Chapter 31

BIOLOGICAL SURETY

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INTRODUCTION

Evidence of human engagement in chemical and biological warfare to terrorize individuals or opposing armies and concurrent efforts to reduce these threats date back to the dawn of civilization. Some of the more prominent reports of possible biological warfare from the past millennium include the poisoning of enemy water wells with rye ergot fungus, a hallucinating agent, by the Assyrians; the use of hellebore roots to poison the drinking water of Kirrha by Solon of Athens (600 BCE); the use of poison arrows dipped in gangrene- and tetanus-causing agents by the Scythian archers of the Trojan war (400 BCE); tossing of venomous snakes onto the opponent ships of Pergamus by Hannibal at Eurymedon (190 BCE); hurling decomposing human bodies into enemy water wells by Emperor Barbarossa at the battle of Tortona (1155); catapulting the cadavers of plague victims over the city walls of Caffa (now Feodosia, Ukraine) by the Tartars (1346); distributing blankets and handkerchiefs from smallpox-infected patients to Native Americans by the British troops (1763); and sale of clothing from yellow fever and smallpox-infected patients by Confederate soldiers to unsuspecting Union troops during the American Civil War.[1-5] Causative agents were linked to infectious diseases by 19th-century scientists Louis Pasteur and Robert Koch. Advances in the field of microbiology soon led to the isolation of microbial agents from diseased humans and animals. Moreover, the development of *in vitro* methods to grow these pathogens in large scale gave those interested in biological weapons a new perspective in selecting an agent based on its ability to cause fear, disease, and mass casualties.

Recognizing the destructive powers of war, especially the devastation caused by chemical and biological weapons, developed nations of the world have attempted to establish international rules of engagement by drafting treaties and declarations that primarily focused on disarmament, laws of war, and war crimes (Table 31-1). The 1st International Peace Conference in 1899 at Hague, The Netherlands, produced the Prohibition of the Use of Projectiles with the Sole Object to Spread Asphyxiating Poisonous Gases.[6] Ratified by all major powers except the United States of America, this declaration states that in any war between signatory powers, the parties will abstain from using projectiles, "the sole object of which is the diffusion of asphyxiating or deleterious gases." The 2nd International Peace Conference held in 1907 prohibited the use of poisons and weapons with poisons.[7] The major accomplishment of these peace conferences was the establishment of an international court for mandatory arbitration and dispute settlement between nations.

Despite the declaration prohibiting projectiles that spread poisonous gases, biological weapons were not unequivocally prohibited. The advent of World War I (WWI) led to rapid progression of chemical and biological weapons, particularly those that were developed and used by the German Army. Various chemical weapons were used extensively during WWI primarily to demoralize, injure, and kill entrenched enemies indiscriminately. These ranged from disabling tear gas to deadly phosgene and chlorine gases. Due to the widespread use of chemical weapons and rapid development of high-explosive agents during this war, WWI is often referred to as "The Chemists' War." With advances in the understanding of bacterial agents during the 19th century, the German Army launched a massive biological weapons campaign against the Allied Forces during WWI. However, instead of targeting humans, they concentrated on infecting livestock (horses and mules) with *Bacillus anthracis* and *Burkholderia mallei.* Several animals died from these infections, but these biological tactics failed to match the success of the chemical warfare efforts.[8]

After the end of WWI and with no lasting peace in sight, the Biological Weapons Convention developed the "Protocol for the Prohibition of the Use in War of Asphyxiating, Poison or Other Gases and the Bacte-

TABLE 31-1

TIMELINE OF INTERNATIONAL RULES AND TREATIES TO LIMIT OR BAN CHEMICAL AND BIOLOGICAL WEAPONS USE

Year	Significant Event
1899	1st International Peace Conference Prohibition of the use of projectiles to spread asphyxiating poisonous gases
1907	2nd International Peace Conference Prohibition of the use of poisons and weapons with poisons
1925	The Geneva Protocol Prohibition of germ (biological) and chemical warfare
1972	Biological Weapons Convention Prohibition of development, production, and stockpiling of biological weapons
1986	The Second Review Conference Establishment of confidence building measures

riological Methods of Warfare," signed in 1925 at Geneva, Switzerland, as an extension of the international peace conferences of 1899 and 1907. Also known as the "Geneva Protocol," this treaty permanently bans the use of all forms of chemical and biological warfare. However, it did not prohibit the use of biological or chemical agents for research and development, storage, and transfer. Many countries that signed on to the Geneva Protocol retained the right to retaliate against biological or chemical weapon attacks with their own arsenals. Treaties, declarations, and protocols produced by the international community continued to lack robust verification methods, leading to distrust among nations and reinvigoration of chemical and biological weapons programs prior to World War II (WWII). Several countries initiated biological warfare programs between the World Wars. The first scientifically informed use of biological agents as weapons began when the Japanese military conducted human experimentation with several infectious agents during combat, targeting military personnel and civilians in Manchuria and China.[1,2,9] During WWII, many countries, including the United States, Canada, United Kingdom, Germany, Japan, and the Soviet Union had active bioweapons programs with stockpiles of military significance. The Japanese military used biological weapons, killing tens of thousands of civilians and military.[1,2,9–12]

