxin (Subtypes A–E), the select agent or toxin is transferred in accordance with § 73.16 or destroyed on-site by a recognized sterilization or inactivation process,

(2) The select agent or toxin is secured against theft, loss, or release during the period between identification of the select agent or toxin and transfer or destruction of such agent or toxin, and any theft, loss, or release of such agent or toxin is reported, and

(3) Unless otherwise directed by the HHS Secretary, the clinical or diagnostic specimens collected from a patient infected with a select agent are transferred in accordance with § 73.16 or destroyed on-site by a recognized sterilization or inactivation process within seven calendar days after delivery of patient care by health care professionals has concluded, and

(4) The identification of the agent or toxin is reported to CDC or APHIS, the specimen provider, and to other appropriate authorities when required by Federal, State, or local law by telephone, facsimile, or email. This report must be followed by submission of APHIS/CDC Form 4 to APHIS or CDC within seven calendar days after identification.

(i) The identification of any of the following HHS select agents or toxins must be immediately reported by telephone, facsimile, or e-mail: *Bacillus cereus* Biovar *anthracis*, Botulinum neurotoxins, Botulinum neurotoxin producing species of *Clostridium*, Ebola viruses, *Francisella tularensis*, Marburg virus, Variola major virus (Smallpox virus), Variola minor (Alastrim), or Yersinia pestis. This report must be followed by submission of APHIS/CDC Form 4 within seven calendar days after identification.

(ii) For all other HHS select agents or toxins, APHIS/CDC Form 4 must be

submitted within seven calendar days after identification.

(iii) Less stringent reporting may be required based on extraordinary circumstances, such as a widespread outbreak.

(iv) A copy of APHIS/CDC Form 4 must be maintained for three years.

(b) Clinical or diagnostic laboratories and other entities that possess, use, or transfer a HHS select agent or toxin that is contained in a specimen presented for proficiency testing will be exempt from the requirements of this part for such agent or toxin contained in the specimen, provided that:

(1) Unless directed otherwise by the HHS Secretary, within 90 calendar days of receipt, the select agent or toxin is transferred in accordance with § 73.16 or destroyed on-site by a recognized sterilization or inactivation process.

(2) The select agent or toxin is secured against theft, loss, or release during the period between identification of the select agent or toxin and transfer or destruction of such agent or toxin, and the theft, loss, or release of such agent or toxin is reported, and

(3) The identification of the select agent or toxin, and its derivative, is reported to CDC or APHIS and to other appropriate authorities when required by Federal, State, or local law. To report the identification of a select agent or toxin, APHIS/CDC Form 4 must be submitted within 90 calendar days of receipt of the select agent or toxin. A copy of the completed form must be maintained for three years.

(c) Unless the HHS Secretary issues an order making specific provisions of this part applicable to protect public health and safety, products that are, bear, or contain listed select agents or toxins that are cleared, approved, licensed, or registered under any of the following laws, are exempt from the provisions of this part insofar as their use meets the requirements of such laws:

(1) The Federal Food, Drug, and Cosmetic Act (21 U.S.C. 301 *et seq.*).

(2) Section 351 of the Public Health Service Act pertaining to biological products (42 U.S.C. 262).

(3) The Act commonly known as the Virus-Serum-Toxin Act (21 U.S.C. 151–159), or

(4) The Federal Insecticide, Fungicide, and Rodenticide Act (7 U.S.C. 136 *et seq.*).

(d) The HHS Secretary may exempt from the requirements of this part an investigational product that is, bears, or contains a select agent or toxin, when such product is being used in an investigation authorized under any Federal Act and additional regulation under this part is not necessary to protect public health and safety.

(1) To apply for an exemption, an individual or entity must submit a completed APHIS/CDC Form 5.

(2) The HHS Secretary shall make a determination regarding the application within 14 calendar days after receipt, provided the application meets all of the requirements of this section and the application establishes that the investigation has been authorized under the cited Act. A written decision granting or denying the request will be issued.

(3) The applicant must notify CDC or APHIS when an authorization for an investigation no longer exists. This exemption automatically terminates when such authorization is no longer in effect.

(e) The HHS Secretary may temporarily exempt an individual or entity from the requirements of this part based on a determination that the exemption is necessary to provide for the timely participation of the individual or entity in response to a domestic or foreign public health emergency. With respect to the emergency involved, the exemption may not exceed 30 calendar days, except that one extension of an additional 30 calendar days may be granted.

[70 FR 13316, Mar. 18, 2005, as amended at 73 FR 61366, Oct. 16, 2008; 77 FR 61112, Oct. 5, 2012; 82 FR 6292, Jan. 19, 2017]

§ 73.6 Exemptions for overlap select agents and toxins.

(a) Clinical or diagnostic laboratories and other entities that possess, use, or transfer an overlap select agent or toxin that is contained in a specimen presented for diagnosis or verification will be exempt from the requirements of this part for such agent or toxin contained in the specimen, provided that:

(1) Unless directed otherwise by the HHS Secretary or Administrator, within seven calendar days after identification, the select agent or toxin is transferred in accordance with § 73.16 or 9 CFR part 121.16 or destroyed on-site by a recognized sterilization or inactivation process,

(2) The select agent or toxin is secured against theft, loss, or release during the period between identification of the select agent or toxin and transfer or destruction of such agent or toxin, and any theft, loss, or release of such agent or toxin is reported, and

(3) Unless otherwise directed by the HHS Secretary or Administrator, the clinical or diagnostic specimens collected from a patient infected with a select agent are transferred in accordance with § 73.16 or destroyed on-site by a recognized sterilization or inactivation process within seven calendar days after delivery of patient care by health care professionals has concluded, and

(4) The identification of the agent or toxin is reported to CDC or APHIS, the specimen provider, and to other appropriate authorities when required by Federal, State, or local law by telephone, facsimile, or email. This report must be followed by submission of APHIS/CDC Form 4 to APHIS or CDC within seven calendar days after identification.

(i) The identification of any of the following overlap select agents or toxins must be immediately reported by telephone, facsimile, or e-mail: *Bacillus anthracis*, *Burkholderia mallei* and *Burkholderia pseudomallei*. This report must be followed by submission of APHIS/CDC Form 4 within seven calendar days after identification.

(ii) For all other overlap select agents or toxins, APHIS/CDC Form 4 must be submitted within seven calendar days after identification.

(iii) Less stringent reporting may be required based on extraordinary circumstances, such as a widespread outbreak.

(iv) A copy of APHIS/CDC Form 4 must be maintained for three years.

