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August 2016

HIGH-CONTAINMENT LABORATORIES

Improved Oversight of Dangerous Pathogens Needed to Mitigate Risk

GAO-16-642

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GAO Highlights

Highlights of GAO-16-642, a report to congressional committees

Why GAO Did This Study

Several incidents involving the shipment of live pathogens, thought to be inactivated, have recently occurred, potentially exposing people to dangerous pathogens that cause infectious diseases, such as the bacterium that causes anthrax.

GAO was asked to evaluate issues related to inactivation of pathogens in high-containment laboratories. This report examines (1) the extent to which incidents involving incomplete inactivation occurred from 2003 through 2015, (2) any challenges that may affect the implementation of inactivation in high-containment laboratories, and (3) the extent to which the Select Agent Program referred violations and enforced regulations related to incidents involving incomplete inactivation. GAO convened an expert meeting with the assistance of the National Academy of Sciences to discuss various issues surrounding inactivation. GAO also reviewed relevant laws, regulations, and guidance, and interviewed officials at laboratories that conduct inactivation.

What GAO Recommends

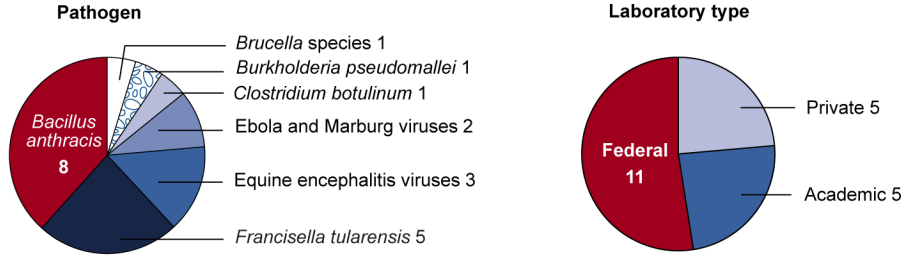
GAO is making six recommendations to HHS and USDA to, among other things, improve the Select Agent Program's oversight of inactivation by revising reporting forms, improving guidance for development and validation of inactivation protocols, and developing consistent criteria for enforcement of incidents involving incomplete inactivation. HHS and USDA agreed with GAO's recommendations.

View GAO-16-642. For more information, contact Timothy M. Persons, Ph.D. at (202) 512-6412 or personst@gao.gov or John Neumann at (202) 512-3841 or neumannj@gao.gov.

What GAO Found

The total number of incidents involving incomplete inactivation—a process to destroy the hazardous effects of pathogens while retaining characteristics for future use—that occurred from 2003 through 2015 is unknown for several reasons. One key reason is that the Select Agent Program—operated by the Departments of Health and Human Services (HHS) and Agriculture (USDA) to oversee certain dangerous pathogens, known as select agents—does not require laboratories to identify such incidents on reporting forms. According to the program, 10 incidents occurred from 2003 through 2015. However, GAO identified an additional 11 incidents that the program did not initially identify. Because the program cannot easily identify incidents involving incomplete inactivation, it does not know the frequency or reason they occur, making it difficult to develop guidance to help mitigate future incidents. The 21 identified incidents involved a variety of pathogens and laboratories, as shown below.

Figure: Twenty-one Identified Incidents Involving Incomplete Inactivation that Occurred from 2003 through 2015 by Pathogen and Laboratory Type



Source: GAO analysis of information from the Federal Select Agent Program. | GAO-16-642

Several challenges affect the implementation of inactivation in high-containment laboratories, including gaps in scientific knowledge and limited guidance. For example, there is limited federal guidance for researchers on the development and validation of inactivation protocols. Validation helps ensure protocols are scientifically sound and produce consistent results. Due to limited guidance, laboratories varied in their interpretation of validated methods of inactivation, resulting in researchers applying differing levels of rigor. Without more comprehensive guidance, as called for by experts, protocols will vary in their scientific soundness, increasing the risk of incomplete inactivation.

The Select Agent Program did not consistently refer incidents involving incomplete inactivation for further investigation and enforcement for violations of select agent regulations. For example, the program referred incidents involving incomplete inactivation at various laboratories, but did not refer two incidents in 2014 that occurred at HHS. A memorandum of understanding between HHS and USDA states that the program should handle incidents consistently. GAO found, however, that the program does not have a consistent, written set of criteria for handling incidents. Without such criteria, the program risks inconsistent enforcement of select agent regulations. This further highlights GAO's previous finding that existing federal oversight of high-containment laboratories is fragmented and self-policing.

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Abbreviations

APHIS	Animal and Plant Health Inspection Service
BMBL	*Biosafety in Microbiological and Biomedical Laboratories*
BSL	biological safety level
CDC	Centers for Disease Control and Prevention
DOD	Department of Defense
EEE	Eastern equine encephalitis
EPA	Environmental Protection Agency
FBI	Federal Bureau of Investigation
HHS	Department of Health and Human Services
NAS	National Academy of Sciences
NIH	National Institutes of Health
OIG	Office of Inspector General
SARS	severe acute respiratory syndrome
USDA	United States Department of Agriculture
VEE	Venezuelan equine encephalitis

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August 30, 2016

The Honorable Fred Upton
Chairman
The Honorable Frank Pallone, Jr.
Ranking Member
Committee on Energy and Commerce
House of Representatives

The Honorable Tim Murphy
Chairman
The Honorable Diana DeGette
Ranking Member
Subcommittee on Oversight and Investigations
Committee on Energy and Commerce
House of Representatives

In May 2015, the Department of Defense (DOD) discovered that one of its laboratories inadvertently sent live *Bacillus anthracis*, the bacterium that causes anthrax, to almost 200 laboratories worldwide over the course of 12 years. The laboratory believed that the samples had been inactivated, that is, the hazardous effects of the pathogen had been destroyed while retaining characteristics of interest for future use.[1] In this case, DOD was inactivating samples to support research on the detection, identification, and characterization of biological threats. Similar incidents have occurred in other countries, including China, where two researchers conducting virus research were exposed to severe acute respiratory syndrome (SARS) coronavirus samples that were incompletely inactivated. The researchers subsequently transmitted SARS to others, leading to several infections and one death in 2004.[2] Researchers in high-containment laboratories may inactivate pathogens for a variety of reasons, such as to develop vaccines or to perform diagnostic testing or other research in a

[1]For the purpose of this report, we focused on inactivation as a process used in laboratories to render pathogens unable to cause disease but retain characteristics of interest for future use, such as for vaccine development.

[2]W. Liang, T. Zhao, Z. Liu, B. Guan, X. He, M. Liu, Q. Chen, G. Liu, J. Wu, R. Huang, X. Xie, and Z. Wu, "Severe Acute Respiratory Syndrome-Retrospect and Lessons of 2004 Outbreak in China," *Biomedical and Environmental Sciences*, 19, (2006): 445-451.

lower safety-level laboratory. Several incidents involving incomplete inactivation have occurred in the United States in recent years, potentially exposing people to dangerous pathogens that can cause infectious diseases.[3]

Federal agencies, universities, private companies, and others operate high-containment laboratories to conduct research on dangerous pathogens, including developing measures to protect public and animal health.[4] Research is conducted on a variety of pathogens in high-containment laboratories, including pathogens classified as select agents. Select agents include specific pathogens such as bacteria, viruses, and toxins that have the potential to pose a severe threat to human, animal, or plant health and safety, or to animal or plant products.[5] The Federal Select Agent Program (Select Agent Program) regulates the possession, use, and transfer of select agents and is comprised of the Department of Health and Human Services' (HHS) Centers for Disease Control and Prevention (CDC) Division of Select Agents and Toxins and the United States Department of Agriculture's (USDA) Animal and Plant Health Inspection Service (APHIS) Agriculture Select Agent Services. In addition, the National Institutes of Health (NIH) conducts oversight and provides guidelines for pathogens that contain recombinant or synthetic nucleic

[3]For the purpose of this report, incidents involving incomplete inactivation include incidents in which researchers had intended to inactivate samples before removing them from containment but failed to do so due to an issue with the inactivation method, a mix-up of samples, or another unforeseen event.

[4]Laboratories that handle pathogens are classified into four biological safety levels (BSL) based on the risk imposed by the pathogens. Laboratories classified as BSL-1 or 2 are suitable for work involving pathogens that pose minimal to moderate hazard to laboratory personnel and the environment whereas high-containment laboratories—BSL-3 and 4 for the purpose of this report—are designed with additional safety measures to protect those working with dangerous pathogens that may cause serious and potentially lethal infection. Each level of containment describes the laboratory practices, safety equipment, and facility safeguards for the level of risk associated with handling particular pathogens. BSL-3 laboratories work with indigenous or exotic pathogens with known potential for airborne transmission or those pathogens that may cause serious and potentially lethal infections. BSL-4 laboratories work with exotic pathogens that pose a high individual risk of life-threatening disease by airborne transmission and for which treatment may not be available.

[5]As of August 2016, 65 select agents or toxins have been determined to have the potential to pose a severe threat to human, animal, or plant health and safety, or to animal or plant products. For the purpose of this report, the term "select agents" encompasses both select agents and toxins and the term "nonviable" refers to the rendering of select agents nonviable and toxins nonfunctional.

acid molecules.[6] For the purpose of this report, "recombinant pathogens" refers to pathogens that contain molecules that are constructed by joining different nucleic acid molecules together (recombinant) or completely new nucleic acid molecules (synthetic). Researchers routinely generate pathogens containing recombinant or synthetic nucleic acid molecules for a variety of purposes, including the creation of vaccines using recombinant material.

A number of concerns have been raised in recent years surrounding the biological safety and security of pathogens in high-containment laboratories. For example, we previously reported on steps the CDC and other agencies have taken to address issues identified by reviews of past safety incidents.[7] Additionally, we reported on issues related to oversight of high-containment laboratories, finding that laboratories that do not work with select agents are subject to limited federal oversight and that existing oversight of high-containment laboratories is duplicative, fragmented, and relies on self-policing.[8] We have also reported on issues associated with the proliferation of high-containment laboratories in the United States,

[6]Department of Health and Human Services, National Institutes of Health, *NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules* (Bethesda, Md.: April 2016). NIH defines recombinant or synthetic nucleic acid molecules as either (1) molecules that are constructed by joining nucleic acid molecules and can replicate in a living cell, or (2) nucleic acid molecules that are synthesized chemically or by other means.

[7]See, for example, GAO, *High-Containment Laboratories: Comprehensive and Up-to-Date Policies and Stronger Oversight Mechanisms Needed to Improve Safety*, GAO-16-305 (Washington, D.C.: Mar. 21, 2016), *High-Containment Laboratories: Preliminary Observations on Federal Efforts to Address Weaknesses Exposed by Recent Safety Lapses*, GAO-15-792T (Washington, D.C.: July 28, 2015), and *High-Containment Laboratories: Recent Incidents of Biosafety Lapses*, GAO-14-785T (Washington, D.C.: July 16, 2014).

[8]GAO, *Overlap and Duplication: Federal Inspections of Entities Registered with the Select Agent Program*, GAO-13-154 (Washington, D.C.: Jan. 31, 2013); *High-Containment Laboratories: National Strategy for Oversight is Needed*, GAO-09-574 (Washington, D.C.: Sept. 21, 2009); and *High-Containment Biosafety Laboratories: Preliminary Observations on the Oversight of the Proliferation of BSL-3 and BSL-4 Laboratories in the United States*, GAO-08-108T (Washington, D.C.: Oct. 4, 2007). In October 2015, a White House report highlighted the need for a transparent U.S. laboratory system. If carried out, recommendations made in that report may, in part, effectively implement some of our past recommendations related to the oversight of high-containment laboratories. We did not examine the status of efforts to implement the White House's recommendations in this review. The White House, *Next Steps to Enhance Biosafety and Biosecurity in the United States* (Washington, D.C.: Oct. 29, 2015).

including risks posed by past biological safety incidents.[9] We have made numerous recommendations, including recommending in 2016 that agencies update policies related to the management of high-containment laboratories and report incidents to senior officials.[10] Agencies have made progress in implementing many of our recommendations but the United States is still without a national strategy and does not have a single entity charged with overseeing the implementation of such a strategy to identify the aggregate risks associated with the expansion of high-containment laboratories and the type of oversight needed. In addition, the National Academy of Sciences, the White House, and federal committees and task forces have raised concerns about biological safety and security, including the management and extent of independent oversight over high-containment laboratories.

In this context, you asked us to evaluate issues related to the inactivation of pathogens in high-containment laboratories. In this report, we evaluated (1) the extent to which incidents involving incomplete inactivation occurred from 2003 through 2015; (2) any challenges that may affect the implementation of inactivation in high-containment laboratories; and (3) the extent to which the Select Agent Program referred violations and enforced regulations related to incidents involving incomplete inactivation.

To conduct this work, we reviewed relevant laws, regulations, and guidance, including guidance issued by the Select Agent Program. We also reviewed relevant documentation and interviewed officials from the federal departments that own and operate high-containment laboratories, as well as officials from some academic and private high-containment

[9]GAO-09-574 and GAO-08-108T.

[10]GAO-16-305.

laboratories.[11] We convened, with the assistance of the National Academy of Sciences (NAS), a meeting with 19 experts to discuss issues related to the inactivation of pathogens in high-containment laboratories. These experts represented academia, the federal government, and industry, and had combined expertise in pathogen and toxin inactivation and control, biological safety, risk assessment, legal requirements, standards development, incident reporting, epidemiology, and statistics.

To evaluate the extent to which incidents involving incomplete inactivation occurred, we analyzed documentation on incidents reported to the CDC, APHIS, and NIH since 2003—when the Select Agent Program began requiring reporting of the theft, loss, and release of select agents—through 2015—the most recent year for which data were available. We took several steps to determine the reliability of the agencies' incident databases, including reviewing agency documents and interviewing agency officials. We determined that the Select Agent Program incident database did not capture some incidents involving incomplete inactivation and was therefore not reliable on its own for establishing the number of incidents, as further discussed in the report. We verified through interviews and documentation each incident identified in the Select Agent Program database as well as additional incidents that we identified. We conducted site visits for 7 of 10 high-containment laboratories and interviewed officials from 8 of the 10 high-containment laboratories that the Select Agent Program originally reported to us as having incidents involving incomplete inactivation.[12] We also interviewed officials from a nongeneralizable sample of 19 high-containment laboratories selected to

[11]The federal departments and their component agencies were the Department of Homeland Security; DOD and its departments of the Army, Navy, and Air Force; Department of Energy and its National Nuclear Security Administration and Office of Science; Department of the Interior and its Fish and Wildlife Service and U.S. Geological Survey; Department of Veterans Affairs and its Veterans Health Administration; HHS and its components of CDC, Food and Drug Administration, and NIH; USDA and its APHIS, Agricultural Research Service, and Food Safety and Inspection Service; and the Environmental Protection Agency (EPA). According to officials from the Department of Veterans Affairs, Interior's Fish and Wildlife Service, and EPA, inactivation is not conducted in any of their high-containment laboratories so we excluded them from our additional work. In addition, the Department of Energy's Office of Science has not operated a high-containment laboratory since 2006 so we also excluded it from our work.

[12]We contacted officials from all 10 high-containment laboratories at which incidents involving incomplete inactivation were originally reported to us by the Select Agent Program to arrange interviews; however, officials from one university and one private laboratory declined to be interviewed.

represent a range of laboratories that work with human and animal pathogens and biological safety levels that had not reported incidents.[13] We compared information learned from interviews with laboratory and agency officials and from federal documents about the definition of inactivation and incidents involving incomplete inactivation with comments from our expert meeting, guidance, and our past work.

To identify challenges that potentially affected the implementation of inactivation in high-containment laboratories, we reviewed relevant documents, such as biological safety manuals, laboratory newsletters, and articles from peer-reviewed literature. We also discussed challenges that exist and safeguards applied to address these challenges in our interviews with agency officials and researchers from high-containment laboratories and during our expert meeting. We compared information from our interviews with that of officials and our review of federal documents on the development and validation of inactivation protocols and application of safeguards with key reports related to biological safety, expert comments, and our past work. We also compared information from our interviews with laboratory officials and our review of related documents on the shipment of inactivated material with expert comments and internal controls from *Standards for Internal Control in the Federal Government*.[14]

To determine how the Select Agent Program referred violations and enforced regulations related to incidents involving incomplete inactivation in high-containment laboratories, we reviewed guidance, inspection reports, and other documents from the Select Agent Program. In our interviews with laboratory and Select Agent Program officials, we discussed steps the Select Agent Program has taken to refer violations and enforce regulations related to incidents involving incomplete inactivation. We compared information we learned from our interviews with Select Agent Program officials and our review of program documents on the enforcement of the select agent regulations with agency guidance on the program and internal controls from *Standards for Internal Control*

[13]The views of these officials are not generalizable to all laboratories, but they provide illustrative examples.