In 1972, US President Richard M Nixon made the decision to abandon biological weapons research and signed the Biological Weapons Convention, the first multilateral disarmament treaty banning development, production, and stockpiling of biological weapons. The US destroyed all biological weapon stockpiles and made the facilities that produced these weapons inoperable. Participant nations in the 2nd Review Conference in 1986 agreed to implement a number of confidence-building measures to prevent ambiguities, doubts, and suspicions and to improve international collaboration toward peaceful biological research.[13]

In 1995, an extremist microbiologist was arrested for obtaining *Yersinia pestis* by mail order in the United States. Concern about the ease with which disease-causing agents could be obtained led the US Congress to pass the Antiterrorism and Effective Death Penalty Act of 1996.[14] This act directed the US Department of Health and Human Services (HHS) to establish: (*a*) a list of biological agents and toxins ("select agents") that pose significant threat to public health and safety; (*b*) procedures for regulating the transfer of these agents; and (*c*) training requirements for entities working with these agents. HHS delegated this authority to the Centers for Disease Control and Prevention (CDC) to establish the Laboratory Registration and Select Agent Transfer Program in 1996. Congress significantly increased the oversight of biological select agents and toxins (BSAT) following the anthrax attacks of 2001 by passing the USA PATRIOT Act (Uniting and Strengthening America by Providing Appropriate Tools Required to Intercept and Obstruct Terrorism Act of 2001),[15] which restricted access to BSAT, and the Bioterrorism Act (Public Health Security and Bioterrorism Preparedness and Response Act of 2002),[16] which included increased safeguards, security measures, and oversight of the possession and use of BSAT. The Bioterrorism Act also granted similar regulatory authority to the US Department of Agriculture (USDA) over select agents that pose severe threat to animal and plant health or products.[17] This led to the establishment of the Federal Select Agent Program (FSAP).

The FSAP consists of the CDC Division of Select Agents and Toxins (CDC-DSAT) and the Animal and Plant Health Inspection Services (APHIS) Agricultural Select Agent Program that oversee the possession, use, transfer, and destruction of BSAT that has the potential to pose severe threat to public, animal, or plant health or to animal or plant products within the United States. This chapter details the key concepts of the FSAP and US Department of the Army's (DA's) Biological Surety Program (BSP) and highlights how implementation protects the worker, the community, and the environment.

BIOLOGICAL SURETY

Biological surety, or "biosurety," is a Department of Defense (DoD) program for commanders and directors to implement and monitor judicious application of core principles pertaining to control of BSAT, biosafety and occupational health, personnel reliability, biosecurity, and emergency response in all military laboratories involved in developing medical countermeasures to BSAT for service members and the public. The principles of safety, security, agent accountability, personnel reliability, and incident response plans formulated by chemical and nuclear surety programs were instrumental during the development of the DA's biological surety regulations.[18] Certain infectious agents and toxins, designated as BSAT, have the potential to pose a severe threat to public health and safety, animal or plant health, or animal or plant products, and their possession, use, and transfer are regulated by the HHS and the USDA under the Select Agent Regulations. In addition, research involving recombinant or synthetic nucleic acid molecules,

including the creation and use of organisms and viruses containing recombinant or synthetic nucleic acid molecules, is regulated by National Institutes of Health (NIH) Office of Biotechnology Activities. The intent of the DoD BSP is to properly safeguard BSAT that is in the possession or custody of DoD facilities against theft, loss, diversion, or unauthorized access or use, and to ensure that operations involving such agents are conducted in a safe, secure, and reliable manner per regulatory requirements.

The CDC-DSAT and APHIS Agriculture Select Agent Services monitor compliance of registered entities to HHS- and USDA-published final rules, outlined in 42 CFR Part 73,[19] 7 CFR Part 331,[20] and 9 CFR Part 121.[21] One of the key components of the BSP that was unique to the DoD is the Biological Personnel Reliability Program (BPRP), which ensures that individuals with access to BSAT meet high standards of reliability and suitability. Recent updates to FSAP regulations require individuals with access to Tier 1 BSAT (Exhibit 31-1) be enrolled in a "suitability" program similar to the DA's BPRP program. With this change, the FSAP and the BSP correspondingly enhance the safety of individuals working with BSAT, protect and safeguard communities with biocontainment laboratories, and monitor the security of BSAT in entities registered and authorized to work with these agents and toxins (Figure 31-1).