(b) Clinical or diagnostic laboratories and other entities that possess, use, or transfer an overlap select agent or toxin that is contained in a specimen presented for proficiency testing will

be exempt from the requirements of this part for such agent or toxin contained in the specimen, provided that:

(1) Unless directed otherwise by the HHS Secretary or Administrator, within 90 calendar days of receipt, the select agent or toxin is transferred in accordance with § 73.16 or 9 CFR part 121.16 or destroyed on-site by a recognized sterilization or inactivation process,

(2) The select agent or toxin is secured against theft, loss, or release during the period between identification of the select agent or toxin and transfer or destruction of such agent or toxin, and the theft, loss, or release of such agent or toxin is reported, and

(3) The identification of the select agent or toxin, and its derivative, is reported to CDC or APHIS and to other appropriate authorities when required by Federal, State, or local law. To report the identification of an overlap select agent or toxin, APHIS/CDC Form 4 must be submitted within 90 calendar days of receipt of the select agent or toxin. A copy of the completed form must be maintained for three years.

(c) Unless the HHS Secretary issues an order making specific provisions of this part applicable to protect public health and safety, products that are, bear, or contain listed select agents or toxins that are cleared, approved, licensed, or registered under any of the following laws, are exempt from the provisions of this part insofar as their use meets the requirements of such laws:

(1) The Federal Food, Drug, and Cosmetic Act (21 U.S.C. 301 *et seq.*),

(2) Section 351 of the Public Health Service Act pertaining to biological products (42 U.S.C. 262),

(3) The Act commonly known as the Virus-Serum-Toxin Act (21 U.S.C. 151-159), or

(4) The Federal Insecticide, Fungicide, and Rodenticide Act (7 U.S.C. 136 *et seq.*).

(d) The HHS Secretary, after consultation with Administrator, may exempt from the requirements of this part an investigational product that is, bears, or contains an overlap select agent or toxin, may be exempted when such product is being used in an investigation authorized under any Federal

Act and additional regulation under this part is not necessary to protect public health and safety.

(1) To apply for an exemption, an individual or entity must submit a completed APHIS/CDC Form 5.

(2) The HHS Secretary shall make a determination regarding the application within 14 calendar days after receipt, provided the application meets all of the requirements of this section and the application establishes that the investigation has been authorized under the cited Act. A written decision granting or denying the request will be issued.

(3) The applicant must notify CDC or APHIS when an authorization for an investigation no longer exists. This exemption automatically terminates when such authorization is no longer in effect.

(e) The HHS Secretary may exempt an individual or entity from the requirements of this part based on a determination that the exemption is necessary to provide for the timely participation of the individual or entity in response to a domestic or foreign public health emergency. The HHS Secretary may extend the exemption once for additional 30 days.

(f) Upon request of the Administrator, the HHS Secretary may exempt an individual or entity from the requirements, in whole or in part, of this part for 30 calendar days if the Administrator has granted the exemption for agricultural emergency. The HHS Secretary may extend the exemption once for an additional 30 calendar days.

[70 FR 13316, Mar. 18, 2005, as amended at 73 FR 61366, Oct. 16, 2008; 77 FR 61112, Oct. 5, 2012; 79 FR 26862, May 12, 2014; 82 FR 6292, Jan. 19, 2017]

§ 73.7 Registration and related security risk assessments.

(a) Unless exempted under § 73.5, an individual or entity shall not possess, use, or transfer any HHS select agent or toxin without a certificate of registration issued by the HHS Secretary. Unless exempted under § 73.6 or 9 CFR part 121.6, an individual or entity shall not possess, use, or transfer overlap select agents or toxins, without a certificate of registration issued by the HHS Secretary and Administrator.

(b) As a condition of registration, each entity is required to be in compliance with the requirements of this part for select agents and toxins listed on the registration regardless of whether the entity is in actual possession of the select agent or toxin. With regard to toxins, the entity registered for possession, use or transfer of a toxin must be in compliance with the requirements of this part regardless of the amount of toxin currently in its possession.

(c) As a condition of registration, each entity must designate an individual to be its Responsible Official. While most registrants are likely to be entities, in the event that an individual applies for and is granted a certificate of registration, the individual will be considered the Responsible Official.

(d)(1) As a condition of registration, the following must be approved by the HHS Secretary or Administrator based on a security risk assessment by the Attorney General:

(i) The individual or entity,
(ii) The Responsible Official, and
(iii) Unless otherwise exempted under this section, any individual who owns or controls the entity.

(2) Federal, State, or local governmental agencies, including public accredited academic institutions, are exempt from the security risk assessments for the entity and the individual who owns or controls such entity.

(3) An individual will be deemed to own or control an entity under the following conditions:¹

(i) For a private institution of higher education, an individual will be deemed to own or control the entity if the individual is in a managerial or executive capacity with regard to the entity's select agents or toxins or with regard to the individuals with access to the select agents or toxins possessed, used, or transferred by the entity.

(ii) For entities other than institutions of higher education, an individual will be deemed to own or control the entity if the individual:

(A) Owns 50 percent or more of the entity, or is a holder or owner of 50 percent or more of its voting stock, or

¹ These conditions may apply to more than one individual.

(B) Is in a managerial or executive capacity with regard to the entity's select agents or toxins or with regard to the individuals with access to the select agents or toxins possessed, used, or transferred by the entity.

(4) An entity will be considered to be an institution of higher education if it is an institution of higher education as defined in section 101(a) of the Higher Education Act of 1965 (20 U.S.C. 1001(a)), or is an organization described in 501(c)(3) of the Internal Revenue Code of 1986, as amended (26 U.S.C. 501(c)(3)).

(5) To obtain a security risk assessment, an individual or entity must submit the information necessary to conduct a security risk assessment to the Attorney General.

(e) To apply for a certificate of registration that covers only HHS select agents or toxins, an individual or entity must submit the information requested in the registration application package (APHIS/CDC Form 1) to CDC. To apply for a certificate of registration that does not cover only HHS select agents or toxins (*i.e.*, covers at least one overlap select agent and/or toxin, or covers any combination of HHS select agents and/or toxins and USDA select agents and/or toxins), an individual or entity must submit the information requested in the registration application package (APHIS/CDC Form 1) to CDC or APHIS, but not both.

(f) Prior to the issuance of a certificate of registration, the Responsible Official must promptly provide notification of any changes to the application for registration by submitting the relevant page(s) of the registration application.

(g) The issuance of a certificate of registration may be contingent upon inspection or submission of additional information, such as the security plan, biosafety plan, incident response plan, or any other documents required to be prepared under this part.

(h) A certificate of registration will be valid for one physical location (a room, a building, or a group of buildings) where the Responsible Official will be able to perform the responsibilities required in this part, for specific

select agents or toxins, and for specific activities.

(i) A certificate of registration may be amended to reflect changes in circumstances (e.g., replacement of the Responsible Official or other personnel changes, changes in ownership or control of the entity, changes in the activities involving any select agents or toxins, or the addition or removal of select agents or toxins).

(1) Prior to any change, the Responsible Official must apply for an amendment to a certificate of registration by submitting the relevant page(s) of the registration application.

(2) The Responsible Official will be notified in writing if an application to amend a certificate of registration has been approved. Approval of the amendment may be contingent upon an inspection or submission of additional information, such as the security plan, biosafety plan, incident response plan, or any other documents required to be prepared under this part.