[14]GAO, *Standards for Internal Control in the Federal Government*, GAO/AIMD-00-21.3.1 (Washington, D.C.: November 1999). GAO has revised and reissued *Standards for Internal Control in the Federal Government*, with the new revision effective as of October 1, 2015. GAO-14-704G (Washington, D.C.: September 2014).

in the Federal Government.[15] For further information on our objectives, scope, and methodology, see appendix 1.

We conducted this performance audit from July 2015 to August 2016 in accordance with generally accepted government auditing standards. Those standards require that we plan and perform the audit to obtain sufficient, appropriate evidence to provide a reasonable basis for our findings and conclusions based on our audit objectives. We believe that the evidence obtained provides a reasonable basis for our findings and conclusions based on our audit objectives.

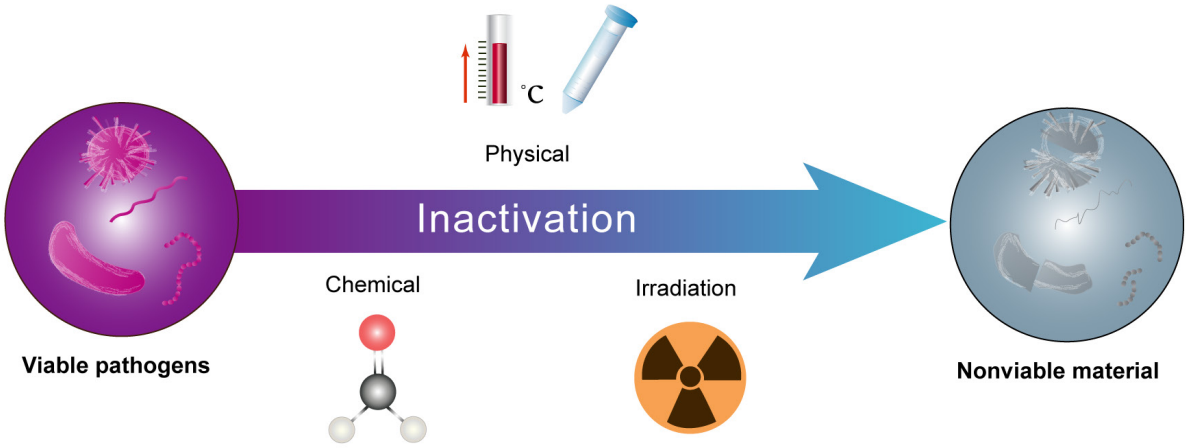
Background

Types of Inactivation Methods

Researchers use various methods in high-containment laboratories to inactivate pathogens, as shown in figure 1, which they select depending on the type of pathogen to be inactivated and intended use of the inactivated material. Once a method is selected, researchers develop a protocol that outlines a detailed plan for the scientific procedure. The frequency with which inactivation is performed in high-containment laboratories varies significantly, with some researchers conducting inactivation on a daily or weekly basis and others conducting inactivation only a few times each year.

[15]GAO/AIMD-00-21.3.1.

Figure 1: Methods Used to Inactivate Pathogens



Source: GAO. | GAO-16-642

Pathogens can be inactivated using physical, irradiation, and chemical methods, each having advantages and disadvantages. For example, inactivating pathogens using heat—a physical method—is generally simple and inexpensive, but may destroy the pathogen's protein structure, thus rendering the pathogen useless for certain research purposes. Inactivating pathogens using irradiation better maintains pathogens' protein structure, but irradiators are costly for most laboratories and subject to additional regulations and security concerns. See table 1 for descriptions of selected types of inactivation methods and their advantages and disadvantages.

Table 1: Description of Selected Inactivation Methods Used in High-Containment Laboratories

Inactivation method	Description	Advantages	Disadvantages
Physical methods of inactivation			
Heat (dry or wet)	Hot-air (dry) or steam under pressure (wet), are used to irreversibly destroy the pathogen's protein structure.	• Simple • Inexpensive • Nontoxic • Rapidly kills most pathogens	• Can damage the pathogen's ability to produce an immune response in its host and may render it useless for research purposes
Filtration[a]	A filter traps intact pathogens while smaller parts of the pathogen pass through.	• Separates pathogens that are not inactivated or are clumping • Works on a wide range of microorganisms	• Not all particles that are smaller than the filter's pore-size pass through, resulting in loss of research material
Irradiation methods of inactivation			
Ionizing radiation	Ionizing radiation causes DNA damage. Some forms of ionizing radiation require radioactive sources, while others do not.	• Disrupts the nucleic acids of an organism while preserving the protein components for research • Gamma radiation has greater ability to penetrate samples than other types of radiation, allowing for successful application on denser materials	• Radioactive source material for gamma radiation requires background checks for individuals and other security checks • Long exposure times • Some types of pathogens are resistant, including spores[b] • Expensive • Sample size and radiation source affect the dose, complicating the inactivation process
Chemical methods of inactivation			
Chemical inactivation	Chemicals inactivate pathogens by (a) destroying the structure of proteins, (b) destroying the integrity of the nucleic acids, (c) negatively affecting the cell's wall or disrupting the cell's membrane, or (d) bonding the proteins during fixation of tissue samples. A wide range of chemicals are used for inactivation.	• Varying concentrations of some chemicals can destroy a wide range of pathogens • Some chemicals act quickly • Flexibility to determine end product (e.g., proteins or nucleic acids) through chemical selection	• Some chemicals can be irritating and toxic to humans • Some chemicals only work on specific pathogens • In certain circumstances, the pathogen can repair itself • Manufactured kits may not specify which chemicals are used. In these cases testing must be done to identify the effects of the chemical before research can start.

Source: GAO analysis of information from peer-reviewed journal articles, experts, and agency documents. | GAO-16-642

[a]As an inactivation method, filtration works by filtering out the actual viable pathogenic materials from the sample (leaving viable material on the filter), as opposed to traditional inactivation methods, which render pathogens nonviable.

[b]Spores are thick-walled cells produced by some bacteria and fungi that are capable of survival in unfavorable environments and are more resistant to antimicrobial agents.

Following inactivation, researchers may test the viability of the material to ensure the pathogen was rendered nonviable. Different methods exist to test the viability of a pathogen, depending on the conditions under which the pathogen grows. For example, viability may be tested by attempting to grow inactivated material on cultured cells or by exposing animals to inactivated material to see if they become infected.

Key Terms Related to Pathogen Inactivation

- **Decontamination:** the removal or count reduction of contaminating pathogens present on an object.
- **Disinfection:** the elimination of nearly all known pathogens but not necessarily all microbial forms, e.g., spores on inanimate objects.
- **High-containment laboratory:** biosafety level (BSL)-3 or 4 facilities in which studies are conducted on a variety of dangerous pathogens and toxins.
- **Inactivation:** a process to render infectious material (e.g., pathogens) unable to cause disease, but retain characteristics of interest for future use.
- **Irradiation:** exposure to radiation (e.g., ultraviolet light, gamma rays, X-rays).
- **Kill curve:** the results of a dose-response experiment where a pathogen is subjected to increasing amounts of the inactivating agent to determine the minimum conditions required to render it nonviable or noninfectious.
- **Nonviable:** a pathogen that is no longer capable of growing, replicating, infecting, or causing disease.
- **Protocol:** a detailed plan for a scientific procedure.
- **Select agent:** in the United States, biological select agents (e.g., bacteria, viruses) and toxins have the potential to pose a severe threat to public, animal, or plant health, or to animal or plant products.
- **Validation:** for the purpose of inactivation methods, the method must be scientifically sound and produce consistent results each time it is used such that the expected result can be ensured. Methods of validation may include (1) use of the exact conditions of a commonly accepted method that has been validated, (2) a published method with adherence to the exact published conditions, or (3) for in-house methods, validation testing should include the specific conditions used and appropriate controls (from the Select Agent Program).

Source: GAO analysis of scientific literature and comments from our expert meeting. | GAO-16-642

Regulation of Pathogens in High-Containment Laboratories

Congress passed the Public Health Security and Bioterrorism Preparedness and Response Act of 2002 to improve the ability of the United States to prevent, prepare for, and respond to bioterrorism and other public health emergencies.[16] This act was one of several acts passed in reaction to the September 11, 2001, terrorist attacks and subsequent anthrax incidents to combat terrorism and address increasing concerns about biological security.[17] It expanded HHS's authority to regulate select agents to include oversight of all laboratories that possess, use, and transfer select agents affecting public health and safety, and granted comparable authority to USDA for select agents posing a threat to plant or animal health, or animal or plant products. CDC's Division of Select Agents and Toxins is responsible for the oversight and regulation of select agents that could pose a threat to public health and safety, such as the Ebola virus. APHIS's Agriculture Select Agent Services is responsible for the oversight and regulation of select agents that could pose a threat to animal or plant health or animal or plant products, such as the virus that causes foot-and-mouth disease. Some select agents, such as *Bacillus anthracis*, are regulated by both agencies because they pose a threat to both human and animal health. In overseeing the Select Agent Program, CDC's Division of Select Agents and Toxins and APHIS's Agriculture Select Agent Services are responsible for ensuring that high-containment laboratories that work with select agents comply with requirements of the select agent regulations.[18] They do this by inspecting laboratories that are registered with the Select Agent Program, ensuring that individuals who work with these agents undergo a security risk assessment, and investigating and enforcing any incidents in which noncompliance with the regulations may have occurred, among other responsibilities. As of May 31, 2016, a total of 286

[16]Pub. L. No. 107-188, title II, 116 Stat. 594 (June 12, 2002). For more information on the background of the Select Agent Program and regulations, see GAO-09-574.

[17]In September and October 2001, letters laced with *Bacillus anthracis* were mailed through the U.S. postal system to two U.S. senators and members of the media. In 2008, the Federal Bureau of Investigation (FBI) alleged that a scientist at the U.S. Army Medical Research Institute of Infectious Diseases was the sole perpetrator of the 2001 attacks.

[18]42 C.F.R. Part 73 (CDC); 7 C.F.R. Part 331 (APHIS-plant); 9 C.F.R. Part 121 (APHIS-animal).

entities were registered with the Select Agent Program.[19] The Select Agent Program maintains a list of select agents and toxins that they are required to review and republish at least biennially.[20]

Guidance on the Management of Pathogens in High-Containment Laboratories

NIH publishes guidelines detailing safety practices for research involving recombinant pathogens.[21] Compliance with the NIH guidelines is a condition of accepting funding awards from NIH for research involving recombinant material. As part of these guidelines, laboratories receiving funding must report any incidents involving recombinant pathogens to NIH. NIH has issued an incident reporting template that may be used to report these incidents.[22]

The *Biosafety in Microbiological and Biomedical Laboratories* (BMBL) manual,[23] although not prescriptive, is a widely-accepted source of

[19]An entity is defined in the select agent regulations as any government agency (federal, state, or local), academic institution, corporation, company, partnership, society, association, firm, sole proprietorship, or other legal entity. Each registered entity may house one or more high-containment laboratories. The total number of high-containment laboratories in the United States is unknown, as we found in 2009. GAO-09-574.

[20]In determining whether to include an agent on the HHS select agent list, the HHS Secretary must consider the following criteria: (1) the effect on human health of exposure to the agent or toxin; (2) the degree of contagiousness of the agent or toxin and the methods by which the agent or toxin is transferred to humans; (3) the availability and effectiveness of pharmacotherapies and immunizations to treat and prevent any illness resulting from infection by the agent or toxin; and (4) any other criteria, including the needs of children and other vulnerable populations, that the Secretary considers appropriate. In determining whether to include an agent or toxin on the USDA list, the USDA Secretary must consider the following criteria: (1) the effect of exposure to the agent or toxin on animal and plant health, and on the production and marketability of animal and plant products; (2) the pathogenicity of the agent or toxin and the methods by which the agent or toxin is transferred to animals or plants; (3) the availability and effectiveness of pharmacotherapies and prophylaxis to treat and prevent any illness caused by the agent or toxin; and (4) any other criteria that the Secretary considers appropriate to protect animal or plant health, or animal or plant products.

[21]Department of Health and Human Services, National Institutes of Health, *NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules*.

[22]According to the guidelines, any significant problems, violations of the NIH guidelines, or any significant research-related accidents and illnesses are to be reported to NIH within 30 days.

[23]Department of Health and Human Services, Centers for Disease Control and Prevention and National Institutes of Health, *Biosafety in Microbiological and Biomedical Laboratories*, 5th ed. (Washington, D.C.: December 2009).

guidance for all research involving pathogens, regardless of whether they are select agents or recombinant pathogens. The manual outlines the principles and practices of biological safety and security and is published in partnership by CDC and NIH. It applies to all biological safety levels of microbiological laboratories, including high-containment laboratories. According to the BMBL manual, biological safety practices are intended to reduce or eliminate exposure of individuals and the environment to potentially dangerous pathogens, and biological security practices are intended to prevent the loss, theft, or misuse of dangerous pathogens and research-related information by limiting access to facilities, research materials, and information.

The Total Number of Incidents Involving Incomplete Inactivation of Pathogens Is Unknown

The total number of incidents involving incomplete inactivation that occurred from 2003 through 2015 is unknown for several reasons, including the inability to easily identify such incidents in existing databases. For those that are known, incidents occurred at federal, academic, and private high-containment laboratories and involved a range of inactivation methods and pathogens.

The Total Number of Incidents Is Unknown Due to an Inability to Easily Identify Incidents and the Absence of Reporting Requirements and a Consistent Definition

The total number of incidents involving incomplete inactivation that occurred from 2003 through 2015 is unknown for three reasons: (1) the inability to easily identify incidents involving incomplete inactivation within incident databases, (2) the absence of reporting requirements for pathogens that are not select agents or recombinant pathogens, and (3) the absence of a clear, consistent definition of inactivation.[24]

Inability to Easily Identify Incidents

First, the Select Agent Program and NIH do not have the ability to easily identify incidents involving incomplete inactivation because their incident reporting forms are not structured to specifically identify this type of

[24]Officials from HHS noted that another reason that the total number of incidents involving incomplete inactivation is unknown is because some incidents may remain undetected if there are no resulting infections or viability testing is not performed.

incident. As a result, neither the Select Agent Program nor NIH (for the oversight of recombinant pathogens) was able to provide us with an accurate number of all incidents involving incomplete inactivation that occurred from 2003 through 2015. Specifically, registered entities are required by federal regulation to report any incidents of theft, loss, or release of select agents to the Select Agent Program, where "release" refers to any instance where pathogens are outside of primary containment, such as an accidental spill of viable pathogens or an incident that results in medical surveillance following an exposure, including those resulting from incomplete inactivation. The Select Agent Program is required to annually report to Congress only on the number and type (e.g., "theft" or "release") of all incidents that have occurred involving select agents. Select Agent Program officials initially told us that there were 10 incidents involving incomplete inactivation reported to the program from 2003 through 2015 (see table 2). NIH officials initially told us that they were unaware of any incidents involving incomplete inactivation involving recombinant pathogens that had occurred in that time frame.

Table 2: Ten Incidents Involving Incomplete Inactivation of Select Agents from 2003 through 2015 Initially Provided to GAO by the Federal Select Agent Program

Laboratory type	Pathogen	Pathogen type	Method of inactivation	Year of incident
Federal	*Bacillus anthracis*	Bacteria	Irradiation	2015
Academic	Venezuelan equine encephalitis virus	Virus	Chemical	2015
Federal	*Bacillus anthracis*	Bacteria	Chemical	2014
Federal	Ebola virus	Virus	Chemical	2014
Academic	*Brucella abortus*, *Brucella melitensis* & *Brucella suis*	Bacteria	Chemical	2012
Private	Eastern equine encephalitis virus	Virus	Chemical	2010
Federal	*Bacillus anthracis*	Bacteria	Chemical	2007
Federal	*Bacillus anthracis*	Bacteria	Chemical	2006
Federal	Botulinum neurotoxin producing species of *Clostridium*	Bacteria	Chemical	2006
Private	*Bacillus anthracis*	Bacteria	Physical	2004

Source: GAO analysis of information from the Federal Select Agent Program, 2016. | GAO-16-642

However, upon review of the Select Agent Program's database of reported incidents, we identified another 11 incidents that involved incomplete inactivation from 2003 through 2015, which we confirmed with the Select Agent Program, in addition to the original list of 10 they provided to us (see table 3).