(3) No change may be made without such approval.

(j) An entity must immediately notify CDC or APHIS if it loses the services of its Responsible Official. In the event that an entity loses the services of its Responsible Official, an entity may continue to possess or use select agents or toxins only if it appoints as the Responsible Official another individual who has been approved by the HHS Secretary or Administrator following a security risk assessment by the Attorney General and who meets the requirements of this part.

(k) A certificate of registration will be terminated upon the written request of the entity if the entity no longer possesses or uses any select agents or toxins and no longer wishes to be registered.

(l) A certificate of registration will be valid for a maximum of three years.

[70 FR 13316, Mar. 18, 2005, as amended at 82 FR 6292, Jan. 19, 2017]

§ 73.8 Denial, revocation, or suspension of registration.

(a) An application may be denied or a certificate of registration revoked or suspended if:

(1) The individual or entity, the Responsible Official, or an individual who

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owns or controls the entity is within any of the categories described in 18 U.S.C. 175b,

(2) The individual or entity, the Responsible Official, or an individual who owns or controls the entity as reasonably suspected by any Federal law enforcement or intelligence agency of:

(i) Committing a crime specified in 18 U.S.C. 2332b(g)(5),

(ii) Knowing involvement with an organization that engages in domestic or international terrorism (as defined in 18 U.S.C. 2331) or with any other organization that engages in intentional crimes of violence, or

(iii) Being an agent of a foreign power (as defined in 50 U.S.C. 1801).

(3) The individual or entity does not meet the requirements of this part, or

(4) It is determined that such action is necessary to protect public health and safety.

(b) Upon revocation or suspension of a certificate of registration, the individual or entity must:

(1) Immediately stop all use of each select agent or toxin covered by the revocation or suspension order,

(2) Immediately safeguard and secure each select agent or toxin covered by the revocation or suspension order from theft, loss, or release, and

(3) Comply with all disposition instructions issued by the HHS Secretary for the select agent or toxin covered by the revocation or suspension.

(c) Denial of an application for registration and revocation of registration may be appealed under § 73.20. However, any denial of an application for registration or revocation of a certificate of registration will remain in effect until a final agency decision has been rendered.

§ 73.9 Responsible Official.

(a) An individual or entity required to register under this part must designate an individual to be the Responsible Official. The Responsible Official must:

(1) Be approved by the HHS Secretary or Administrator following a security risk assessment by the Attorney General,

(2) Be familiar with the requirements of this part,

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(3) Have authority and responsibility to act on behalf of the entity,

(4) Ensure compliance with the requirements of this part,

(5) Have a physical (and not merely a telephonic or audio/visual) presence at the registered entity to ensure that the entity is in compliance with the select agent regulations and be able to respond in a timely manner to onsite incidents involving select agents and toxins in accordance with the entity's incident response plan, and

(6) Ensure that annual inspections are conducted for each registered space where select agents or toxins are stored or used in order to determine compliance with the requirements of this part. The results of each inspection must be documented, and any deficiencies identified during an inspection must be corrected and the corrections documented.

(7) Ensure that individuals are provided the contact information for the HHS Office of Inspector General Hotline and the USDA Office of Inspector General Hotline so that they may anonymously report any biosafety or security concerns related to select agents and toxins.

(8) Investigate to determine the reason for any failure of a validated inactivation procedure or any failure to remove viable select agent from material. If the Responsible Official is unable to determine the cause of a deviation from a validated inactivation procedure or a viable select agent removal method; or receives a report of any inactivation failure after the movement of material to another location, the Responsible Official must report immediately by telephone or email the inactivation or viable agent removal method failure to CDC or APHIS.

(9) Review, and revise as necessary, each of the entity's validated inactivation procedures or viable select agent removal methods. The review must be conducted annually or after any change in Principal Investigator, change in the validated inactivation procedure or viable select agent removal method, or failure of the validated inactivation procedure or viable select agent removal method. The review must be documented and training

must be conducted if there are any changes to the validated inactivation procedure, viable select agent removal method, or viability testing protocol.

(b) An entity may designate one or more individuals to serve as an alternate Responsible Official, who acts for the Responsible Official in his/her absence. These individuals must have the authority and control to ensure compliance with the regulations when acting as the Responsible Official.

(c) The Responsible Official must report the identification and final disposition of any select agent or toxin contained in a specimen presented for diagnosis or verification.

(1) The identification of any of the following select agents or toxins must be immediately reported by telephone, facsimile, or e-mail: *Bacillus anthracis*, *Bacillus cereus* Biovar *anthracis*, Botulinum neurotoxins, Botulinum neurotoxin producing species of *Clostridium*, *Burkholderia mallei*, *Burkholderia pseudomallei*, *Francisella tularensis*, Ebola viruses, Marburg virus, Variola major virus (Smallpox virus), Variola minor (Alastrim), or *Yersinia pestis*. The final disposition of the agent or toxin must be reported by submission of APHIS/CDC Form 4 within seven calendar days after identification. A copy of the completed form must be maintained for three years.

(2) To report the identification and final disposition of any other select agent or toxin, APHIS/CDC Form 4 must be submitted within seven calendar days after identification. A copy of the completed form must be maintained for three years.

(3) Less stringent reporting may be required based on extraordinary circumstances, such as a widespread outbreak.

(d) The Responsible Official must report the identification and final disposition of any select agent or toxin contained in a specimen presented for proficiency testing. To report the identification and final disposition of a select agent or toxin, APHIS/CDC Form 4 must be submitted within 90 calendar days of receipt of the agent or toxin. A

copy of the completed form must be maintained for three years.

[70 FR 13316, Mar. 18, 2005, as amended at 77 FR 61112, Oct. 5, 2012; 82 FR 6292, Jan. 19, 2017]

§ 73.10 Restricting access to select agents and toxins; security risk assessments.

(a) An individual or entity required to register under this part may not provide an individual access to a select agent or toxin, and an individual may not access a select agent or toxin, unless the individual is approved by the HHS Secretary or Administrator, following a security risk assessment by the Attorney General.

(b) An individual will be deemed to have access at any point in time if the individual has possession of a select agent or toxin (e.g., ability to carry, use, or manipulate) or the ability to gain possession of a select agent or toxin.

(c) Each individual with access to select agents or toxins must have the appropriate education, training, and/or experience to handle or use such agents or toxins.

(d) To apply for access approval, each individual must submit the information necessary to conduct a security risk assessment to the Attorney General.

(e) A person with a valid approval from the HHS Secretary or Administrator to have access to select agents and toxins may request, through his or her Responsible Official, that the HHS Secretary or Administrator provide their approved access status to another registered individual or entity for a specified period of time. A Responsible Official must immediately notify the Responsible Official of the visited entity if the person's access to select agents and toxins has been terminated.

(f) An individual's security risk assessment may be expedited upon written request by the Responsible Official and a showing of good cause (e.g., public health or agricultural emergencies, national security, or a short term visit by a prominent researcher). A written decision granting or denying the request will be issued.

(g) An individual's access approval will be denied or revoked if the individual is within any of the categories described in 18 U.S.C. 175b.

(h) An individual's access approval may be denied, limited, or revoked if:

(1) The individual is reasonably suspected by any Federal law enforcement or intelligence agency of committing a crime specified in 18 U.S.C. 2332b(g)(5), knowing involvement with an organization that engages in domestic or international terrorism (as defined in 18 U.S.C. 2331) or with any other organization that engages in intentional crimes of violence, or being an agent of a foreign power (as defined in 50 U.S.C. 1801), or

(2) It is determined such action is necessary to protect public health and safety.

(i) An individual may appeal the HHS Secretary's decision to deny, limit, or revoke access approval under § 73.20.

(j) Access approval is valid for a maximum of three years.

(k) The Responsible Official must immediately notify CDC or APHIS when an individual's access to select agents or toxins is terminated by the entity and the reasons therefore.

[70 FR 13316, Mar. 18, 2005, as amended at 77 FR 61112, Oct. 5, 2012; 82 FR 6293, Jan. 19, 2017]

§ 73.11 Security.

(a) An individual or entity required to register under this part must develop and implement a written security plan. The security plan must be sufficient to safeguard the select agent or toxin against unauthorized access, theft, loss, or release.

(b) The security plan must be designed according to a site-specific risk assessment and must provide graded protection in accordance with the risk of the select agent or toxin, given its intended use. A current security plan must be submitted for initial registration, renewal of registration, or when requested.

(c) The security plan must:

(1) Describe procedures for physical security, inventory control, and information systems control.

(2) Contain provisions for the control of access to select agents and toxins including the safeguarding of animals

(including arthropods) or plants intentionally or accidentally exposed to or infected with a select agent, against unauthorized access, theft, loss or release.

(3) Contain provisions for routine cleaning, maintenance, and repairs.

(4) Establish procedures for removing unauthorized or suspicious persons.

(5) Describe procedures for addressing loss or compromise of keys, keycards, passwords, combinations, etc. and protocols for changing access permissions or locks following staff changes.

(6) Contain procedures for reporting unauthorized or suspicious persons or activities, loss or theft of select agents or toxins, release of select agents or toxins, or alteration of inventory records, and

(7) Contain provisions for ensuring that all individuals with access approval from the HHS Secretary or Administrator understand and comply with the security procedures.

(8) Describe procedures for how the Responsible Official will be informed of suspicious activity that may be criminal in nature and related to the entity, its personnel, or its select agents or toxins; and describe procedures for how the entity will notify the appropriate Federal, State, or local law enforcement agencies of such activity.

(9) Contain provisions for information security that:

(i) Ensure that all external connections to systems which manage security for the registered space are isolated or have controls that permit only authorized and authenticated users;

(ii) Ensure that authorized and authenticated users are only granted access to select agent and toxin related information, files, equipment (*e.g.*, servers or mass storage devices) and applications as necessary to fulfill their roles and responsibilities, and that access is modified when the user's roles and responsibilities change or when their access to select agents and toxins is suspended or revoked;

(iii) Ensure that controls are in place that are designed to prevent malicious code (such as, but not limited to, computer virus, worms, spyware) from compromising the confidentiality, integrity, or availability of information systems which manage access to spaces

registered under this part or records in § 73.17;

(iv) Establish a robust configuration management practice for information systems to include regular patching and updates made to operating systems and individual applications; and

(v) Establish procedures that provide backup security measures in the event that access control systems, surveillance devices, and/or systems that manage the requirements of section 17 of this part are rendered inoperable.

(10) Contain provisions and policies for shipping, receiving, and storage of select agents and toxins, including documented procedures for receiving, monitoring, and shipping of all select agents and toxins. These provisions must provide that an entity will properly secure containers on site and have a written contingency plan for unexpected shipments.

(d) An individual or entity must adhere to the following security requirements or implement measures to achieve an equivalent or greater level of security:

(1) Allow access only to individuals with access approval from the HHS Secretary or Administrator,

(2) Allow individuals not approved for access from the HHS Secretary or Administrator to conduct routine cleaning, maintenance, repairs, or other activities not related to select agents or toxins only when continuously escorted by an approved individual if the potential for access to select agents or toxins exists,

(3) Provide for the control of select agents and toxins by requiring freezers, refrigerators, cabinets, and other containers where select agents or toxins are stored to be secured against unauthorized access (e.g., card access system, lock boxes),

(4) Inspect all suspicious packages before they are brought into or removed from the area where select agents or toxins are used or stored,

(5) Establish a protocol for intra-entity transfers under the supervision of an individual with access approval from the HHS Secretary or Administrator, including chain-of-custody documents and provisions for safeguarding against theft, loss, or release,

(6) Require that individuals with access approval from the HHS Secretary or Administrator refrain from sharing with any other person their unique means of accessing a select agent or toxin (e.g., keycards or passwords),

(7) Require that individuals with access approval from the HHS Secretary or Administrator immediately report any of the following to the Responsible Official:

(i) Any loss or compromise of keys, passwords, combination, etc.,

(ii) Any suspicious persons or activities,

(iii) Any loss or theft of select agents or toxins,

(iv) Any release of a select agent or toxin, and

(v) Any sign that inventory or use records for select agents or toxins have been altered or otherwise compromised, and

(vi) Any loss of computer, hard drive or other data storage device containing information that could be used to gain access to select agents or toxins.

(8) Separate areas where select agents and toxins are stored or used from the public areas of the building.

(e) Entities must conduct complete inventory audits of all affected select agents and toxins in long-term storage when any of the following occur:

(1) Upon the physical relocation of a collection or inventory of select agents or toxins for those select agents or toxins in the collection or inventory;

(2) Upon the departure or arrival of a principal investigator for those select agents and toxins under the control of that principal investigator; or

(3) In the event of a theft or loss of a select agent or toxin, all select agents and toxins under the control of that principal investigator.

(f) In addition to the requirements contained in paragraphs (c) and (d) of this section, the security plan for an individual or entity possessing a Tier I select agent or toxin must also:

(1) Describe procedures for conducting a pre-access suitability assessment of persons who will have access to a Tier I select agent or toxin;

(2) Describe procedures for how an entity's Responsible Official will coordinate their efforts with the entity's

safety and security professionals to ensure security of Tier 1 select agents and toxins and share, as appropriate, relevant information; and

(3) Describe procedures for the ongoing assessment of the suitability of personnel with access to a Tier 1 select agent or toxin. The procedures must include:

(i) Self- and peer-reporting of incidents or conditions that could affect an individual's ability to safely have access to or work with select agents and toxins, or to safeguard select agents and toxins from theft, loss, or release;

(ii) The training of employees with access to Tier 1 select agents and toxins on entity policies and procedures for reporting, evaluation, and corrective actions concerning the assessment of personnel suitability; and

(iii) The ongoing suitability monitoring of individuals with access to Tier 1 select agents and toxins.