Table 3: Eleven Additional Incidents Involving Incomplete Inactivation of Select Agents from 2003 through 2015 Identified by GAO and Confirmed by the Federal Select Agent Program

Laboratory type	Pathogen	Pathogen type	Method of inactivation	Year of incident
Academic	*Burkholderia pseudomallei*	Bacteria	Physical	2014
Private	*Francisella tularensis*	Bacteria	Chemical	2014
Federal	*Francisella tularensis*	Bacteria	Chemical	2011
Private	*Bacillus anthracis*	Bacteria	Physical and Chemical	2010
Private	Marburg virus and Ebola virus	Virus	Chemical	2009
Federal	*Bacillus anthracis*	Bacteria	Physical	2008
Academic	*Francisella tularensis*	Bacteria	Physical and Chemical	2008
Federal	*Francisella tularensis*	Bacteria	Chemical	2007
Academic	*Francisella tularensis*	Bacteria	Chemical	2007
Federal	*Bacillus anthracis*	Bacteria	Chemical	2006
Federal	Venezuelan equine encephalitis virus	Virus	Chemical	2006

Source: GAO analysis of information from the Federal Select Agent Program, 2016. | GAO-16-642

Equine Encephalitis Viruses

Deceased Horse from a Venezuelan Equine Encephalitis Outbreak in Texas, 1976

According to the Centers for Disease Control and Prevention (CDC), the equine encephalitis viruses are mosquito-transmitted diseases that can cause severe inflammation of the brain (encephalitis) in horses and humans. Eastern equine encephalitis (EEE) most commonly occurs in the eastern United States and Canada while Venezuelan equine encephalitis (VEE) most commonly occurs in South and Central America but has spread to the United States.

Although a rarely seen illness in humans, approximately 33 percent of individuals with EEE die from the disease and many survivors are left with significant brain damage; infected horses have variable death rates as high as 90 percent. VEE is the most infectious of the equine encephalitis viruses and the United States weaponized VEE as an offensive incapacitating agent before the termination of its biological weapons program.

These viruses are highly infectious by the aerosol route and have caused more than 160 laboratory-acquired infections, according to the *Biosafety in Microbiological and Biomedical Laboratories* (BMBL) manual.

Source: GAO analysis of scientific literature, agency documents, and the BMBL manual. CDC Public Health Image Library, James Stewart (photo) | GAO-16-642

According to officials, the Select Agent Program is not required to specifically report the number of incidents involving incomplete inactivation, as a subset of incidents of theft, loss, or release, to any outside entity. Therefore, identifying this subset of incidents in the database was difficult because reporting forms used to track the theft, loss, and release of select agents are not structured to specifically indicate whether an incident involved incomplete inactivation, nor require laboratories to include "incomplete inactivation" in the description of the incident.[25] As a result, officials cannot easily search their databases to identify such incidents once the information on the reporting forms is entered into the database. According to Select Agent Program officials, the current structure of the reporting forms could affect their understanding of the magnitude of the problem, and a more extensive analysis of the full report descriptions for all incidents in the database could identify additional incidents involving incomplete inactivation.

Similar to the Select Agent Program, NIH has an incident reporting form and requires laboratories under its purview to report incidents involving recombinant pathogens. We identified four incidents involving incomplete inactivation of recombinant pathogens that occurred from 2003 through 2015, which were reported to NIH but were not provided to us, through a review of incident reporting forms (see table 4).[26] NIH later confirmed that these four incidents did involve incomplete inactivation. For example, due to an equipment failure in 2014, researchers at an academic high-containment laboratory inadvertently moved viable samples of a recombinant pathogen thought to be inactivated outside of containment. The university reported the incident to NIH, but NIH officials did not initially identify this incident as resulting from incomplete inactivation. As with the Select Agent Program's form, NIH's reporting form for incidents involving recombinant pathogens is not structured to specifically indicate whether an incident involved incomplete inactivation, nor requires laboratories to include "incomplete inactivation" in the description of the incident, leading to difficulty in identifying such reports in its database.

[25]The Select Agent Program uses a reporting document called a "Form 3" to document incidents of theft, loss, or release of select agents.

[26]These four incidents all involved pathogens that were also select agents—and thus also reported to the Select Agent Program and listed in tables 2 and 3 above—in addition to being recombinant pathogens.

Table 4: Four Incidents Involving Incomplete Inactivation of Recombinant or Synthetic Pathogens from 2003 through 2015 Identified by GAO and Confirmed by the National Institutes of Health (NIH)

Laboratory type	Pathogen	Pathogen type	Method of inactivation	Year of incident
Academic	*Burkholderia pseudomallei*	Bacteria	Physical	2014
Academic	*Brucella abortus*, *Brucella melitensis* & *Brucella suis*	Bacteria	Chemical	2012
Federal	*Francisella tularensis*	Bacteria	Chemical	2011
Academic	*Francisella tularensis*	Bacteria	Chemical	2007

Source: GAO analysis of information from NIH, 2016. | GAO-16-642

Note: These four incidents all involved pathogens that were also select agents—and thus also reported to the Federal Select Agent Program—in addition to being recombinant pathogens.

These examples demonstrate challenges the Select Agent Program and NIH have with identifying which incidents involve incomplete inactivation for the pathogens they regulate. Because the Select Agent Program and NIH cannot easily identify which incidents involve incomplete inactivation on reporting forms and within incident databases, they do not know the frequency or reason these incidents occur, making it difficult to develop guidance to help prevent future incidents.

A CDC internal review of the Select Agent Program issued in 2015 noted the need to include subcategories of "release," "loss," and other additional fields on reporting forms to more consistently identify and categorize incidents moving forward.[27] In addition, *Standards for Internal Control in the Federal Government* states that agencies are to employ control activities, such as the accurate recording of events, to help ensure that management's directives are carried out and actions are taken to address risks.[28] Our prior work on safety reporting systems has noted that report formats should allow for a sufficient description of events that align with analysis decisions, including the ability to effectively perform root cause analysis on high-priority issues.[29] In addition, a 2016 report we issued on biological safety in high-containment laboratories highlighted the importance of analyzing all incident reports to identify potential trends.[30]

[27]Centers for Disease Control and Prevention, *90 Day Internal Review of the Division of Select Agents and Toxins* (Atlanta, Ga.: Oct. 22, 2015).

[28]GAO/AIMD-00-21.3.1.

[29]GAO, *Biological Laboratories: Design and Implementation Considerations for Safety Reporting Systems*, GAO-10-850 (Washington, D.C.: Sept. 10, 2010).

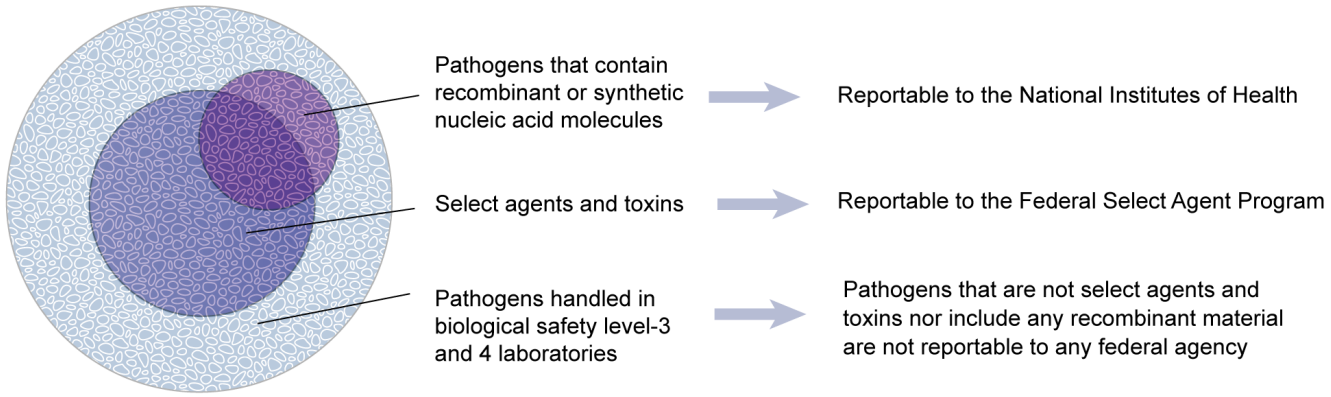
[30]GAO-16-305.

Officials from the Select Agent Program stated that they plan to revise their reporting forms in response to the 2015 internal CDC review mentioned above and issue new guidance associated with the new forms, thus allowing officials to search the database for new and more consistent information. However, as of April 2016, Select Agent Program officials had not yet determined what additional information to include on the forms. Moreover, as of May 2016, NIH officials told us that they did not plan to update their reporting form.

Absence of Reporting Requirements

Second, the total number of incidents involving incomplete inactivation in high-containment laboratories that occurred from 2003 through 2015 is unknown because federal incident reporting, in general, is required only for (1) incidents that involve select agents, which are reportable to the Select Agent Program; and (2) incidents that involve recombinant pathogens, which are reportable to NIH. Thus, incidents involving incomplete inactivation of pathogens that are neither select agents nor recombinant pathogens, such as West Nile virus, are generally not required to be reported to any federal agency (see fig. 2).[31]

Figure 2: Federal Reporting Requirements for Incidents in High-Containment Laboratories



Note: The circle sizes do not represent the number of each of the pathogen groups.

Source: GAO. | GAO-16-642

[31]Laboratory officials told us that in some situations, they may notify a local or state health organization if an incident with a nonselect agent raises significant public health or safety concerns.

Reporting is required for select agents because the Select Agent Program has determined that they have the potential to "pose a severe threat to public and agricultural health and safety." However, nonselect agents also have the potential to cause disease if not properly inactivated. For example, during the course of our review, we found an incident involving the incomplete inactivation of *Mycobacterium tuberculosis*, a nonselect agent that causes the disease tuberculosis, in one laboratory. Because there are no federal reporting requirements for incidents involving pathogens that are neither select agents nor recombinant pathogens, only the laboratory in which the inactivation procedure failed was aware of the incident. Some experts from our meeting noted that it would be beneficial if all pathogens in high-containment received the same level of scrutiny and had the same biological safety controls in place when leaving high containment, whether the sample is a select agent or not. However, one expert also noted that when the Select Agent Program was created, its focus was more on the biological security risks associated with pathogens rather than biological safety, which may contribute to what appears to be an artificial distinction between select and nonselect agents for incident reporting. As a way to address the issue of incident reporting in a broader scope, we recommended in 2016 that federal high-containment laboratories report all incidents, whether they involve select agents or not, to senior agency officials.[32]

No Clear, Consistent Definition of Inactivation

Third, the total number of incidents involving incomplete inactivation that occurred from 2003 through 2015 is also unknown because there is currently no clear and consistent definition of inactivation in guidance or regulations issued by the Select Agent Program, NIH (for oversight of recombinant pathogens), or the BMBL manual.[33] As a result, researchers may not consistently define inactivation, which potentially affects how and when they report incidents involving incomplete inactivation. Experts at our meeting stated there is a need for a clear, consistent definition of inactivation across key federal guidance documents, with some experts noting that the lack of a consistent definition can make it difficult to understand when an incident occurs. The BMBL manual also emphasizes the need for clear definitions to avoid misuse and confusion of key terms used in research, but does not itself define inactivation. In addition, our

[32]GAO-16-305.

[33]These guidance documents do include some information on inactivation, but do not include a definition.

past work has shown that the use of standardized definitions is key to ensuring that information is reported consistently.[34]

Officials from the Select Agent Program, NIH, and CDC agreed that there is a need for a clear and consistent definition of inactivation across guidance documents. Specifically, the Select Agent Program is in the process of revising the select agent regulations, which program officials told us will include a definition of inactivation; however, the program has received a number of comments from the public in response to these proposed changes and officials told us that further alterations will be made to the proposed rule before it is finalized and submitted.[35] Officials from NIH, responsible for the oversight of recombinant pathogens, noted they released an update to the NIH guidelines in April 2016 and currently do not have any other planned updates.[36] NIH and CDC are in the process of updating the BMBL manual and officials involved noted they did not yet know the extent to which inactivation would be covered in the next edition of the manual, but that they would consider any comments on how to improve the BMBL as they move forward in the drafting process.[37] It is unclear to what extent the planned changes to the select agent regulations and the BMBL manual will provide a clear and consistent definition of inactivation. Officials from NIH responsible for recombinant pathogens and officials in charge of the BMBL manual noted that they

[34]Based on our previous reporting, we have found that metrics should be reportable in a consistent fashion, and that a key part of consistent reporting is ensuring that standardized definitions, methodologies, and procedures will be used. In addition, we have reported that inconsistent definitions limit the comparability of programs across agencies. See GAO, *Defense Inventory: Actions Underway to Implement Improvement Plan, but Steps Needed to Enhance Efforts,* GAO-12-493 (Washington, D.C.: May 3, 2012).

[35]Centers for Disease Control and Prevention, *Possession, Use, and Transfer of Select Agents and Toxins; Biennial Review of the List of Select Agents and Toxins and Enhanced Biosafety Requirements*, Notice of Proposed Rule Making, 81 Fed. Reg. 2805 (Jan. 19, 2016); Animal and Plant Health Inspection Service, *Agricultural Bioterrorism Protection Act of 2002; Biennial Review and Republication of the Select Agent and Toxin List; Amendments to the Select Agent and Toxin Regulations*, Proposed Rule, 81 Fed. Reg. 2762 (Jan. 19, 2016). According to USDA and HHS officials, the final rule is scheduled to be published in October 2016 and effective in December 2016.

[36]Department of Health and Human Services, National Institutes of Health, *NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules*.

[37]According to CDC and NIH officials, they do not currently have an expected date for the issuance of the next edition of the BMBL manual.

would consider the results of the new select agent regulations to inform the changes made to their own documents, as they relate to inactivation.

Without the ability to easily identify incidents involving incomplete inactivation on reporting forms, the Select Agent Program and NIH are unable to easily search their databases to know the frequency and causes of incidents related to the pathogens they regulate. In addition, without a clear and consistent definition of inactivation across key federal guidance, researchers may not know when to include incomplete inactivation in an incident report, potentially affecting the number of incidents reported to the Select Agent Program and NIH (for recombinant pathogens). Collectively, these issues prevent these agencies from knowing the extent to which incomplete inactivation occurs and whether these incidents are being properly identified, analyzed, and addressed. Not knowing the magnitude of the problem may inhibit their ability to achieve program missions of investigating any incidents in which noncompliance may have occurred.

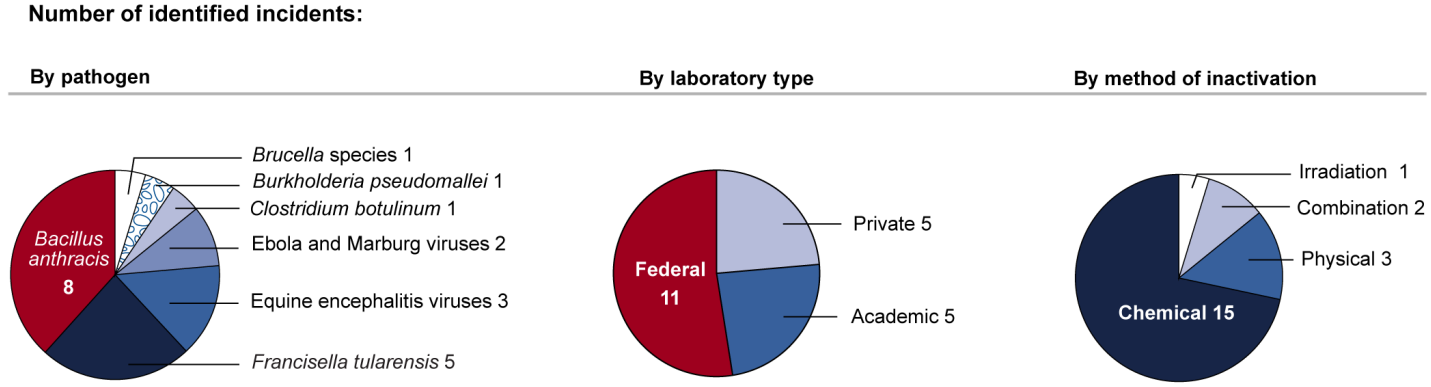
Identified Incidents Involving Incomplete Inactivation Occurred at a Variety of Laboratories and Involved a Range of Methods and Pathogens

The 21 incidents involving incomplete inactivation from 2003 through 2015 that we identified occurred at different types of high-containment laboratories—specifically federal laboratories, academic institutions, and private companies.[38] In addition, these incidents involved all methods of inactivation—including irradiation, chemical, and physical (e.g., heat) inactivation—and a variety of pathogens (see fig. 3). Our review identified some similarities in the 21 identified incidents involving incomplete inactivation, with just over half of the cases occurring at federal laboratories, over a third of incidents involving *Bacillus anthracis*, and about three-quarters of the incidents involving chemical inactivation. According to agency officials, none of the incidents involving incomplete inactivation identified in this report resulted in human infection, severe illness, or death. Because the total number of times inactivation is conducted in each laboratory is unknown, it is impossible to determine the

[38]The 21 incidents include the 10 incidents reported to us by the Select Agent Program and the additional 11 incidents that we identified that occurred from 2003 through 2015 and were confirmed by the Select Agent Program. The similarities between incidents discussed in this report cannot be generalized beyond the scope of these 21 incidents. In discussing examples throughout this report, we are only identifying the DOD and CDC laboratories whose incidents involving incomplete inactivation are known to the general public through public reports.

overall risk of incomplete inactivation or the contribution of the pathogen, type of laboratory, or method of inactivation to the overall risk.

Figure 3: Number of Identified Incidents Involving Incomplete Inactivation from 2003 through 2015 by Pathogen, Laboratory Type, and Method, as Derived from a Review of Information from the Federal Select Agent Program



Source: GAO analysis of information from the Federal Select Agent Program. | GAO-16-642

Eight of the 21 identified incidents involving incomplete inactivation that occurred from 2003 through 2015 involved *Bacillus anthracis*. This finding reflects a theme heard during our expert meeting and interviews that *Bacillus anthracis*, especially in spore form,[39] is one of the most difficult pathogens to inactivate. One high-profile incident occurred at DOD's Life Sciences Division at Dugway Proving Ground (Dugway) in Utah over the course of 12 years, in which 575 shipments of incompletely inactivated *Bacillus anthracis* were sent to 194 laboratories and contractors around the world from 2004 through 2015 (see fig. 4). A DOD review of the incident, completed in December 2015, determined that there was insufficient evidence to establish a single failure as the proximate cause for the inadvertent shipment of incompletely inactivated *Bacillus*

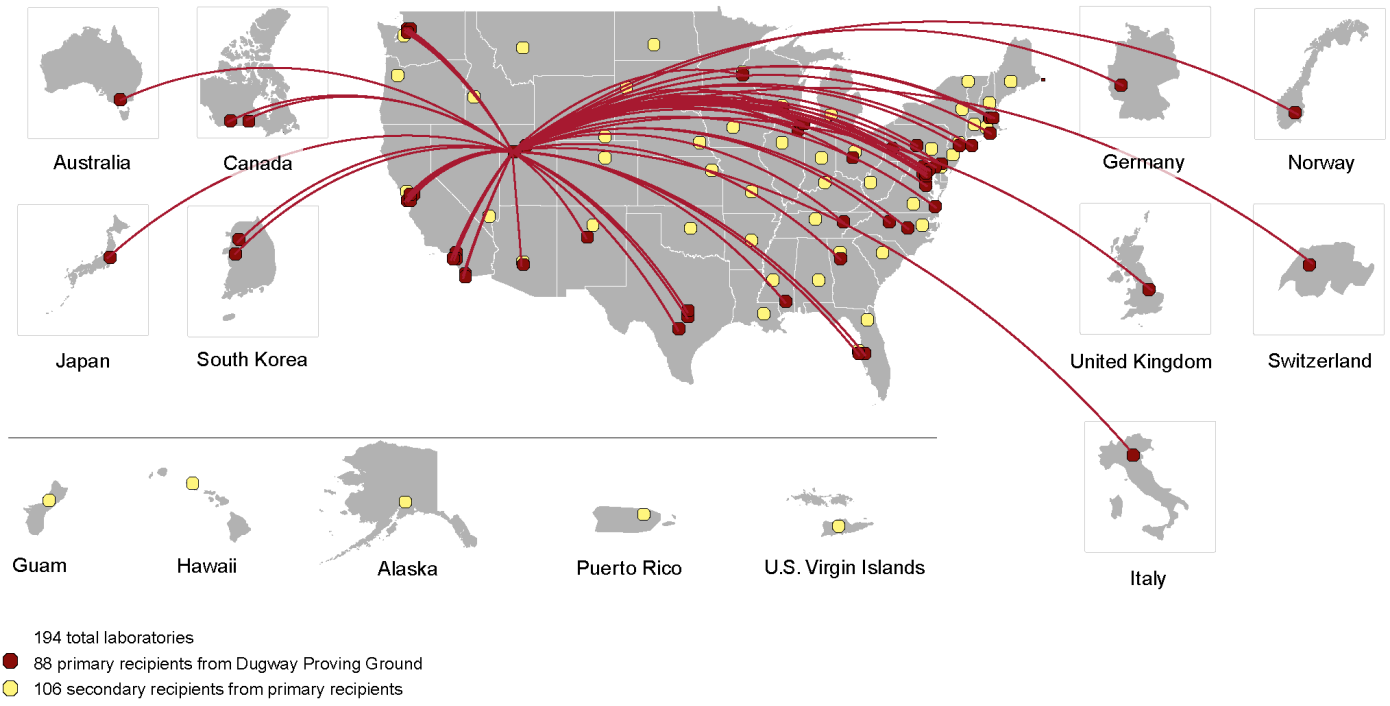
[39]Spores are thick-walled resting cells produced by some bacteria and fungi that are capable of survival in unfavorable environments and are more resistant to antimicrobial agents than vegetative cells.

anthracis.[40] However, the report stated that the equipment used to irradiate the samples experienced several malfunctions. A researcher at the facility noted that these malfunctions included a nonfunctioning turntable, a broken motor, and misplaced indicator strips that measure the amount of radiation being applied, which may have contributed to incomplete inactivation. In addition, the report stated that senior management at Dugway "allowed a culture of complacency to flourish at the facility, resulting in laboratory personnel who did not always follow rules, regulations, and procedures." As a result of this incident, DOD currently has a working group looking into best practices for the inactivation of *Bacillus anthracis* by irradiation.[41]

[40]Department of the Army, *AR 15-6 Investigation Report: Individual and Institutional Accountability for the Shipment of Viable Bacillus anthracis from Dugway Proving Ground* (Washington, D.C.: Dec. 17, 2015). The report also notes that it was the Ames strain of anthrax, an extremely harmful strain.

[41]In August 2015, the Secretary of the Army directed the formation of an Army Biosafety Task Force, to prepare an implementation plan to address the findings and recommendations in the July 2015 DOD report: Department of Defense, *Review Committee Report: Inadvertent Shipment of Live Bacillus anthracis Spores by DOD* (Washington, D.C.: July 13, 2015). This plan includes research into the best way to inactivate anthrax.

Figure 4: Sites around the World that Received Viable *Bacillus anthracis* (anthrax) Samples from 2004 through 2015 Thought to be Inactivated from the Department of Defense's Dugway Proving Ground



Source: GAO analysis of information from the Department of Defense and Centers for Disease Control and Prevention. | GAO-16-642

About three-quarters (15 of 21) of identified incidents involving incomplete inactivation that occurred from 2003 through 2015 involved inactivation using only chemical methods; two of these occurred at CDC in 2014. For example, in June 2014, CDC researchers transferred samples of *Bacillus anthracis* thought to be inactivated from a high-containment laboratory to a lower safety level laboratory to test equipment used to detect pathogens.[42] Up to 70 staff members at CDC were potentially exposed to

[42]These samples were being prepared for a preliminary assessment of whether using matrix-assisted laser desorption/ionization time-of-flight (MALDI-TOF) mass spectrometry, a technology that can be used for rapid bacterial species identification, could be used by emergency response laboratories. Centers for Disease Control and Prevention, *Report on the Potential Exposure to Anthrax* (Atlanta, Ga.: July 11, 2014).

viable samples.[43] CDC determined that the overriding factor contributing to this incident was lack of a written plan approved by senior staff or scientific leadership to ensure that the research design was appropriate and met all laboratory safety requirements. Another incident at CDC involved Ebola virus samples, wherein inadequate safeguards did not minimize human error, resulting in a potential release in December 2014.[44] Scientists inadvertently switched samples designated for live Ebola virus studies with samples intended for studies with inactivated material. As a result, the samples with viable Ebola virus, instead of the samples with inactivated Ebola virus, were transferred out of a BSL-4 laboratory to a laboratory with a lower safety level for additional analysis. While no one contracted Ebola virus in this instance, the consequences could have been dire for the personnel involved as there are currently no approved treatments or vaccines for this virus.[45] According to the BMBL manual, there are limited treatment options for any pathogen that must be handled in a BSL-4 laboratory.

About one-quarter (6 of 21) of identified incidents that occurred from 2003 through 2015 were related to issues with inactivation protocols—that is, a detailed plan for how inactivation will be carried out. Specifically, researchers used protocols from other laboratories without testing those protocols in their own laboratories, used flawed protocols, or did not verify the effectiveness of protocols they developed themselves.[46] For example, in December 2010, a researcher at a private laboratory transferred samples of what was mistakenly thought to be inactivated Eastern equine encephalitis virus to another laboratory. The researcher had used a different laboratory's protocol for chemical inactivation without verifying its effectiveness under the conditions in his own laboratory, resulting in

[43]Centers for Disease Control and Prevention, *Report on the Potential Exposure to Anthrax*.

[44]Centers for Disease Control and Prevention, *Report on the Potential Exposure to Ebola Virus* (Atlanta, Ga.: Feb. 4, 2015).

[45]According to a World Health Organization statement dated October 2015, there are no vaccines to protect against the Ebola virus that are licensed for use in humans. Clinical trials for several candidate vaccines are in various phases of development and a safe and effective vaccine is hoped for by the end of 2015. As of April 2016, vaccines for Ebola virus were still in the experimental phase, with one clinical trial underway to assess the safety and efficacy of a candidate vaccine.

[46]The discussions on the contributing factors of incidents involving inactivation are not discrete categories, as some incidents resulted from multiple causes.

incomplete inactivation of samples. In addition, following an incident at an academic institution, researchers identified flaws in their protocol. Specifically, they discovered that the amount of chemical in the protocol was not enough to inactivate the samples, and that the proportion of sample used to test for viability was not sufficient. Both of these factors contributed to incompletely inactivated samples being removed from a high-containment laboratory. Some experts from our meeting, as well as researchers we interviewed, confirmed that it is important to verify a protocol in-house before it is used. In addition, 4 of the 21 incidents that occurred from 2003 through 2015 occurred after researchers did not follow protocols that had previously been verified to work in their laboratories.

Lastly, about one-quarter (5 of 21) of identified incidents that occurred from 2003 through 2015 involved equipment or other issues (such as mislabeling), and about one-quarter (5 of 21) of these incidents involved issues with viability testing—either the absence of viability testing or the removal of a sample before the viability test was complete. One incident involved both equipment and viability testing issues. Specifically, at one university, an equipment failure resulted in incomplete inactivation of samples, which were not tested for viability before removing them from containment. Researchers at the university used heat to inactivate *Burkholderia pseudomallei* (the bacterium that causes Whitmore's Disease, a disease that primarily affects the lungs) without realizing that the heating block had not achieved the optimal temperature to ensure inactivation. As a result, samples that still contained viable pathogens were unknowingly removed from containment. Officials from the university told us that viability testing was not required before the samples were removed from containment because they had done the inactivation step "thousands of times" in the past, and past samples had always been nonviable.

We identified some themes across these identified incidents, but in general, incidents involving incomplete inactivation occurred in all types of high-containment laboratories, involved a wide range of pathogens, and involved a variety of methods. Moreover, different contributing factors led to incomplete inactivation among the identified incidents, with multiple factors contributing to some incidents. Overall, no one type of laboratory, pathogen, inactivation method, or underlying cause was responsible for all of the identified incidents involving incomplete inactivation that occurred from 2003 through 2015.

Gaps in Science and Limited Guidance Affect the Implementation of Inactivation in High-Containment Laboratories

Several challenges affect the implementation of inactivation in high-containment laboratories including (1) gaps in the scientific knowledge of protocol development and implementation, (2) limited federal guidance for the development of inactivation protocols, (3) inconsistent implementation of safeguards to help ensure inactivation is properly conducted, and (4) varied documentation requirements for the shipment of inactivated material. Experts in our meeting stated that such challenges may affect laboratories' ability to mitigate the risk of incidents involving incomplete inactivation.

Gaps in Science Affect the Development and Implementation of Inactivation Protocols

Insufficient scientific information exists to guide the development and implementation of inactivation protocols, which could result in incomplete inactivation, according to peer-reviewed literature and our group of experts. Moreover, a DOD report reviewing the Dugway incident stated that a contributing factor to the release of viable pathogens were gaps in scientific understanding of inactivation and viability testing.[47] These scientific gaps include:

- **Mechanisms of inactivation**: It is important for researchers to understand the mechanism of inactivation, according to experts from our meeting, but this is not always clearly understood. For example, *how* some chemicals, such as iodine, achieve inactivation of pathogens is unknown, which may lead to confusion when developing inactivation protocols. Scaling up a protocol—e.g., inactivating a larger sample than what the protocol stipulates, with an equal increase in the amount of the inactivating agent—may not achieve inactivation of pathogens when using some inactivation methods but the reasons why this occurs are unknown. In addition, officials told us that researchers sometimes perform inactivation procedures using manufactured chemical kits, in which the chemical composition may be proprietary. According to experts we interviewed, it may be difficult for researchers to determine the mechanism of inactivation and the factors that may affect the effectiveness of such chemical kits (e.g., temperature or exposure time).

[47]Department of Defense, *Review Committee Report: Inadvertent Shipment of Live Bacillus anthracis Spores by DOD*.

- **Repair mechanisms**: Inactivation of certain pathogens can be difficult because pathogens can sometimes reverse or repair the damage caused by inactivation processes, according to an expert from our meeting; however, the science as to how and to what extent repair occurs is unknown. For example, some peer-reviewed journal articles state that *Bacillus anthracis* may be able to repair itself following inactivation, but the extent and conditions of repair processes have not been determined.[48] A DOD report on the Dugway incident stated that there is limited scientific research on the ability of spores to repair or heal themselves following irradiation.[49]

- **Kill curves:** Kill curves are an important calculation used to determine the amount of exposure to an inactivating agent (e.g., an amount of chemical, exposure time, or radiation dose) necessary to render pathogens nonviable, according to a key textbook on inactivation.[50] An expert we interviewed stated that gaps in the understanding of calculating kill curves can influence the development of inactivation protocols and may lead to an increased risk of incomplete inactivation. Specifically, there is not a clear understanding of how different factors may affect the calculation of kill curves. For example, using test tubes made of different types of material can affect the amount of inactivating agent (e.g., radiation or heat) needed, and the temperature at which irradiation is being performed can also influence the calculation of the kill curve. A DOD report stated that DOD routinely operated outside validated experimental data for the kill curve, irradiating samples with large numbers of pathogens without concurrently increasing the radiation dose necessary to achieve inactivation.[51]

[48]H. Yang, M. Yung, L. Li, J.A. Hoch, C.M. Ryan, U.K. Kar, P. Souda, J.P. Whitelegge, and J.H. Miller, "Evidence that YycJ is a Novel 5'-3' Double-stranded DNA Exonuclease Acting in *Bacillus anthracis* Mismatch Repair," *DNA Repair* (2013): 334-46; H. Yang, M. Yung, C. Sikavi, J.H. Miller, "The Role of *Bacillus anthracis* RecD2 Helicase in DNA Mismatch Repair," *DNA Repair* (2011): 1121-30.

[49]Department of Defense, *Review Committee Report: Inadvertent Shipment of Live Bacillus anthracis Spores by DOD*.

[50]Seymour S. Block, *Disinfection, Sterilization, and Preservation*, 5th ed. (Baltimore, Md.: Lippincott Williams & Wilkins, 2001).

[51]Department of Defense, *Review Committee Report: Inadvertent Shipment of Live Bacillus anthracis Spores by DOD*.

- **Viability testing:** Viability testing is a procedure to determine the extent to which viable pathogens remain in a sample after an inactivation process, according to experts and officials. However, the proportion of sample needed for viability testing is not well understood and may affect the ability of laboratories to determine if pathogens that have undergone inactivation are still viable. More specifically, the proportion of a sample used for testing varies greatly—anywhere from 1 to 50 percent, according to agency officials and documents—which affects the level of confidence about the effectiveness of inactivation procedures. In addition, experts we met with noted that it may not be possible to prove that a sample is 100 percent inactivated without testing 100 percent of the sample, which would leave no inactivated material for research purposes. Therefore, there will always be an element of uncertainty involved with inactivation of pathogens. In addition, many factors influence the ability for pathogens to grow—including length of time, the type of media the pathogen is grown in or on, and others—but how these factors affect pathogen growth are not always clearly understood.