(4) Entities with Tier 1 select agents and toxins must prescribe the following security enhancements:

(i) Procedures that will limit access to a Tier 1 select agent or toxin to only those individuals who are approved by the HHS Secretary or Administrator, following a security risk assessment by the Attorney General, have had an entity-conducted pre-access suitability assessment, and are subject to the entity's procedures for ongoing suitability assessment;

(ii) Procedures that limit access to laboratory and storage facilities outside of normal business hours to only those specifically approved by the Responsible Official or designee;

(iii) Procedures for allowing visitors, their property, and vehicles at the entry and exit points to the registered space, or at other designated points of entry to the building, facility, or compound that are based on the entity's site-specific risk assessment;

(iv) A minimum of three security barriers where each security barrier adds to the delay in reaching secured areas where select agents and toxins are used or stored. One of the security barriers must be monitored in such a way as to detect intentional and unintentional circumventing of established access control measures under all conditions (day/night, severe weather, etc.)

The final barrier must limit access to the select agent or toxin to personnel approved by the HHS Secretary or Administrator, following a security risk assessment by the Attorney General.

(v) All registered space or areas that reasonably afford access to the registered space must be protected by an intrusion detection system (IDS) unless physically occupied;

(vi) Personnel monitoring the IDS must be capable of evaluating and interpreting the alarm and alerting the designated security response force or law enforcement;

(vii) For powered access control systems, describe procedures to ensure that security is maintained in the event of the failure of access control systems due to power disruption affecting registered space;

(viii) The entity must:

(A) Determine that the response time for security forces or local police will not exceed 15 minutes where the response time is measured from the time of an intrusion alarm, or report of a security incident, to the arrival of the responders at the first security barrier or;

(B) Provide security barriers that are sufficient to delay unauthorized access until the response force arrives in order to safeguard the select agents and toxins from theft, intentional release, or unauthorized access. The response time is measured from the time of an intrusion alarm, or report of a security incident, to the arrival of the responders at the first security barrier.

(5) Entities that possess Variola major virus and Variola minor virus must have the following additional security requirements:

(i) Require personnel with independent unescorted access to Variola major or Variola minor virus to have a Top Secret security clearance;

(ii) Require Variola major or Variola minor virus storage locations to be under the surveillance of closed circuit television that is monitored;

(iii) After hours access procedures for Variola major or Variola minor virus must require notification of the entity's security staff prior to entry into the Variola laboratory and upon exit;

(iv) Require that observation zones be maintained in outdoor areas adjacent to the physical barrier at the perimeter of the entity and be large enough to permit observation of the activities of people at that barrier in the event of its penetration;

(v) Provide for a minimum of four barriers for the protection of the Variola major or Variola minor virus, one of which must be a perimeter fence;

(vi) Require a numbered picture badge identification subsystem to be used for all individuals who are authorized to access Variola major or Variola minor without escort;

(vii) Require the use, at all times, of properly trained and equipped security force personnel able to interdict threats identified in the site specific risk assessment;

(viii) Identify security force personnel designated to strengthen onsite response capabilities, and that will be onsite and available at all times to carry out their assigned response duties;

(ix) Provide for security patrols to periodically check external areas of the registered areas to include physical barriers and building entrances;

(x) Require that all on-duty security force personnel shall be capable of maintaining continuous communication with support and response assets by way of security operations center;

(xi) Require that Variola major and Variola minor material in long term storage be stored in tamper-evident systems;

(xii) Require that all spaces containing working or permanent Variola major or Variola minor stocks be locked and protected by an intrusion alarm system that will alarm upon the unauthorized entry of a person anywhere into the area;

(xiii) Require that alarms required pursuant to this section annunciate in a continuously manned security operations center located within the facility; and

(xiv) Require that the security operations center shall be located within a building so that the interior is not visible from the perimeter of the protected area.

(g) In developing a security plan, an individual or entity should consider the document entitled, "Security Guidance for Select Agent or Toxin Facilities." This document is available on the National Select Agent Registry at <http://www.selectagents.gov/>.

(h) The plan must be reviewed annually and revised as necessary. Drills or exercises must be conducted at least annually to test and evaluate the effectiveness of the plan. The plan must be reviewed and revised, as necessary, after any drill or exercise and after any incident. Drills or exercises must be documented to include how the drill or exercise tested and evaluated the plan, any problems that were identified and corrective action(s) taken, and the names of registered entity personnel participants.

[70 FR 13316, Mar. 18, 2005, as amended at 77 FR 61112, Oct. 5, 2012; 79 FR 26862, May 12, 2014; 82 FR 6293, Jan. 19, 2017]

§ 73.12 Biosafety.

(a) An individual or entity required to register under this part must develop and implement a written biosafety plan that is commensurate with the risk of the select agent or toxin, given its intended use. The biosafety plan must contain sufficient information and documentation to describe the biosafety and containment procedures for the select agent or toxin, including any animals (including arthropods) or plants intentionally or accidentally exposed to or infected with a select agent. The current biosafety plan must be submitted for initial registration, renewal of registration, or when requested. The biosafety plan must include the following provisions:

(1) The hazardous characteristics of each agent or toxin listed on the entity's registration and the biosafety risk associated with laboratory procedures related to the select agent or toxin;

(2) Safeguards in place with associated work practices to protect entity personnel, the public, and the environment from exposure to the select agent or toxin including, but not limited to: Personal protective equipment and other safety equipment; containment equipment including, but not limited to, biological safety cabinets, animal caging systems, and centrifuge safety

containers; and engineering controls and other facility safeguards;

(3) Written procedures for each validated method used for disinfection, decontamination or destruction, as appropriate, of all contaminated or presumptively contaminated materials including, but not limited to: Cultures and other materials related to the propagation of select agents or toxins, items related to the analysis of select agents and toxins, personal protective equipment, animal caging systems and bedding (if applicable), animal carcasses or extracted tissues and fluids (if applicable), laboratory surfaces and equipment, and effluent material; and

(4) Procedures for the handling of select agents and toxins in the same spaces with non-select agents and toxins to prevent unintentional contamination.

(b) The biosafety and containment procedures must be sufficient to contain the select agent or toxin (e.g., physical structure and features of the entity, and operational and procedural safeguards).

(c) In developing a biosafety plan, an individual or entity should consider:

(1) The CDC/NIH publication, “Biosafety in Microbiological and Biomedical Laboratories.” This document is available on the National Select Agent Registry Web site at <http://www.selectagents.gov>.

(2) The “NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules,” (NIH Guidelines). This document is available on the National Select Agent Registry Web site at <http://www.selectagents.gov>.