Gaps in the science of inactivation and viability testing led to ad hoc and sometimes iterative development of protocols among some laboratories, which could increase the risk of incomplete inactivation. For example, one senior Dugway official told us that they would put a sample in the irradiator until it received a dose of radiation commonly accepted to be sufficient to inactivate *Bacillus anthracis*,[52] then take it out and determine whether it was inactivated by growing a portion of the sample and testing it. If viable *Bacillus anthracis* was found, they would irradiate it for additional time until the sample was deemed inactivated by the viability testing procedure. Multiple such failures of inactivation at Dugway did not initiate a review of inactivation or viability testing protocols until the shipment of viable pathogens was discovered in May 2015.

[52]According to officials from Dugway, researchers in high-containment laboratories at Dugway used 40 kiloGrays as the radiation dose for inactivation of all pathogens, which they indicated had been successful at irradiating anthrax in the past. A Gray is a measurement of radiation and is defined as the absorption of one joule of radiation energy per kilogram of matter. It is a physical quantity, and does not take into account any biological context.

GAO Identification of Potential Safety Issue Using Chemical Buffers

Image of the Ebola Virus Particle

In 2004, researchers reported in a journal that a manufactured chemical buffer inactivated certain pathogens and, subsequently, researchers in some high-containment laboratories used this buffer for inactivation. Several years later, other researchers discovered that this buffer was not always effective, finding that it did not inactivate Ebola virus in 67 percent of samples. We identified at least one high-containment laboratory that had a policy to use this chemical buffer for inactivation without testing for viability. GAO briefed Federal Select Agent Program officials about the inefficacy of the chemical buffer and in January 2016, the Federal Select Agent Program alerted laboratories that this method was not appropriate to inactivate select agents without proper validation of the method.

Source: GAO analysis of scientific literature, agency documents, and interviews with agency officials. Frederick A. Murphy (photo) | GAO-16-642

A number of factors contribute to these scientific gaps, according to experts and officials we interviewed. For example, there is little funding solely dedicated to research on inactivation, making it difficult for laboratories to conduct research to address scientific gaps on this topic.[53] In addition, experts from our meeting and officials from high-containment laboratories we visited pointed out that even when research on inactivation methods is conducted, publishing that research is sometimes challenging because inactivation methods may be part of a larger research question and thus not a priority for scientists or journals. Furthermore, some journals may not publish inactivation methods if there is no perceived impact of the research.

One key theme discussed during our expert meeting was the need for more research and sharing of such information to overcome scientific gaps in inactivation and viability testing. Moreover, officials from the majority of federal agencies with high-containment laboratories that we interviewed stated that it would be beneficial to the scientific community to better coordinate and share scientific information on inactivation. The Federal Experts Security Advisory Panel—an interagency panel led by HHS and USDA to address policy issues relevant to the security of select agents—recommended in 2014 that a robust, federally-supported program of applied biological safety research be developed and maintained.[54] According to HHS officials, this panel is a potential venue for coordinating research on inactivation and viability testing across high-containment laboratories, with inactivation as one element of the broader research agenda. USDA and other agency officials agreed that this panel could help coordinate research. Without coordination of research and actions taken to increase scientific information related to inactivation and viability testing across high-containment laboratories, there may continue to be gaps in scientific understanding of inactivation and viability testing, increasing the risk of incomplete inactivation.

[53]According to officials, CDC initiated an intramural biological safety research program in fiscal year 2016 that includes some research into the inactivation of pathogens.

[54]Federal Experts Security Advisory Panel, *Report of the Federal Experts Security Advisory Panel* (Washington, D.C.: December 2014). On July 2, 2010, President Obama signed Executive Order 13546 “Optimizing the Security of Biological Select Agents and Toxins,” which created and tasked the Federal Experts Security Advisory Panel to address policy issues relevant to the security of select agents. According to HHS officials, this research agenda has not yet been developed.

Limited Guidance Affects the Development of Inactivation Protocols

There is limited federal guidance for researchers on the development and validation of inactivation protocols. Major sources for technical guidance that researchers commonly use, such as the BMBL manual and NIH guidelines, as well as guidance from the Select Agent Program, provide little detailed information on development and validation of inactivation protocols. In lieu of guidance, we found that researchers in laboratories we visited often developed inactivation protocols at a laboratory level and that protocols sometimes varied within the same department, agency, or laboratory, which may increase the risk of incomplete inactivation. For example, according to DOD documents, at the time the Dugway incident was discovered, DOD was using different protocols for the inactivation of *Bacillus anthracis* spores by irradiation at each of its high-containment laboratories, as well as different viability testing protocols which likely varied in effectiveness.

After protocols are developed, we found that researchers may or may not take steps to validate their efficacy. A validated method, as defined by the Select Agent Program for the purpose of inactivation, is a method that must be scientifically sound and produce consistent results each time it is used such that the expected result can be ensured.[55] Due to limited guidance, high-containment laboratories we visited varied in their interpretation of what constitutes a validated method of inactivation, resulting in researchers applying differing levels of rigor to validation of inactivation protocols. For example, the BMBL manual and NIH guidelines do not provide a definition of validation or give examples of what constitutes validation of a protocol. Similarly, the select agent regulations are currently limited in their guidance on validation of inactivation protocols. In recent proposals to amend the select agent regulations, CDC and APHIS suggested changes to the select agent regulations that will require laboratories to use a validated protocol for inactivation of dangerous pathogens to prevent the release of viable pathogens; however, these suggested changes do not define how inactivation

[55]The Select Agent Program further defines validation in guidance as methods that may include (1) use of the exact conditions of a commonly accepted method that has been validated as applied; (2) a published method with adherence to the exact published conditions; or (3) for in-house methods, validation testing should include the specific conditions used and appropriate controls. Federal Select Agent Program, *Non-viable Select Agents and Nonfunctional Select Toxins and Rendering Samples Free of Select Agents and Toxins*. Accessed on May 16, 2016, http://www.selectagents.gov/guidance-nonviable.html.

protocols are to be validated.[56] An expert from our meeting and laboratory officials we interviewed identified concerns with the Select Agent Program's criteria for what constitutes the validation of a protocol. In particular, an expert from our meeting suggested that some of the Select Agent Program's accepted ways of validating methods are not adequately rigorous.[57] For example, guidance from the Select Agent Program states that using a published method is sufficient. However, during our meeting, experts agreed that methods should be reproduced in each high-containment laboratory they will be used in to ensure consistent, reproducible results.

Another key theme discussed during our expert meeting was the need for more comprehensive and consistent federal guidance on the development and validation of inactivation protocols. In addition, the Federal Expert Security Advisory Panel report recommended that institutional biosafety programs require validation of inactivation protocols,[58] and our past work has also emphasized the importance of validation more generally.[59] Without more comprehensive and consistent federal guidance on the development and validation of inactivation protocols, protocols will vary in their scientific soundness and effectiveness, increasing the risk of some protocols not always achieving inactivation.

[56]81 Fed. Reg. 2805 (Jan. 19, 2016) (CDC); 81 Fed. Reg. 2762 (Jan. 19, 2016) (APHIS).

[57]Federal Select Agent Program, *Non-viable Select Agents and Nonfunctional Select Toxins and Rendering Samples Free of Select Agents and Toxins*. Accessed on May 16, 2016, http://www.selectagents.gov/guidance-nonviable.html.

[58]Federal Experts Security Advisory Panel, *Report of the Federal Experts Security Advisory Panel*.

[59]GAO, *Anthrax: Agency Approaches to Validation and Statistical Analyses Could Be Improved*, GAO-15-80 (Washington, D.C.: Dec. 19, 2014).

Inconsistent Application of Safeguards Affects the Implementation of Inactivation in High-Containment Laboratories

High-containment laboratories we visited did not consistently apply safeguards when conducting inactivation, and there is limited federal guidance on doing so. According to a CDC report,[60] an underlying factor in the potential release of the Ebola virus at CDC was the limited implementation of safeguards. Below are five examples of safeguards identified by agency documents and experts that were inconsistently applied at laboratories we visited:

- **Viability testing**: Despite the science gaps surrounding viability testing, it is still considered an important safeguard, in certain situations, for helping ensure inactivation is attained, according to experts from our meeting. However, we found that this safeguard was not always consistently applied in the laboratories we visited. For example, according to a CDC report, one factor that contributed to the 2014 incident involving *Bacillus anthracis* at CDC was that material was transferred out of containment without first confirming it was nonviable through a viability test.[61] Experts we interviewed stated that in certain situations, laboratories should always test the viability of inactivated samples, such as when laboratories use inactivated samples to test vaccines or when inactivating the spore form of *Bacillus anthracis*, because of the challenges in doing so, as previously noted. In other instances, viability testing is not always possible or necessary, according to experts we interviewed. For example, experts noted that some pathogens, such as *Mycobacterium tuberculosis*, take a long time to grow and therefore viability testing would require waiting several weeks before the inactivated samples could be used, potentially delaying research. Other pathogens require animals for viability testing, which can be cost prohibitive, take additional time, and entail euthanizing animals.

- **Verification mechanisms**: Verification mechanisms are a safeguard to ensure internal protocols are followed, according to CDC officials and agency documents. However, at many laboratories we visited, verification practices, to confirm that inactivation protocols were successfully performed, varied. Verification mechanisms used by some high-containment laboratories included checklists and

[60]Centers for Disease Control and Prevention, *Report on the Potential Exposure to Ebola Virus*.

[61]According to officials, CDC staff tested samples for viability but did not wait long enough before reporting the results as negative.

Incidents from the 1950s, 1970s, and 1980s Involving Incompletely Inactivated Vaccines

One purpose for conducting inactivation is to create vaccines, which may use inactivated pathogens to stimulate a person's immune system to produce immunity to the disease caused by that pathogen. However, incompletely inactivating the pathogen during the course of developing a vaccine can have serious consequences. For example, in 1955, incomplete inactivation of the poliovirus vaccine led to 40,000 cases of polio, left 51 children permanently paralyzed, and caused 5 deaths in the United States. In addition, in the 1970s and 1980s, incompletely inactivated vaccines caused an outbreak of foot-and-mouth disease among livestock in Western Europe. Foot-and-mouth disease is a highly contagious disease caused by a virus that infects cloven-hoofed animals, such as cattle, pigs, and sheep. Foot-and-mouth disease rarely infects humans but has a great potential for causing severe economic loss.

Source: GAO analysis of scientific literature. Centers for Disease Control and Prevention Public Health Image Library, Charles Farmer (photo). | GAO-16-642

secondary verification steps, such as having a second individual observe a researcher performing the critical inactivation steps. As a result of incidents involving transfers of potentially viable pathogens in 2014, CDC implemented policies directing the use of a verification mechanism to ensure that critical inactivation steps were followed every time inactivation was performed. Other high-containment laboratories we visited had no verification mechanisms in place to ensure inactivation procedures were followed, potentially increasing the risk of incomplete inactivation.

- **Periodic updates to protocols**: According to a DOD report, laboratories should have subject matter experts periodically review and update laboratory protocols to ensure that they have the most up-to-date knowledge. In addition, *Standards for Internal Control in the Federal Government* states that agencies should accurately document internal control activities, such as reviews and updates of their policies.[62] We found that the extent to which inactivation protocols were reviewed and updated to reflect emerging scientific research varied across laboratories. Some high-containment laboratories we visited had a process for reviewing all of their inactivation protocols on an annual basis while other laboratories did not. Periodically reviewing protocols ensures that inactivation protocols are updated to reflect emerging scientific research.

- **Strong safety culture**: Another key safeguard is having a strong safety culture that encourages safe practices, according to laboratory officials and experts we interviewed. We found that laboratories we visited varied in the extent to which they focused on safety. According to several agency officials and experts, identifying and mitigating potential safety issues in high-containment laboratories, including ones that may contribute to incidents involving incomplete inactivation, requires a cultural emphasis on safety. A 2015 report to CDC stated that leadership commitment toward safety at the agency was inconsistent and insufficient at multiple levels.[63] CDC officials told us that they were taking steps to address issues related to safety culture, and a subsequent follow-up report stated that the CDC

[62]GAO/AIMD-00-21.3.1.

[63]Advisory Committee to the Director of the Centers for Disease Control and Prevention, *Recommendations of the Advisory Committee to the Director Concerning Laboratory Safety at CDC* (Atlanta, Ga.: Jan. 13, 2015).

leadership was engaged and committed to promoting laboratory and research safety.[64] Issues related to safety culture have also been identified at DOD. For example, officials at Dugway reported safety issues beyond incidents involving incomplete inactivation and, as noted, a DOD review from December 2015 identified issues related to safety culture at the facility.[65] According to officials and experts, laboratory safety culture is enhanced by an open and transparent environment that encourages nonpunitive reporting of incidents and near-misses. We also found in past work that monitoring safety culture in laboratories is important so that managers remain aware of areas likely to lead to serious problems.[66]

- **Sharing lessons learned:** The sharing of lessons learned as a result of post incident analysis can encourage the implementation of additional safeguards, according to experts. However, we found that laboratories varied in the extent to which they shared lessons learned. Several high-containment laboratories we interviewed internally shared lessons learned through newsletters, training updates, and e-mailed notices, whereas others lacked mechanisms for conveying this information. For example, several researchers told us that they share lessons learned within their respective high-containment laboratories, but there are not always mechanisms in place to share this type of information with others outside of their laboratories or agencies. Officials from the Select Agent Program acknowledged that there were a number of opportunities for the program to improve the sharing of lessons learned.[67] We reported on the importance of sharing lessons learned in the past, recommending in March 2016 that

[64]Advisory Committee to the Director of the Centers for Disease Control and Prevention, *Report of the Advisory Committee to the Director, CDC; Follow-up on CDC Progress* (Atlanta, Ga.: Oct. 29, 2015).

[65]Department of the Army, *AR 15-6 Investigation Report – Individual and Institutional Accountability for the Shipment of Viable Bacillus anthracis from Dugway Proving Ground.* The Life Science Division at Dugway Proving Ground had its select agent registration suspended on August 31, 2015, due to biological safety lapses.

[66]GAO-10-850.

[67]Officials from the Select Agent Program stated that they share lessons learned with registered entities during annual webcasts and in the publication of scientific papers. In addition, they share information throughout the year through “Select Agent Grams” or “SA Grams” when they have important information or updates to communicate, including those related to guidance and policy documents. The Select Agent Program also shares lessons learned internally through inspector training.

departments with high-containment laboratories share lessons learned related to laboratory safety and security with laboratory personnel within their departments.[68]

It is important for researchers in high-containment laboratories to apply safeguards when developing and implementing inactivation protocols to mitigate the risk of incomplete inactivation and share information on lessons learned, according to experts from our meeting and agency documents. Without safeguards, officials risk not effectively implementing inactivation, potentially leading to incomplete inactivation. According to a CDC report, an overriding cause of the potential release of Ebola virus at CDC was inadequate safeguards to sufficiently minimize the possibility that human error could result in exposure to dangerous pathogens.[69]

Varied Documentation Requirements for the Shipment of Inactivated Material Hinders Incident Mitigation

According to experts, once an incident involving incomplete inactivation has taken place, documentation of the shipment of the inactivated pathogens can provide an important safeguard, if it is still viable and needs to be destroyed to prevent potential exposures or release. However, we found through our review of agency documents and interviews with agency officials that laboratories vary in their documentation requirements for inactivated pathogens. The BMBL manual currently provides no guidance for laboratories to create requirements to document the transfer of inactivated material. As a result, some laboratories document the shipment of inactivated material through a material transfer certificate or in laboratory logbooks, but others do not maintain any records on the movement of inactivated material. To illustrate, DOD did not immediately know all of the places that viable *Bacillus anthracis* had been sent following discovery of the Dugway incident. According to DOD, it took several months to identify all of the places that received viable *Bacillus anthracis*.[70] Experts from our meeting stated that documenting shipments of inactivated material would be beneficial for facilitating the identification of laboratories that were inadvertently shipped viable material. In addition, *Standards for Internal Control in the Federal Government* states agencies are to employ control

[68]GAO-16-305.

[69]Centers for Disease Control and Prevention, *Report on the Potential Exposure to Ebola Virus*.

[70]According to DOD officials, DOD was eventually able to track all of the shipments.

activities, such as the accurate recording of transactions and events, to help ensure actions are taken to address risks.[71] Without guidance in the BMBL manual to document the shipment of inactivated pathogens, laboratories are at risk of being unable to locate pathogens in a timely manner, which is important if material thought to be inactivated is determined to still be viable. An expert noted that technologies in other fields may facilitate the documentation of the shipment of material, as is currently done in the food industry.

The Select Agent Program Inconsistently Referred Violations and Enforced Regulations Related to Incidents Involving Incomplete Inactivation

The two agencies that comprise the Select Agent Program—CDC and APHIS—did not consistently refer incidents involving incomplete inactivation for further investigation and enforcement to the HHS Office of Inspector General (OIG) or APHIS's Investigative and Enforcement Services for violations of select agent regulations. For example, the APHIS component of the program did not refer two 2014 incidents it was investigating at CDC laboratories involving incomplete inactivation, while the CDC component of the program referred a number of incidents that it investigated at federal, private, and academic laboratories.[72] We found that it was unclear why some incidents were referred and enforced and not others. Table 5 shows referral and enforcement information related to the 21 identified incidents involving incomplete inactivation of select agents that occurred from 2003 through 2015.

Table 5: Referral and Enforcement Actions by the Centers for Disease Control and Prevention (CDC), Animal and Plant Health Inspection Service (APHIS), and Department of Health and Human Services' Office of Inspector General (OIG) for the 21 Identified Incidents Involving Incomplete Inactivation of Select Agents that Occurred from 2003 through 2015

Laboratory type	Select agent(s) or toxin	Year of incident	Lead agency for investigation	Referred for investigation?[a]	Enforcement action by Federal Select Agent Program[b]	Enforcement action taken by the OIG
Federal	*Bacillus anthracis*	2015	CDC	Yes	Suspension of registration and corrective action plan	Notice of violation letter sent
Federal	*Bacillus anthracis*	2014	APHIS	No	--	N/A[c]

[71]GAO/AIMD-00-21.3.1.

[72]Beginning in October 2012, CDC and APHIS agreed to have APHIS lead inspections of CDC laboratories and CDC lead inspections of APHIS laboratories.

Laboratory type	Select agent(s) or toxin	Year of incident	Lead agency for investigation	Referred for investigation?[a]	Enforcement action by Federal Select Agent Program[b]	Enforcement action taken by the OIG
Federal	Ebola virus	2014	APHIS	No	--	N/A[c]
Federal	*Francisella tularensis*	2011	CDC	Yes[d]	--	Closed without enforcement action
Federal	*Bacillus anthracis*	2008	CDC	No	--	N/A[c]
Federal	*Francisella tularensis*	2007	CDC	Yes	Withdrew registration prior to suspension	Closed without enforcement action
Federal	*Bacillus anthracis*	2007	CDC	Yes	--	Notice of violation letter sent
Federal	*Bacillus anthracis*	2006	CDC	No	--	N/A[c]
Federal	Venezuelan equine encephalitis virus	2006	CDC	No	--	N/A[c]
Federal	*Bacillus anthracis*	2006	CDC	Yes	--	Closed without enforcement action
Federal	Botulinum neurotoxin producing species of *Clostridum*	2006	CDC	Yes	--	Notice of violation letter sent
Academic	Venezuelan equine encephalitis virus	2015	CDC	No	--	N/A[c]
Academic	*Burkholderia pseudomallei*	2014	CDC	No	--	N/A[c]
Academic	*Brucella abortus*, *Brucella melitensis* & *Brucella suis*	2012	CDC	Yes[d]	Corrective action plan	Under investigation
Academic	*Francisella tularensis*	2008	CDC	Yes	Corrective action plan	Notice of violation letter sent
Academic	*Francisella tularensis*	2007	CDC	No	--	N/A[c]
Private	*Francisella tularensis*	2014	CDC	No	--	N/A[c]
Private	Eastern equine encephalitis virus	2010	CDC	Yes	Corrective action plan	Closed without enforcement action
Private	*Bacillus anthracis*	2010	CDC	No	--	N/A[c]
Private	Marburg virus and Ebola virus	2009	CDC	No	--	N/A[c]
Private	*Bacillus anthracis*	2004	CDC	Yes	Suspension of principal investigator's work	$150,000 penalty

Legend: -- = no action taken

Source: GAO analysis of information from the Federal Select Agent Program, 2016. | GAO-16-642

[a]In general, CDC refers violations to the HHS OIG for enforcement and APHIS refers violations to APHIS's Investigative and Enforcement Services.

[b]The Federal Select Agent Program established the corrective action plan program in March 2008.

[c]Because this incident was not referred to the HHS OIG or APHIS Investigative and Enforcement Services, the enforcement action taken is not applicable.

[d]According to officials from the Federal Select Agent Program, this incident was referred to the HHS OIG as part of multiple violations.

Select agents may only be transferred in a manner outlined in the select agent regulations and any release of select agents that causes occupational exposure or release outside of primary containment must be reported to the Select Agent Program. Failure to report the release of a select agent that is still viable because of incomplete inactivation, as well as transferring these agents without proper authorization, would be a violation of the select agent regulations. If the Select Agent Program identifies a possible violation of the select agent regulations, several types of enforcement actions may be taken, as follows:

- **Administrative actions:** The Select Agent Program can suspend or revoke a registered entity's certification of registration, or deny an entity's application to possess, use, or transfer select agents.

- **Referrals to the HHS OIG or APHIS's Investigative and Enforcement Services:** The Select Agent Program may refer violations to HHS OIG or APHIS's Investigative and Enforcement Services,[73] which can levy civil monetary penalties (up to $250,000 for an individual for each violation and up to $500,000 for an entity for each violation); issue a Notice of Violation letter; or close the case.

- **Referral to the FBI:** The Select Agent Program can refer possible violations involving criminal negligence, criminal intent, or suspicious activity or person to the FBI for further investigation. Criminal enforcement may include imprisonment for up to 5 years, a fine, or both.

According to an interagency memorandum of understanding regarding the Select Agent Program, CDC and APHIS should maintain consistency in the application and enforcement of the select agent regulations. In

[73]According to USDA officials, the Select Agent Program and APHIS's Investigative and Enforcement Services may also refer incidents to the USDA OIG but officials were not aware of any such referrals for violations of the select agent regulations.

addition, as noted, *Standards for Internal Control in the Federal Government* states that agencies are to employ control activities, such as appropriately documenting transactions and internal controls.[74] We found, however, that APHIS and CDC did not use the same set of criteria for referring violations for investigation by the HHS OIG or APHIS's Investigative and Enforcement Services, nor clearly documented the bases for referring or not referring violations. Specifically, CDC has an internal written policy that lists criteria for referrals, such as knowingly or negligently transferring a select agent without prior authorization,[75] whereas APHIS has no written policy and officials verbally described the general process to us. According to APHIS officials, they did not refer the two 2014 CDC laboratory incidents to Investigative and Enforcement Services because they did not believe the incidents were caused by any clear wrongdoing or persistent issues. However, APHIS did not provide any documentation on this decision. In other instances, the CDC component of the Select Agent Program referred incidents that appeared to us to be equally or less serious, yet this decision-making process was not clearly documented for all cases.[76]

In addition, it was unclear to us why the Select Agent Program took certain administrative actions, such as revoking or suspending an entity's registration or requiring a corrective action plan, in response to some violations and not others. For example, the program required one private and two academic laboratories to develop corrective action plans following incidents involving incomplete inactivation but never required federal laboratories to develop corrective action plans following such incidents until the widespread Dugway incident in 2015, as shown in table 5. Moreover, a CDC internal review of the Select Agent Program from 2015 also identified issues related to the program's enforcement of violations. In particular, the review stated that the program's enforcement

[74]GAO/AIMD-00-21.3.1.

[75]According to this policy, CDC's Division of Select Agents and Toxins has a list of 12 criteria for when an apparent violation of 42 CFR part 73 could constitute a basis for referral to the HHS OIG, and a list of 8 criteria for when an apparent violation should constitute a basis for referral to the FBI. Some of the criteria overlap, such as the knowing possession, use, or transfer of a select agent or toxin by a nonregistered individual or entity.

[76]Officials from the Select Agent Program told us that there is reasoning behind their processes for referring violations and taking enforcement actions but the reasoning is not always clearly documented for each specific case.

options were limited and difficult to scale to the range of findings on inspections and recommended that the program prioritize and strengthen enforcement actions to the highest risk violations.[77]

The Select Agent Program recently took some steps in an effort to increase consistency in the application and enforcement of select agent regulations. In responding to a draft of this report, the program provided a draft, joint CDC-APHIS document that provides some guidance on when to refer violations and options for enforcement actions.[78] The program shared this draft document with registered entities for review and comment in June 2016. However, program officials did not provide us with a time frame or plan for finalizing and implementing the draft document. Moreover, it is not yet clear to what extent this document will improve the understanding and transparency of the program's enforcement, and it does not define how or when decisions to refer violations and take enforcement actions will be documented.

Without consistent criteria and documentation of decisions for referring violations and enforcing regulations related to incidents involving incomplete inactivation, the Select Agent Program cannot ensure that its regulatory approach to overseeing high-containment laboratories is applied consistently. These inconsistencies, in conjunction with our past work, also raise larger questions about the potential limitation of the Select Agent Program as a whole to effectively and independently oversee high-containment laboratories, both within HHS and across other federal agencies. Select Agent Program officials and an expert from our group noted that the Select Agent Program is independent in its oversight of HHS laboratories as it organizationally exists in a separate part of the department from the HHS agencies that have high-containment laboratories. However, as we have noted in our prior work, existing federal oversight of high-containment laboratories is fragmented and

[77]Centers for Disease Control and Prevention, *90 Day Internal Review of the Division of Select Agents and Toxins*. The CDC internal review also made other recommendations, including that the Select Agent Program produce a report on other approaches to increasing compliance with regulations based on review of other regulatory programs (e.g., nuclear research and aviation safety).

[78]The draft document outlines the severity of various violations and lists when they should be referred to the HHS OIG, APHIS Investigative and Enforcement Services, or FBI. The document also outlines examples of violations and options for enforcement actions.

largely self-policing, raising questions about whether the government framework and oversight are adequate.

Conclusions

Important research on dangerous pathogens depends on the ability of researchers to inactivate these pathogens so that research can proceed without posing an unnecessary risk to human and animal health. HHS, DOD, and other departments and agencies have taken some initial steps to address recent highly publicized incidents involving incomplete inactivation at federal laboratories, such as conducting additional research to improve inactivation methods for certain pathogens. Nevertheless, weaknesses remain in the federal government's oversight of inactivation, as well as related research. In particular, without the ability to easily identify incidents involving incomplete inactivation on reporting forms and a clear and consistent definition of inactivation, HHS and USDA do not know the extent to which incomplete inactivation occurs and whether incidents are being properly identified, analyzed, and addressed. In addition, without coordination of research and actions taken to increase scientific information on inactivation and viability testing across high-containment laboratories, there may continue to be gaps in scientific understanding of inactivation, increasing the risk of incomplete inactivation. In light of the Federal Experts Security Advisory Panel's recommendation to develop a research program on applied biological safety, HHS and USDA are positioned to coordinate research efforts on inactivation and viability testing across high-containment laboratories. Moreover, until HHS and USDA develop comprehensive and consistent guidance on the development, validation, and implementation of inactivation protocols—to include the application of safeguards—researchers will continue to apply differing levels of rigor, resulting in variability in the level of scientific soundness and effectiveness of inactivation protocols. Furthermore, in the absence of HHS guidance on documenting the shipment of inactivated pathogens, laboratories are at risk of being unable to locate these pathogens in a timely manner if they are later determined to be viable, as was seen in the Dugway case. Lastly, without consistent criteria and documentation across the Select Agent Program for referring violations and enforcing regulations, the Select Agent Program cannot ensure that its regulatory approach to overseeing high-containment laboratories is applied consistently—particularly between federal and nonfederal laboratories. This risk is of particular concern given the number of incidents at federal high-containment laboratories and raises questions about the appearance of a lack of independence in the regulation of these laboratories. Moreover, the challenges associated with inactivation when taken into consideration with our past work further illustrates the challenge posed by not having a

single federal agency in charge of determining the aggregate risk associated with high-containment laboratories. In particular, our past findings on the risks posed by the proliferation of high-containment laboratories and the limited federal oversight of those laboratories that do not work with select agents highlights our concerns that existing oversight of high-containment laboratories is fragmented, at times duplicative, and relies on self-policing.

Recommendations for Executive Action

To mitigate the risk to human and animal health due to incidents involving incomplete inactivation of dangerous pathogens used in high-containment laboratories, we are making the following six recommendations:

To understand the extent to which incomplete inactivation occurs and whether incidents are being properly identified, analyzed, and addressed, we recommend that the Secretary of Health and Human Services direct CDC and NIH and that the Secretary of Agriculture direct APHIS to:

- develop clear definitions of inactivation for use within their respective guidance documents that are consistent across the Select Agent Program, NIH's oversight of recombinant pathogens, and the *Biosafety in Microbiological and Biomedical Laboratories* manual; and

- revise reporting forms within their respective areas of oversight to help identify when incidents involving incomplete inactivation occur and analyze the information reported to help identify the causes of incomplete inactivation to mitigate the risk of future incidents.

To increase scientific information on inactivation and viability testing, we recommend that the Secretaries of Health and Human Services and Agriculture coordinate research efforts and take actions to help close gaps in the science of inactivation and viability testing across high-containment laboratories.

To help ensure that inactivation protocols are scientifically sound and are effectively implemented, we recommend that the Secretary of Health and Human Services direct CDC and NIH and that the Secretary of Agriculture direct APHIS to create comprehensive and consistent guidance for the development, validation, and implementation of inactivation protocols—to include the application of safeguards—across the Select Agent Program, NIH's oversight of recombinant pathogens, and the *Biosafety in Microbiological and Biomedical Laboratories* manual.

To help ensure that dangerous pathogens can be located in the event there is an incident involving incomplete inactivation, we recommend that the Secretary of Health and Human Services direct the Directors of CDC and NIH, when updating the *Biosafety in Microbiological and Biomedical Laboratories* manual, to include guidance on documenting the shipment of inactivated material.

To help ensure more consistent enforcement for violations involving incomplete inactivation of select agents, we recommend that the Secretary of Health and Human Services direct CDC and that the Secretary of Agriculture direct APHIS to develop and implement consistent criteria and documentation requirements for referring violations to investigative entities and enforcing regulations related to incidents involving incomplete inactivation.

Agency Comments

We provided a draft of this report for review and comment to USDA, DOD, the Department of Homeland Security, HHS, the Department of the Interior, and the Environmental Protection Agency (EPA). Written responses from USDA, DOD, and HHS are reprinted in appendixes III through V. The Department of Homeland Security, the Department of the Interior, and EPA did not provide written comments. Of the two departments to which we made recommendations, both USDA and HHS agreed with all recommendations. In their written responses, they provided additional information about steps they are taking to improve biological safety and security in high-containment laboratories and to address our recommendations. For example, in October 2015, HHS created a biological safety and security council to coordinate and collaborate across the department. In addition, in response to our recommendation that HHS and USDA coordinate research efforts on the science of inactivation and viability testing, the departments stated that they are taking steps to develop a federally-supported program to improve laboratory biological safety, including examining current gaps related to inactivation. HHS and USDA also described other actions that are underway, including revising the select agent regulations, which they stated that they expect to finalize in October 2016, and developing guidance on enforcement of regulations. USDA, HHS, and DOD also provided technical comments, which we incorporated as appropriate.

As agreed with your offices, unless you publicly announce the contents of this report earlier, we plan no further distribution until 30 days from the report date. At that time, we will send copies of this report to the

appropriate congressional committees; the Secretaries of Agriculture, Defense, Health and Human Services, Homeland Security, and the Interior; the Administrator of EPA; and other interested parties. In addition, the report will be available at no charge on the GAO website at http://www.gao.gov.

If you or your staff members have any questions concerning this report, please contact Timothy M. Persons, Chief Scientist, at (202) 512-6412 or personst@gao.gov or John Neumann, Director, Natural Resources and Environment, at (202) 512-3841 or neumannj@gao.gov. Contact points for our Offices of Congressional Relations and Public Affairs may be found on the last page of this report. Key contributors to the report are listed in appendix VI.

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Appendix I: Objectives, Scope, and Methodology

This report evaluates (1) the extent to which incidents involving incomplete inactivation occurred from 2003 through 2015; (2) any challenges that may affect the implementation of inactivation in high-containment laboratories; and (3) the extent to which the Select Agent Program referred violations and enforced regulations related to incidents involving incomplete inactivation.