(d) The biosafety plan must include an occupational health program for individuals with access to Tier 1 select agents and toxins, and those individuals must be enrolled in the occupational health program.

(e) The plan must be reviewed annually and revised as necessary. Drills or exercises must be conducted at least annually to test and evaluate the effectiveness of the plan. The plan must be reviewed and revised, as necessary, after any drill or exercise and after any incident. Drills or exercises must be documented to include how the drill or exercise tested and evaluated the plan, any problems that were identified and

corrective action(s) taken, and the names of registered entity personnel participants.

[70 FR 13316, Mar. 18, 2005, as amended at 77 FR 61114, Oct. 5, 2012; 82 FR 6293, Jan. 19, 2017]

§ 73.13 Restricted experiments.

(a) An individual or entity may not conduct, or possess products resulting from, the following experiments unless approved by and conducted in accordance with the conditions prescribed by the HHS Secretary:

(1) Experiments that involve the deliberate transfer of, or selection for, a drug resistance trait to select agents that are not known to acquire the trait naturally, if such acquisition could compromise the control of disease agents in humans, veterinary medicine, or agriculture.

(2) Experiments involving the deliberate formation of synthetic or recombinant DNA containing genes for the biosynthesis of select toxins lethal for vertebrates at an LD[50] <100 ng/kg body weight.

(b) The HHS Secretary may revoke approval to conduct any of the experiments in paragraph (a) of this section, or revoke or suspend a certificate of registration, if the individual or entity fails to comply with the requirements of this part.

(c) To apply for approval to conduct any of the experiments in paragraph (a) of this section, an individual or entity must submit a written request and supporting scientific information. A written decision granting or denying the request will be issued.

[70 FR 13316, Mar. 18, 2005, as amended at 77 FR 61114, Oct. 5, 2012; 79 FR 26862, May 12, 2014]

§ 73.14 Incident response.

(a) An individual or entity required to register under this part must develop and implement a written incident response plan based upon a site specific risk assessment.² The incident response plan must be coordinated with any entity-wide plans, kept in the

²Nothing in this section is meant to supersede or preempt incident response requirements imposed by other statutes or regulations.

workplace, and available to employees for review. The current incident response plan must be submitted for initial registration, renewal of registration, or when requested.

(b) The incident response plan must fully describe the entity's response procedures for the theft, loss, or release of a select agent or toxin; inventory discrepancies; security breaches (including information systems); severe weather and other natural disasters; workplace violence; bomb threats and suspicious packages; and emergencies such as fire, gas leak, explosion, power outage, and other natural and man-made events.

(c) The response procedures must account for hazards associated with the select agent or toxin and appropriate actions to contain such select agent or toxin, including any animals (including arthropods) or plants intentionally or accidentally exposed to or infected with a select agent.

(d) The incident response plan must also contain the following information:

(1) The name and contact information (e.g., home and work) for the individual or entity (e.g., responsible official, alternate responsible official(s), biosafety officer, etc.),

(2) The name and contact information for the building owner and/or manager, where applicable,

(3) The name and contact information for tenant offices, where applicable,

(4) The name and contact information for the physical security official for the building, where applicable,

(5) Personnel roles and lines of authority and communication,

(6) Planning and coordination with local emergency responders,

(7) Procedures to be followed by employees performing rescue or medical duties,

(8) Emergency medical treatment and first aid,

(9) A list of personal protective and emergency equipment, and their locations,

(10) Site security and control,

(11) Procedures for emergency evacuation, including type of evacuation, exit route assignments, safe distances, and places of refuge, and

(12) Decontamination procedures.

(e) Entities with Tier 1 select agents and toxins must have the following additional incident response policies or procedures:

(1) The incident response plan must fully describe the entity's response procedures for failure of intrusion detection or alarm system; and

(2) The incident response plan must describe procedures for how the entity will notify the appropriate Federal, State, or local law enforcement agencies of suspicious activity that may be criminal in nature and related to the entity, its personnel, or its select agents or toxins.

(f) The plan must be reviewed annually and revised as necessary. Drills or exercises must be conducted at least annually to test and evaluate the effectiveness of the plan. The plan must be reviewed and revised, as necessary, after any drill or exercise and after any incident. Drills or exercises must be documented to include how the drill or exercise tested and evaluated the plan, any problems that were identified and corrective action(s) taken, and the names of registered entity personnel participants.

[70 FR 13316, Mar. 18, 2005, as amended at 77 FR 61114, Oct. 5, 2012; 82 FR 6293, Jan. 19, 2017]

§ 73.15 Training.

(a) An individual or entity required to register under this part must provide information and training on biocontainment, biosafety, security (including security awareness), and incident response to:

(1) Each individual with access approval from the HHS Secretary or Administrator. The training must address the particular needs of the individual, the work they will do, and the risks posed by the select agents or toxins. The training must be accomplished prior to the individual's entry into an area where a select agent is handled or stored, or within 12 months of the date the individual was approved by the HHS Secretary or the Administrator for access, whichever is earlier.

(2) Each individual not approved for access to select agents and toxins by the HHS Secretary or Administrator before that individual enters areas under escort where select agents or

toxins are handled or stored (*e.g.*, laboratories, growth chambers, animal rooms, greenhouses, storage areas, shipping/receiving areas, production facilities, etc.). Training for escorted personnel must be based on the risk associated with accessing areas where select agents and toxins are used and/or stored. The training must be accomplished prior to the individual's entry into where select agents or toxins are handled or stored (*e.g.*, laboratories, growth chambers, animal rooms, greenhouses, storage areas, shipping/receiving areas, production facilities, etc.).

(b) Entities with Tier 1 select agents and toxins must conduct annual insider threat awareness briefings on how to identify and report suspicious behaviors.

(c) Refresher training must be provided annually for individuals with access approval from the HHS Secretary or Administrator or at such time as the registered individual or entity significantly amends its security, incident response, or biosafety plans.

(d) The Responsible Official must ensure a record of the training provided to each individual with access to select agents and toxins and each escorted individual (*e.g.*, laboratory workers, visitors, etc.) is maintained. The record must include the name of the individual, the date of the training, a description of the training provided, and the means used to verify that the employee understood the training.

(e) The Responsible Official must ensure and document that individuals are provided the contact information of the HHS Office of Inspector General Hotline and the USDA Office of Inspector General Hotline so that they may anonymously report any safety or security concerns related to select agents and toxins.

[77 FR 61114, Oct. 5, 2012, as amended at 82 FR 6293, Jan. 19, 2017]

§ 73.16 Transfers.

(a) Except as provided in paragraphs (c) and (d) of this section, a select agent or toxin may only be transferred to individuals or entities registered to possess, use, or transfer that agent or toxin. A select agent or toxin may only be transferred under the conditions of

this section and must be authorized by CDC or APHIS prior to the transfer.⁴

(b) A transfer may be authorized if:

(1) The sender:

(i) Has at the time of transfer a certificate of registration that covers the particular select agent or toxin to be transferred and meets all requirements in this part,

(ii) Meets the exemption requirements for the particular select agent or toxin to be transferred, or

(iii) Is transferring the select agent or toxin from outside the United States and meets all import requirements.