To address our objectives, we reviewed relevant laws, regulations, and guidance, including the *Biosafety in Microbiological and Biomedical Laboratories* (BMBL) manual and guidance issued by the Select Agent Program.[1] We also reviewed relevant documentation and interviewed officials from the federal departments that own and operate high-containment laboratories (biological safety level (BSL)-3, BSL-4, or both), as well as officials from some academic and private high-containment laboratories.[2] The federal departments and their component agencies were the Department of Homeland Security; the Department of Defense (DOD) and its departments of the Army, Navy, and Air Force;[3] Department of Energy and its National Nuclear Security Administration and Office of Science; Department of the Interior and its Fish and Wildlife Service and U.S. Geological Survey; Department of Veterans Affairs and its Veterans Health Administration; Department of Health and Human Services (HHS) and its components of Centers for Disease Control and Prevention (CDC), Food and Drug Administration, and the National Institutes of Health (NIH); United States Department of Agriculture (USDA) and its Animal and Plant Health Inspection Service (APHIS),[4] Agricultural Research Service, and Food Safety and Inspection Service; and the United States Environmental Protection Agency (EPA). According to officials from the Department of Veterans Affairs, Interior's Fish and

[1]Department of Health and Human Services, Centers for Disease Control and Prevention and National Institutes of Health, *Biosafety in Microbiological and Biomedical Laboratories*, 5th ed. (Washington, D.C.: December 2009).

[2]As of May 31, 2016, a total of 286 entities were registered with the Select Agent Program. The total number of high-containment laboratories in the United States is unknown, as we found in 2009. See GAO, *High-Containment Laboratories: National Strategy for Oversight is Needed*, GAO-09-574 (Washington, D.C.: Sept. 21, 2009).

[3]We did not interview any officials from high-containment laboratories operated by the Air Force or Navy.

[4]We excluded pathogens under APHIS's Plant Protection and Quarantine program from our review because there were no incidents involving incomplete inactivation of plant pathogens.

Wildlife Service, and EPA, inactivation is not conducted in any of their high-containment laboratories so we excluded them from our scope. In addition, the Department of Energy's Office of Science has not operated a high-containment laboratory since 2006, so we also excluded it from our scope.

To obtain expert views on inactivation related to all of our objectives, we convened a meeting with 19 experts to discuss various issues surrounding inactivation of pathogens in high-containment laboratories. This meeting was held at the National Academy of Sciences (NAS) in February 2016, and staff at NAS assisted in identifying experts for this meeting. To identify the experts appropriate for the meeting, we worked iteratively with NAS staff to identify and review biographical information and relevant qualifications of experts, as well as factors such as representation from academia, industry, and federal government and expertise in a range of areas. The Board on Life Sciences of NAS solicited nominations for the expert panel from its extensive contacts in the biology and risk assessment community, academia, and organizations interested in biodefense. These contacts included current and former committee members, current and former members of NAS's Board on Life Sciences, and select members of NAS. NAS initially identified a list of approximately 110 nominees. From this initial list, NAS selected experts based on their knowledge and expertise in pathogen and toxin inactivation and control, biological safety, risk assessment, legal requirements, standards development, incident reporting, epidemiology, and statistics, as well as their experience in academic, industry, and federal government sectors. In order to facilitate discussion among participants, NAS did not include any federal government employees from the Select Agent Program. Once we came to agreement with NAS on the final list of 19 experts for the meeting, these experts were evaluated for any conflicts of interest. A conflict of interest was considered to be any current financial or other interest that might conflict with the service of an individual because it (1) could impair objectivity and (2) could create an unfair competitive advantage for any person or organization. We discussed internally all potential conflicts. The 19 experts were determined to be free of conflicts of interest, and the group as a whole was judged to have no inappropriate biases. See appendix II for a list of the experts.

The 2-day expert meeting was comprised of eight sessions covering a range of topics, such as incidents involving incomplete inactivation, scientific issues, and standards and guidance. We developed the session topics based on our researchable objectives and issues that were

identified in our audit work, including our review of the peer-reviewed literature, analysis of agency documents, and interviews with agency and laboratory officials. The meeting was recorded and transcribed to ensure that we accurately captured the experts' statements, and we reviewed and analyzed the transcripts as a source of evidence. Although the expert meeting was not designed to reach a formal consensus on the issues, a number of themes emerged from the group's discussion to which there was general agreement. The group generally agreed on various issues and had several suggestions for how to address them. Following the meeting, we asked five of the experts to review our draft report to ensure expert comments and scientific concepts were appropriately captured. In selecting experts to review our draft, we first excluded all foreign individuals because the draft had not undergone a sensitivity review, as well as all federal officials because federal agencies had separate opportunities to comment on the draft during the agencies' official comment period. Then, from the remaining experts, we selected experts to represent a range of expertise, including (1) one expert from industry, (2) one biological safety officer, (3) one policy expert, (4) one director of a high-containment laboratory, and (5) one individual with legal expertise. We incorporated comments from these experts into our final report.

To evaluate the extent to which incidents involving incomplete inactivation occurred, we analyzed documentation on incidents reported to the CDC, APHIS, and NIH since 2003—when reporting of incidents involving the theft, loss, and release of select agents was first required under the Select Agent Program—through 2015—the most recent year for which data were available. We also interviewed officials from CDC and APHIS on the reporting of incidents to the Select Agent Program, and officials from NIH on the reporting of incidents involving recombinant pathogens. We took several steps to determine the reliability of the agencies' incident databases, including interviewing agency officials and reviewing agency documents. We determined that the Select Agent Program incident database did not capture some cases of inactivation and was therefore not reliable on its own for establishing the number of incidents. We verified through interviews and documentation each incident identified in the Select Agent Program database as well as additional incidents that we identified. We conducted site visits for 7 of 10 high-containment laboratories and interviewed officials from 8 of the 10 high-containment laboratories at which incidents involving incomplete inactivation were originally reported to us by the Select Agent Program. We contacted officials from all 10 high-containment laboratories at which incidents involving incomplete inactivation were originally reported to us to arrange interviews; however, officials from one university and one private

laboratory declined to be interviewed. We also interviewed officials from a nongeneralizable sample of 19 high-containment laboratories across the country that had not reported incidents, which were generally selected to represent a range of high-containment laboratories that work with human and animal pathogens and biological safety levels. The views of these officials are not generalizable to all laboratories, but they provide illustrative examples. We also interviewed officials from the Department of Labor's Occupational Health and Safety Administration and HHS's National Institute for Occupational Safety and Health to determine if they were aware of any incidents involving incomplete inactivation at high-containment laboratories. Because these agencies were not aware of any incidents involving incomplete inactivation and did not have any requirements related to the reporting of such incidents, we did not include them in our additional work.

We compared information learned from interviews with laboratory and agency officials and from federal documents about the definition of inactivation and incidents involving incomplete inactivation with comments from our expert meeting, the BMBL manual, and our past work.[5] Specifically, experts, the BMBL manual, and our past work emphasized the need for clear definitions to avoid confusion and maintain consistent reporting. In this respect, we considered the extent to which the definitions were consistent across the Select Agent Program, NIH's oversight of recombinant pathogens, and the BMBL manual. We also analyzed reporting forms for identification of incidents involving incomplete inactivation from the Select Agent Program and NIH's oversight of recombinant pathogens.

To identify challenges that potentially affect the implementation of inactivation in high-containment laboratories, we reviewed relevant documents, such as inactivation protocols, biological safety manuals, laboratory newsletters, and articles from peer-reviewed literature. We also discussed challenges that exist and safeguards applied to address these challenges in our interviews with agency officials and researchers from

[5]Based on our previous reporting, we have found that metrics should be reportable in a consistent fashion, and that a key part of consistent reporting is ensuring that standardized definitions, methodologies, and procedures will be used, as noted. In addition, we have reported that inconsistent definitions limit the comparability of programs across agencies. See GAO, *Defense Inventory: Actions Underway to Implement Improvement Plan, but Steps Needed to Enhance Efforts,* GAO-12-493 (Washington, D.C.: May 3, 2012).

high-containment laboratories and during our expert meeting. We also interviewed officials from the Department of Commerce's National Institute of Standards and Technology to learn more about the process for developing scientific standards, and officials from CDC's Laboratory Response Network to discuss standard protocols used by the network. We compared information we learned from our interviews with that of agency and laboratory officials and our review of federal documents on the development and validation of inactivation protocols and application of safeguards with key reports related to biological safety, expert comments, and our past work. In particular, we considered the extent to which current guidance was consistent with a Federal Expert Security Advisory Panel report that recommended that institutional biosafety programs require validation of all standard operating procedures for inactivation;[6] our past work, which has emphasized the importance of validation more generally;[7] and comments during our expert meeting, which emphasized the need to apply safeguards when developing and carrying out inactivation protocols. We also compared information from our interviews with laboratory officials and our review of related documents on the shipment of inactivated material with expert comments and internal controls from *Standards for Internal Control in the Federal Government*.[8]

To determine how the Select Agent Program referred violations and enforced regulations related to incidents involving incomplete inactivation in high-containment laboratories, we reviewed guidance, inspection reports, and other documents from the Select Agent Program, APHIS's Investigative and Enforcement Services, and the USDA and HHS Offices of Inspector General (OIG). In our interviews with laboratory and Select Agent Program officials, we discussed steps the Select Agent Program has taken to refer violations and enforce regulations related to incidents involving incomplete inactivation. We also interviewed officials from the Investigative and Enforcement Services and HHS and USDA OIG to better understand their processes for enforcing the select agent regulations. We compared information we learned from our interviews

[6]Federal Experts Security Advisory Panel, *Report of the Federal Experts Security Advisory Panel* (Washington, D.C.: December 2014).

[7]GAO, *Anthrax: Agency Approaches to Validation and Statistical Analyses Could Be Improved*, GAO-15-80 (Washington, D.C.: Dec. 19, 2014).

[8]GAO, *Standards for Internal Control in the Federal Government*, GAO/AIMD-00-21.3.1 (Washington, D.C.: November 1999).

with Select Agent Program officials and our review of program documents on the enforcement of violations of the select agent regulations with agency guidance on the program and internal controls from *Standards for Internal Control in the Federal Government*.[9] In particular, an interagency memorandum of understanding on the Select Agent Program states that agencies should maintain consistency in the application and enforcement of select agent regulations, and *Standards for Internal Control in the Federal Government* states that agencies are to employ control activities, such as appropriately documenting transactions and internal controls. We considered the extent to which enforcement referrals and actions were consistent with these documents.

We conducted this performance audit from July 2015 to August 2016 in accordance with generally accepted government auditing standards. Those standards require that we plan and perform the audit to obtain sufficient, appropriate evidence to provide a reasonable basis for our findings and conclusions based on our audit objectives. We believe that the evidence obtained provides a reasonable basis for our findings and conclusions based on our audit objectives.

[9]GAO/AIMD-00-21.3.1.

Appendix II: List of Experts

The names and affiliations of the experts who participated in the group discussion held February 11-12, 2016 in Washington, D.C., are as follows:

- Allan Bennett, Ph.D., General Project Manager, Public Health England
- Robert Buchanan, Ph.D., Professor, University of Maryland
- Lawrence Blyn, Ph.D., Senior Director, Ibis Biosciences, Abbott
- Charles Gerba, Ph.D., Professor, University of Arizona
- Joshua Goldberg, J.D., Attorney, Goldberg Legal Services
- Jens-Peters Gregersen, Ph.D., GlaxoSmithKline Vaccines
- Gigi Kwik Gronvall, Ph.D., Senior Associate, University of Pittsburgh Medical Center
- Molly Isbell, Ph.D., Director, Signature Science
- Richard Jaffe, Ph.D., Director, Medical Countermeasure Strategy & Requirements Division, Office of Policy and Planning, Assistant Secretary for Preparedness and Response, Department of Health and Human Services
- Barbara Johnson, Ph.D., Owner, Biosafety Biosecurity International
- Thomas Ksiazek, Ph.D., Professor, University of Texas Medical Branch
- Jens Kuhn, Ph.D., Lead Virologist, Integrated Research Facility at Fort Detrick
- Justin Lessler, Ph.D., Associate Professor, Johns Hopkins University
- Benito Marinas, Ph.D., Professor, University of Illinois
- Brian O'Shea, Ph.D., Senior Biological Safety Officer, Battelle Memorial Institute
- Karlene Roberts, Ph.D., Professor Emeritus, University of California, Berkeley

- Sophie Smither, Ph.D., Principal Scientist, Defence Science and Technology Laboratory
- Jeanette Thurston-Enriquez, Ph.D., Science Program and Analysis Officer, United States Department of Agriculture
- David Wunschel, Ph.D., Staff Scientist, Pacific Northwest National Laboratory

The comments of most of these experts represented the views of the experts themselves and not the agency, university, or company they are affiliated with.

Appendix III: Comments from the Department of Agriculture

United States Department of Agriculture

Office of the Secretary
Washington D.C. 20250

JUN 2 3 2016

Dr. Timothy M. Persons, Ph.D.
Chief Scientist
and
Mr. John Neumann
Director, Natural Resources and Environment
Government Accountability Office
441 G Street NW
Washington, DC 20548

Dear Dr. Persons and Mr. Neumann:

Thank you for providing the United States Department of Agriculture (USDA) the opportunity to comment on the Government Accountability Office's (GAO) Draft Report "High Containment Laboratories: Improved Oversight of Dangerous Pathogens Needed to Mitigate Risk" (16-642). We have addressed the Recommendations made to the Secretary of Agriculture.

GAO Recommendation (1)

To understand the extent incomplete inactivation occurs and whether incidents are being properly identified, analyzed, and addressed, GAO recommends that the Secretary of Health and Human Services (HHS) direct the Centers for Disease Control and Prevention (CDC) and National Institutes of Health (NIH) and that **the Secretary of Agriculture direct the Animal and Plant Health Inspection Service (APHIS) to develop clear definitions of inactivation for use within their respective guidance documents that are consistent across the Select Agent Program, NIH's oversight of recombinant pathogens, and the *Biosafety in Microbiological and Biomedical Laboratories* manual.**

USDA Response

USDA agrees with this Recommendation. USDA, in collaboration with HHS, has proposed revisions to the select agent regulations to provide definitions of inactivation, as well as the definition of viability testing. The final rule is expected to be published in October 2016. In association with the final rule, the Federal Select Agent Program will post new guidance to assist entities with the development and implementation of inactivation procedures, as well as with viability testing.

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Dr. Persons and Mr. Neumann:
Page 2

GAO Recommendation (2)

To understand the extent incomplete inactivation occurs and whether incidents are being properly identified, analyzed, and addressed, GAO recommends that the Secretary of HHS direct CDC and NIH and that **the Secretary of Agriculture direct APHIS to revise reporting forms within their respective areas of oversight to help identify when incidents involving incomplete inactivation occur and analyze the information reported to help identify the causes of incomplete inactivation to mitigate the risk of future incidents.**

USDA Response

USDA agrees with this Recommendation. The Federal Select Agent Program is planning to update APHIS/CDC Form 3 (Report of Theft, Loss, or Release of Select Agents and Toxins) to include definitions of release types, such as inactivation failure. The Federal Select Agent Program is also planning to update the related guidance document, "Incident Form to Report Potential Theft, Loss Release or Occupational Exposure." Once the drafts of Form 3 and related guidance are finalized, the Federal Select Agent Program will distribute the documents to the regulated community for comment before seeking approval from the Office of Management and Budget.

GAO Recommendation (3)

To increase scientific information related to inactivation and viability testing, GAO recommends that the Secretaries of HHS and **Agriculture coordinate research efforts and take actions to help close gaps in the science of inactivation and viability testing across high-containment laboratories.**

USDA Response

USDA agrees with this Recommendation. USDA concurs with the recommendation to coordinate research efforts and take actions to help close gaps in the science of inactivation. USDA, along with HHS, in our roles as co-chairs of the Federal Experts Security Advisory Plan (FESAP) examined current gaps related to inactivation of high-containment laboratories.

USDA recognizes the importance of research related to the science of inactivation in high-containment laboratories. USDA and HHS are leading the implementation (with support from other federal agencies) of FESAP's Recommendation 1.6 to "develop and maintain a robust federally-supported program of applied biosafety research to create additional evidence-based practices and technologies, and to update existing practices and operations." USDA believes support for applied biosafety research could yield evidence-based improvements and would address inactivation, disinfection, decontamination, and sterilization methods as areas of focus. However, USDA cautions that there has been no new funding directed towards a federally-supported program of applied biosafety research.

USDA and HHS are also leading the implementation of FESAP's Recommendation 1.3 to "require that an appropriately constituted and qualified review entity validate local policies, laboratory protocols, and mitigation plans involving the inactivation, sterilization, or decontamination of biohazardous materials at research institutions." Implementation of Recommendation 1.3 is currently underway and requires collaboration between research personnel and institutional biosafety program staff, development of a risk assessment, and critical expert reviews of the data generated regarding the validation process. The outcome for federal agencies' will be more consistent oversight and scientific understanding of processes for inactivation, sterilization, and decontamination of biohazards in high-containment laboratories.