(2) At the time of transfer, the recipient has a certificate of registration that includes the particular select agent or toxin to be transferred and meets all of the requirements of this part.

(c) A select agent or toxin that is contained in a specimen for proficiency testing may be transferred without prior authorization from CDC or APHIS provided that, at least seven calendar days prior to the transfer, the sender reports to CDC or APHIS the select agent or toxin to be transferred and the name and address of the recipient.

(d) On a case-by-case basis, the HHS Secretary may authorize a transfer of a select agent or toxin, not otherwise eligible for transfer under this part under conditions prescribed by the HHS Secretary.

(e) To obtain authorization for transfer, APHIS/CDC Form 2 must be submitted.

(f) After authorization is provided by APHIS or CDC, the packaging of the select agent(s) and toxin(s) is performed by an individual approved by the HHS Secretary or Administrator to have access to select agents and toxins and is in compliance with all applicable laws concerning packaging.

(g) The sender must comply with all applicable laws governing packaging and shipping.

(h) Transportation in commerce starts when the select agent(s) or toxin(s) are packaged for shipment and

⁴This section does not cover transfers within an entity when the sender and the recipient are covered by the same certificate of registration.

ready for receipt by a courier transporting select agent(s) or toxin(s) and ends when the package is received by the intended recipient who is an individual approved by the HHS Secretary or Administrator to have access to select agents and toxins, following a security risk assessment by the Attorney General.

(i) The recipient must submit a completed APHIS/CDC Form 2 within two business days of receipt of a select agent or toxin.

(j) The recipient must immediately notify CDC or APHIS if the select agent or toxin has not been received within 48 hours after the expected delivery time, or if the package containing select agents or toxins has been damaged to the extent that a release of the select agent or toxin may have occurred.

(k) An authorization for a transfer shall be valid only for 30 calendar days after issuance, except that such an authorization becomes immediately null and void if any facts supporting the authorization change (e.g., change in the certificate of registration for the sender or recipient, change in the application for transfer).

(l) A registered individual or entity transferring an amount of a HHS toxin otherwise excluded under the provisions of § 73.3(d) must:

(1) Transfer the amounts only after the transferor uses due diligence and documents that the recipient has a legitimate need (e.g., prophylactic, protective, bona fide research, or other peaceful purpose) to handle or use such toxins. Information to be documented includes, but is not limited, to the recipient information, toxin and amount transferred, and declaration that the recipient has legitimate purpose to store and use such toxins.

(2) Report to CDC if they detect a known or suspected violation of Federal law or become aware of suspicious activity related to a toxin listed in § 73.3(d) of this part.

[70 FR 13316, Mar. 18, 2005, as amended at 77 FR 61115, Oct. 5, 2012; 79 FR 26862, May 12, 2014; 82 FR 6294, Jan. 19, 2017]

§ 73.17 Records.

(a) An individual or entity required to register under this part must main-

tain complete records relating to the activities covered by this part. Such records must include:

(1) An accurate, current inventory for each select agent (including viral genetic elements, recombinant and/or synthetic nucleic acids, and organisms containing recombinant and/or synthetic nucleic acids) held in long-term storage (placement in a system designed to ensure viability for future use, such as in a freezer or lyophilized materials), including:

(i) The name and characteristics (e.g., strain designation, GenBank Accession number, etc.),

(ii) The quantity acquired from another individual or entity (e.g., containers, vials, tubes, etc.), date of acquisition, and the source,

(iii) Where stored (e.g., building, room, and freezer or other storage container),

(iv) When moved from storage and by whom and when returned to storage and by whom,

(v) The select agent used, purpose of use, and, when applicable, final disposition,

(vi) Records created under § 73.16 and 9 CFR 121.16 (Transfers),

(vii) For intra-entity transfers (sender and the recipient are covered by the same certificate of registration), the select agent, the quantity transferred, the date of transfer, the sender, and the recipient, and

(viii) Records created under § 73.19 and 9 CFR part 121.19 (Notification of theft, loss, or release).

(2) An accurate, current accounting of any animals or plants intentionally or accidentally exposed to or infected with a select agent (including number and species, location, and appropriate disposition);

(3) Accurate, current inventory for each toxin held, including:

(i) The name and characteristics,

(ii) The quantity acquired from another individual or entity (e.g., containers, vials, tubes, etc.), date of acquisition, and the source,

(iii) The initial and current quantity amount (e.g., milligrams, milliliters, grams, etc.),

(iv) The toxin used and purpose of use, quantity, date(s) of the use and by whom,

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(v) Where stored (e.g., building, room, and freezer or other storage container),

(vi) When moved from storage and by whom and when returned to storage and by whom including quantity amount,

(vii) Records created under § 73.16 and 9 CFR part 121.16 (Transfers),

(viii) For intra-entity transfers (sender and the recipient are covered by the same certificate of registration), the toxin, the quantity transferred, the date of transfer, the sender, and the recipient,

(ix) Records created under § 73.19 and 9 CFR part 121.19 (Notification of theft, loss, or release), and

(x) If destroyed, the quantity of toxin destroyed, the date of such action, and by whom,

(4) A current list of all individuals that have been granted access approval from the HHS Secretary or Administrator,

(5) Information about all entries into areas containing select agents or toxins, including the name of the individual, name of the escort (if applicable), and date and time of entry,

(6) Accurate, current records created under § 73.9 and 9 CFR part 121.9 (Responsible Official), § 73.11 and 9 CFR part 121.11 (Security), § 73.12 and 9 CFR part 121.12 (Biosafety), § 73.14 and 9 CFR part 121.14 (Incident response), and § 73.15 and 9 CFR part 121.15 (Training), and

(7) A written explanation of any discrepancies.

(8) For select agents or material containing select agents or regulated nucleic acids that can produce infectious forms of any select agent virus that have been subjected to a validated inactivation procedure or a procedure for removal of viable select agent:

(i) A written description of the validated inactivation procedure or viable select agent removal method used, including validation data;

(ii) A written description of the viability testing protocol used;

(iii) A written description of the investigation conducted by the entity Responsible Official involving an inactivation or viable select agent removal failure and the corrective actions taken;

(iv) The name of each individual performing the validated inactivation or viable select agent removal method;

(v) The date(s) the validated inactivation or viable select agent removal method was completed;

(vi) The location where the validated inactivation or viable select agent removal method was performed; and

(vii) A certificate, signed by the Principal Investigator, that includes the date of inactivation or viable select agent removal, the validated inactivation or viable select agent removal method used, and the name of the Principal Investigator. A copy of the certificate must accompany any transfer of inactivated or select agent removed material.

(b) The individual or entity must implement a system to ensure that all records and data bases created under this part are accurate and legible, have controlled access, and authenticity may be verified.