GAO Recommendation (4)

To help ensure inactivation protocols are scientifically sound and are effectively implemented, GAO recommends that the Secretary of HHS direct CDC and NIH and that **the Secretary of Agriculture direct APHIS to create comprehensive and consistent guidance for the development, validation, and implementation of inactivation protocols—to include the application of safeguards—across the Select Agent Program, NIH's oversight of recombinant pathogens, and the *Biosafety in Microbiological and Biomedical Laboratories* manual.**

USDA Response

USDA agrees with this Recommendation. As stated in our response to Recommendation #1, USDA and HHS have proposed revisions to the select agent regulations to provide definitions of inactivation and viability testing. The final rule is expected to be published in October 2016. In association with the final rule, the Federal Select Agent Program will post guidance to assist entities with development and implementation of inactivation procedures and viability testing.

GAO Recommendation (6)

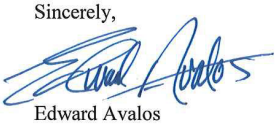
To help ensure more consistent enforcement for violations involving incomplete inactivation of select agents, GAO recommends that the Secretary of HHS direct CDC and that **the Secretary of Agriculture direct APHIS to develop and implement consistent criteria and documentation requirements for referring violations to investigative entities and enforcing regulations related to incidents involving incomplete inactivation.**

USDA Response

USDA agrees with this Recommendation. The Federal Select Agent Program has developed categories of inspection departures including incomplete inactivation grouped by level of risk, along with enforcement options that may be applied for each category. Violations are grouped into a three-tier risk scoring system of low, moderate, or serious severity. The Federal Select Agent Program plans to communicate these risk-

scoring categories to the regulated community by the end of June 2016 for comment and to provide visibility concerning the application of enforcement options for incidents involving incomplete inactivation. After analyzing the comments from the regulated community, the Federal Select Agent Program plans to finalize the risk-scoring system as a tool for the Federal Select Agent Program to ensure consistency in enforcement actions.

Sincerely,



Edward Avalos
Under Secretary
Marketing and Regulatory Programs

Appendix IV: Comments from the Department of Defense

ASSISTANT SECRETARY OF DEFENSE
3050 DEFENSE PENTAGON
WASHINGTON, DC 20301-3050

NUCLEAR, CHEMICAL, AND
BIOLOGICAL DEFENSE PROGRAMS

JUN 20 2016

Dr. Timothy M. Persons
Director, Applied Research and Methods
U.S. Government Accountability Office
441 G Street, N.W.
Washington, DC 20548

Dear Dr. Persons:

This is the Department of Defense (DoD) response to the Government Accountability Office (GAO) Draft Report, GAO-16-642, "HIGH-CONTAINMENT LABORATORIES: Improved Oversight of Dangerous Pathogens Needed to Mitigate Risk," dated June 8, 2016 (GAO Code 460640).

The Department appreciates the opportunity to review the draft report and has no comments. We value the analysis provided by the GAO; the GAO's observations will inform efforts of the DoD Biological Select Agents and Toxins Biosafety Program and improve oversight.

Sincerely,

Arthur T. Hopkins
Principal Deputy
Performing the Duties of the ASD(NCB)

Appendix V: Comments from the Department of Health and Human Services

DEPARTMENT OF HEALTH & HUMAN SERVICES

OFFICE OF THE SECRETARY

Assistant Secretary for Legislation
Washington, DC 20201

JUN 30 2016

John Neumann
Director, Natural Resources and Environment
U.S. Government Accountability Office
441 G Street NW
Washington, DC 20548

Dear Mr. Neumann:

Attached are comments on the U.S. Government Accountability Office's (GAO) report entitled, "*High-Containment Laboratories: Improved Oversight of Dangerous Pathogens Needed to Mitigate Risk*" (GAO-16-642).

The Department appreciates the opportunity to review this report prior to publication.

Sincerely,

Jim R. Esquea
Assistant Secretary for Legislation

Attachment

GENERAL COMMENTS OF THE DEPARTMENT OF HEALTH AND HUMAN SERVICES (HHS) ON THE GOVERNMENT ACCOUNTABILITY OFFICE'S DRAFT REPORT ENTITLED: HIGH-CONTAINMENT LABORATORIES: IMPROVED OVERSIGHT OF DANGEROUS PATHOGENS NEEDED TO MITIGATE RISK (GAO-16-642)

The U.S. Department of Health and Human Services (HHS) appreciates the opportunity from the Government Accountability Office (GAO) to review and comment on this draft report.

HHS is strongly committed to ensuring that high containment laboratories operate safely and securely while conducting research, diagnostics, and response activities critical to the safety and protection of the American people.

In October 2015, the Department established the HHS Biosafety and Biosecurity Coordinating Council in order to, on behalf of the Secretary, provide a high-level and formal mechanism to coordinate and collaborate on biosafety and biosecurity issues across the Department. The Council will advise the Secretary and senior leadership of the Department on biosafety and biosecurity matters; foster coordination and collaboration among HHS Operating and Staff Divisions (OPDIVS and STAFFDIVS); recommend Department-wide policy; facilitate the sharing of best practices related to training and other biosafety and biosecurity matters; facilitate consistent messaging related to biosafety and biosecurity issues; and build upon existing activities and authorities within the Department. The Council is not intended to assume direct responsibilities over the management or execution of individual agencies' biosafety and biosecurity programs or incident management of events.

Among other responsibilities, the Council has been tasked with the following responsibilities:

- Develop a coordinating framework to coordinate and improve biosafety and biosecurity standards and activities across the Department to include identification of key actions to enhance biosafety and biosecurity; progress on such actions; and opportunities to further enhance biosafety and biosecurity;
- Serve as the Department level coordinating point of contact for biosafety and biosecurity matters with the Executive Office of the President, other federal departments and agencies, and other stakeholders;
- Coordinate implementation of U.S. Government-wide recommendations on biosafety and biosafety practices resulting from parallel federal and non-federal reviews (Federal Experts Security Advisory Panel [FESAP] and Fast Track Action Committee on Select Agent Regulations [FTAC-SAR] recommendations); and
- Coordinate development of a system for increased transparency related to notification of key laboratory incidents.

In addition to actions taken by HHS at the departmental level to strengthen biosafety and biosecurity, HHS has also been collaborating with federal partners to improve and strengthen biosafety and biosecurity. On October 29, 2015, the United States Government (USG) released two sets of recommendations, one from the FESAP (http://www.phe.gov/s3/Documents/fesap.pdf) and another from the FTAC-SAR (http://www.phe.gov/s3/Documents/ftac-sar.pdf). Both groups were co-chaired by HHS. These recommendations are key elements of progress toward strengthening the government's biosafety and biosecurity practices and the oversight system. The recommendations of both groups are

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GENERAL COMMENTS OF THE DEPARTMENT OF HEALTH AND HUMAN SERVICES (HHS) ON THE GOVERNMENT ACCOUNTABILITY OFFICE'S DRAFT REPORT ENTITLED: HIGH-CONTAINMENT LABORATORIES: IMPROVED OVERSIGHT OF DANGEROUS PATHOGENS NEEDED TO MITIGATE RISK (GAO-16-642)

complementary and will help further ensure that life science efforts that benefit the global community in countering biological threats are carried out safely and securely.

The USG expects that implementing the FESAP and FTAC-SAR recommended actions will strengthen biosafety and biosecurity practices and oversight activities and has developed a plan (http://www.phe.gov/s3/Documents/fesap-ftac-ip.pdf) to do so. The plan includes concrete actions to optimize biosafety and biosecurity policies and practices, as well as oversight. Steps are currently being taken to enhance the culture of responsibility; strengthen oversight; promote outreach and education; conduct applied biosafety research; develop an incident reporting system; enhance material accountability and inspection processes; and update regulations and guidance. An approach will be implemented to determine the appropriate number of high-containment U.S. laboratories required to possess, use, or transfer BSAT.

In addition to the aforementioned efforts, HHS is collaborating with other federal partners to support implementation of efforts to strengthen biosafety and biosecurity including incident reporting, training, and inspections. By sharing best practices and leveraging USG-wide work on biosafety and biosecurity, the Department will continue to improve the operation of high containment laboratories while supporting their vital mission.

Recommendation

To understand the extent incomplete inactivation occurs and whether incidents are being properly identified, analyzed, and addressed, GAO recommends that the Secretary of HHS direct the Centers for Disease Control and Prevention (CDC) and the National Institutes of Health (NIH) and the Secretary of Agriculture direct Animal and Plant Health Inspection Service (APHIS) to:

- Develop clear definitions of inactivation for use within their respective guidance documents that are consistent across the Select Agent Program, NIH's oversight of recombinant pathogens, and the *Biosafety in Microbiological and Biomedical Laboratories* manual; and
- Revise reporting forms within their respective areas of oversight to help identify when incidents involving incomplete inactivation occur and analyze the information reported to help identify the causes of incomplete inactivation to mitigate the risk of future incidents.

HHS Response

HHS concurs with GAO's recommendation. As applicable, when the term inactivation is used in any guidance documents related to the oversight of recombinant or synthetic nucleic acid molecules and the *Biosafety in Microbiological and Biomedical Laboratories* (BMBL), NIH will consider harmonizing with the Select Agent Program to provide clear and consistent definitions of inactivation.

NIH will also consider revising its template for reporting incidents subject to the *NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules* to include "incomplete inactivation" as a type of incident in the field related to the nature of the incident. However, NIH

GENERAL COMMENTS OF THE DEPARTMENT OF HEALTH AND HUMAN SERVICES (HHS) ON THE GOVERNMENT ACCOUNTABILITY OFFICE'S DRAFT REPORT ENTITLED: HIGH-CONTAINMENT LABORATORIES: IMPROVED OVERSIGHT OF DANGEROUS PATHOGENS NEEDED TO MITIGATE RISK (GAO-16-642)

notes that use of the NIH incident reporting template is not mandatory. While institutions are encouraged to use the reporting template, reports may be submitted in any format.

Additionally, CDC, in collaboration with the U.S. Department of Agriculture (USDA), has proposed revisions to the select agent regulations to provide definitions of inactivation and viability testing. The final rule is expected to be published in October 2016. Developing functional definitions of inactivation and viability testing that gain consensus in the field will be a complex process that will require evolving over time. The Federal Select Agent Program is considering changes to the APHIS/CDC Form 3 (Report of Theft, Loss, or Release of Select Agents and Toxins) to include definitions of release types (i.e., inactivation failure) and a more usable guidance document. Once the draft is finalized, the form and guidance document will be distributed to the regulated community for feedback prior to seeking approval from the Office of Management and Budget. It should be noted that the reporting form (Form 3) is only one part of the investigation process for release incidents. Direct communication with the entity to explore root causes and ensure proper actions have been taken to protect people and secure select agents is a critical part of the process.

Recommendation

To increase scientific information related to inactivation and viability testing, GAO recommends that the Secretaries of HHS and Agriculture coordinate research efforts and take actions to help close gaps in the science of inactivation and viability testing across high-containment laboratories.

HHS Response

HHS concurs with GAO's recommendation. As co-chairs of the FESAP, HHS and USDA have examined current gaps related to inactivation. HHS and USDA have taken measures to support implementation of the FESAP recommendation to develop and maintain a robust federally supported program of applied biosafety research to create additional evidence-based practices and technologies, and to update existing practices and operations (FESAP 1.6). Applied biosafety research could yield evidence-based improvements that could potentially influence inactivation, disinfection, decontamination, and sterilization methods.

In 2016, CDC's Office of the Associate Director for Laboratory Science and Safety established the Laboratory Safety Science and Innovation Intramural Research Fund (LaSSI). The LaSSI Fund provides one-time funding, up to $250,000 per venture, for projects that:

- Provide data to improve laboratory safety standards or guidelines;
- Develop tools to improve laboratory safety procedures and/or enhance the quality of science;
- Measurably improve laboratory safety procedures and/or enhance the quality of science; and
- Improve laboratory safety and/or quality through innovative techniques.

In fiscal year 2016, the LaSSI Fund awarded over $1.3 million for 13 intramural projects. Some of the awards will work toward understanding inactivation conditions for significant biological

GENERAL COMMENTS OF THE DEPARTMENT OF HEALTH AND HUMAN SERVICES (HHS) ON THE GOVERNMENT ACCOUNTABILITY OFFICE'S DRAFT REPORT ENTITLED: HIGH-CONTAINMENT LABORATORIES: IMPROVED OVERSIGHT OF DANGEROUS PATHOGENS NEEDED TO MITIGATE RISK (GAO-16-642)

pathogens, including Middle East respiratory syndrome coronavirus, polio, Zika, and hemorrhagic fever viruses.

Also related to the issue of inactivation, the FESAP developed a recommendation to require that an appropriately constituted and qualified review entity validate local policies, laboratory protocols, and mitigation plans involving the inactivation, sterilization, or decontamination of biohazardous materials at research institutions (FESAP 1.3). Implementation of the recommendation is currently underway. The review process will require collaboration between research personnel and institutional biosafety program staff and will include a risk assessment and critical expert reviews of the data generated as part of the validation process.

One anticipated outcome of the implementation of the FESAP 1.3 recommendation is more consistent oversight and scientific understanding of processes for inactivation, sterilization, and decontamination of biohazards.

Moving forward, HHS looks forward to working with GAO and partners to assist in the implementation of applicable recommendations and Congressional actions.

Recommendation

To help ensure inactivation protocols are scientifically sound and are effectively implemented, GAO recommends that the Secretary of HHS direct CDC and NIH and that the Secretary of Agriculture direct APHIS to create comprehensive and consistent guidance for the development, validation, and implementation of inactivation protocols- to include the application of safeguards – across the Select Agent Program, NIH's oversight of recombinant pathogens, and the BMBL manuals.

HHS Response

HHS concurs with GAO's recommendation. HHS and USDA have proposed revisions to the select agent regulations to provide definitions of inactivation and viability testing. The final rule is expected to be published in October 2016. In association with the final rule, the Federal Select Agent Program will be posting guidance to assist entities with development, validation, and implementation of inactivation procedures and viability testing. There is complexity in these methods and needs for them such that there will be unintended consequences on research and development associated with the choices made. This will require ongoing attention and evolution of approaches.

Additionally, HHS will examine this recommendation to the *NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules* and the BMBL and, as applicable, consider developing guidance related to the development, validation, and implementation of inactivation protocols that is harmonized with any guidance provided by the Select Agent Program.

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GENERAL COMMENTS OF THE DEPARTMENT OF HEALTH AND HUMAN SERVICES (HHS) ON THE GOVERNMENT ACCOUNTABILITY OFFICE'S DRAFT REPORT ENTITLED: HIGH-CONTAINMENT LABORATORIES: IMPROVED OVERSIGHT OF DANGEROUS PATHOGENS NEEDED TO MITIGATE RISK (GAO-16-642)

Recommendation
To help ensure that dangerous pathogens can be located in the event there is an incident involving incomplete inactivation, GAO recommends that the Secretary of HHS direct the Directors of CDC and NIH, when updating the *BMBL* manual, to include guidance on documenting the shipment of inactivated material.

HHS Response
HHS concurs with GAO's recommendation. CDC and NIH will work together to consider including guidance to entities on documenting the shipment of inactivated material when revising the BMBL in order to harmonize with guidance provided by the Select Agent Program.

Recommendation
To help ensure more consistent enforcement for violations involving incomplete inactivation of select agents, GAO recommends that the Secretary of HHS direct CDC and that the Secretary of Agriculture direct APHIS to develop and implement consistent criteria and documentation requirements for referring violations to investigative entities and enforcing regulations related to incidents involving incomplete inactivation.

HHS Response
HHS concurs with GAO's recommendation. The Federal Select Agent Program has developed categories of inspection departures grouped according to the level of risk and related enforcement options that may be applied for each, which includes issues related to incomplete inactivation. The Federal Select Agent Program plans to communicate the enforcement options table to the regulated community by the end of June to provide visibility to the application of enforcement options and seek feedback. Feedback will aid in further reconciliation of referral thresholds between HHS and USDA. The Federal Select Agent Program acknowledges the needs for consistency and is moving in that direction. However, enforcement actions will never be automatic. It should also be noted that referral to investigative entities is a significant decision and requires judgment. It is one method, a punitive method, of enforcing the regulations. Far more work is done by the Federal Select Agent Program to facilitate compliance and to escalate oversight to ensure compliance than referral to investigative entities.

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Appendix VI: Contacts and Staff Acknowledgments

GAO Contacts

Timothy M. Persons, (202) 512-6412 or personst@gao.gov
John Neumann, (202) 512-3841 or neumannj@gao.gov

Staff Acknowledgments

In addition to the individuals named above, Mary Denigan-Macauley (Assistant Director), Sushil Sharma (Assistant Director), Pille Anvelt, Amy Bowser, Caitlin Dardenne, Ashley Grant, Dani Greene, Ushna Ilyas, Lesley Rinner, Amber Sinclair, and Elizabeth Wood made key contributions to this report.