(c) The individual or entity must promptly produce upon request any information that is related to the requirements of this part but is not otherwise contained in a record required to be kept by this section. The location of such information may include, but is not limited to, biocontainment certifications, laboratory notebooks, institutional biosafety and/or animal use committee minutes and approved protocols, and records associated with occupational health and suitability programs. All records created under this part must be maintained for 3 years.

[70 FR 13316, Mar. 18, 2005, as amended at 77 FR 61115, Oct. 5, 2012; 82 FR 6294, Jan. 19, 2017]

§ 73.18 Inspections.

(a) Without prior notification, the HHS Secretary, shall be allowed to inspect any site at which activities regulated by this part are conducted and shall be allowed to inspect and copy any records relating to the activities covered by this part.

(b) Prior to issuing a certificate of registration to an individual or entity, the HHS Secretary may inspect and evaluate the premises and records to ensure compliance with this part.

§ 73.19 Notification of theft, loss, or release.

(a) Upon discovery of the theft or loss of a select agent or toxin, an individual or entity must immediately notify CDC or APHIS and appropriate Federal, State, or local law enforcement agencies. Thefts or losses must be reported even if the select agent or toxin is subsequently recovered or the responsible parties are identified.

(1) The theft or loss of a select agent or toxin must be reported immediately by telephone, facsimile, or e-mail. The following information must be provided:

(i) The name of the select agent or toxin and any identifying information (e.g., strain or other characterization information),

(ii) An estimate of the quantity lost or stolen,

(iii) An estimate of the time during which the theft or loss occurred,

(iv) The location (building, room) from which the theft or loss occurred, and

(v) The list of Federal, State, or local law enforcement agencies to which the individual or entity reported, or intends to report the theft or loss.

(2) A completed APHIS/CDC Form 3 must be submitted within seven calendar days.

(b) Upon discovery of a release of an agent or toxin causing occupational exposure or release of a select agent or toxin outside of the primary barriers of the biocontainment area, an individual or entity must immediately notify CDC or APHIS.

(1) The release of a select agent or toxin must be reported by telephone, facsimile, or e-mail. The following information must be provided:

(i) The name of the select agent or toxin and any identifying information (e.g., strain or other characterization information),

(ii) An estimate of the quantity released,

(iii) The time and duration of the release,

(iv) The environment into which the release occurred (e.g., in building or outside of building, waste system),

(v) The location (building, room) from which the release occurred,

(vi) The number of individuals potentially exposed at the entity,

(vii) Actions taken to respond to the release, and

(viii) Hazards posed by the release.

(2) A completed APHIS/CDC Form 3 must be submitted within seven calendar days.

§ 73.20 Administrative review.

(a) An individual or entity may appeal a denial, revocation, or suspension of registration under this part. The appeal must be in writing, state the factual basis for the appeal, and be submitted to the HHS Secretary within 30 calendar days of the decision.

(b) An individual may appeal a denial, limitation, or revocation of access approval under this part. The appeal must be in writing, state the factual basis for the appeal, and be submitted to the HHS Secretary within 180 calendar days of the decision.

(c) The HHS Secretary's decision constitutes final agency action.

[77 FR 61115, Oct. 5, 2012]

§ 73.21 Civil money penalties.

(a) The Inspector General of the Department of Health and Human Services is delegated authority to conduct investigations and to impose civil money penalties against any individual or entity in accordance with regulations in 42 CFR part 1003 for violations of the regulations in this part, as authorized by the Public Health Security and Bioterrorism Preparedness and Response Act of 2002 (Pub. L. 107-188). The delegation of authority includes all powers contained in section 6 of the Inspector General Act of 1978 (5 U.S.C. App.).

(b) The administrative law judges in, assigned to, or detailed to the Departmental Appeals Board have been delegated authority to conduct hearings and to render decisions in accordance with 42 CFR part 1005 with respect to the imposition of civil money penalties, as authorized by the Public Health Security and Bioterrorism Preparedness and Response Act of 2002 (Pub. L. 107-188). This delegation includes, but is not limited to, the authority to administer oaths and affirmations, to subpoena witnesses and documents, to examine witnesses, to

exclude or receive and give appropriate weight to materials and testimony offered as evidence, to make findings of fact and conclusions of law, and to determine the civil money penalties to be imposed.

(c) The Departmental Appeals Board of the Department of Health and Human Services is delegated authority to make final determinations with respect to the imposition of civil money penalties for violations of the regulations of this part.

PART 75—STANDARDS FOR THE ACCREDITATION OF EDUCATIONAL PROGRAMS FOR AND THE CREDENTIALING OF RADIOLOGIC PERSONNEL

Sec.

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APPENDIX G TO PART 75—STANDARDS FOR LICENSING DENTAL HYGIENISTS AND DENTAL ASSISTANTS IN DENTAL RADIOGRAPHY

AUTHORITY: Sec. 979 of the Consumer-Patient Radiation Health and Safety Act of 1981, Pub. L. 97-35, 95 Stat. 599-600 (42 U.S.C. 10004).

SOURCE: 50 FR 50717, Dec. 11, 1985, unless otherwise noted.

§75.1 Background and purpose.

(a) The purpose of these regulations is to implement the provisions of section 979 of the Consumer-Patient Radiation Health and Safety Act of 1981, 42 U.S.C. 10004, which requires the establishment by the Secretary of Health and Human Services of standards for

the accreditation of programs for the education of certain persons who administer radiologic procedures and for the credentialing of such persons.

(b) Section 979 requires the Secretary, after consultation with specified Federal agencies, appropriate agencies of States, and appropriate professional organizations, to promulgate by regulation the minimum standards described above. These standards distinguish between the occupations of (1) radiographer, (2) dental hygienist, (3) dental assistant, (4) nuclear medicine technologist, and (5) radiation therapy technologist. In the interest of public safety and to prevent the hazards of improper use of medical radiation identified by Congress in its determination of the need for standards, the Secretary is also authorized to prepare standards for other occupational groups utilizing ionizing and non-ionizing radiation as he/she finds appropriate. However, the standards set out below are limited to the five occupational groups listed above, utilizing ionizing radiation. Nothing in these accreditation standards is intended to discriminate against proprietary schools.

§75.2 Definitions.

All terms not defined herein shall have the meaning given them in the Act. As used in this part:

Accreditation, as applied to an educational program, means recognition, by a State government or by a nongovernmental agency or association, of a specialized program of study as meeting or exceeding certain established qualifications and educational standards. As applied to a health care or educational institution, *accreditation* means recognition, by a State government or by a nongovernmental agency or association, of the institution as meeting or exceeding certain established standards or criteria for that type of institution.

Act means the Consumer-Patient Radiation Health and Safety Act of 1981, 42 U.S.C. 10001-10008.

Continuing competency means the maintenance of knowledge and skills and/or demonstrated performance that are adequate and relevant to professional practice needs.