EXHIBIT 31-1

LIST OF TIER 1 BIOLOGICAL SELECT AGENTS AND TOXINS

Botulinum neurotoxins
Botulinum neurotoxin producing species of *Clostridium*
Ebola virus
Francisella tularensis
Marburg virus
Variola major virus (smallpox virus)
Variola minor virus (alastrim)
Yersinia pestis
Bacillus anthracis
Burkholderia mallei
Burkholderia pseudomallei
Foot-and-mouth disease virus
Rinderpest virus

Reproduced from: Centers for Disease Control and Prevention; Animal and Plant Health Inspection Services. List of Select Agents and Toxins. 12 September 2013. http://www.selectagents.gov/Select%20Agents%20and%20Toxins%20List.html. Accessed June 25, 2014.

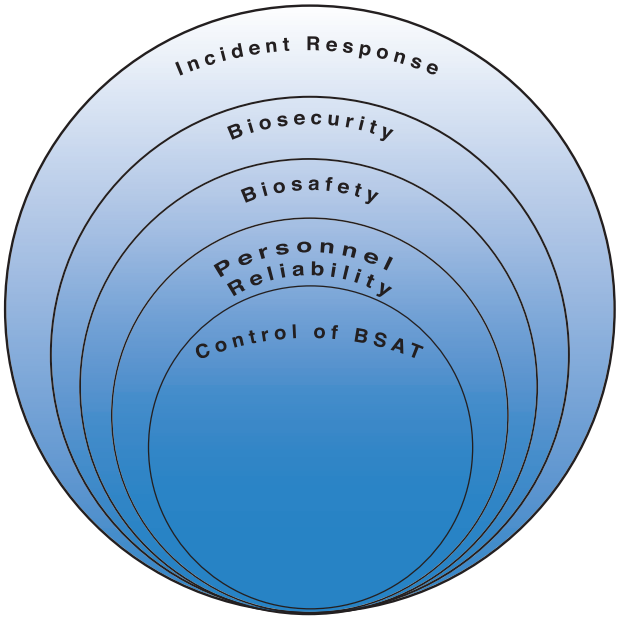

Figure 31-1. Key elements of the Federal Select Agent Program and Biological Surety Program.

Control of Biological Select Agents and Toxins

In accordance with 42 CFR Part 73,[19] the CDC-DSAT regulates agents and toxins that pose a severe threat to public health and safety. The APHIS Agriculture Select Agent Services regulates biological agents that pose a significant threat to plant and plant products in accordance with 7 CFR Part 331.[20] Agents that cause severe threat to humans, animals, and animal products are known as the "overlap agents" and are regulated by the CDC-DSAT and APHIS Agriculture Select Agent Services in accordance with 9 CFR Part 121.[21] In 2010, US President Barack Obama, through Executive Order 13546[22] directed HHS and USDA to: (*a*) designate a subset of BSAT (Tier 1,[23] see Exhibit 31-1) that presents the greatest risk of deliberate misuse with the most significant potential to cause mass casualties or devastating effects to the economy, critical infrastructure, or public confidence; (*b*) explore options for graded protection of Tier 1 BSAT to permit tailored risk management practices based on relevant contextual factors; and (*c*) consider reducing the overall number of agents and toxins on the select agents list. Federal BSAT regulations (42 CFR Part 73, 7 CFR Part 331, and 9 CFR Part 121) have been revised in accordance with Executive Order 13546.[20–22]

The FSAP mandates the appointment of a responsible official (RO) and an alternate responsible official (ARO) within each registered entity to monitor

compliance with the regulations governing select agents and toxins (SATs). Entities are authorized to appoint multiple AROs. The RO is granted authority and control to ensure compliance with FSAP regulations. In the absence of the RO, the ARO monitors entity compliance to FSAP regulations. In the DoD, a unit commander with a mission to conduct BSAT work (eg, development of diagnostics, medical countermeasures, etc) appoints an RO to monitor compliance of the entity to DoD, Army, federal, state, and local regulations governing BSAT. Regulatory oversight on entities that have a need to possess, use, and transfer BSAT is initiated by submission of various CDC APHIS forms that are specific for each regulatory component (Exhibit 31-2).[24]

Registration for Possession, Use, and Transfer of Biological Select Agents and Toxins

The FSAP requires all individuals, laboratories, and entities to register for possession, use, and transfer of BSAT. The first step in this process involves providing information through the completion of APHIS/CDC Form 1, Registration for Possession, Use, and Transfer of Select Agents and Toxins;[25] as described in 7 CFR 331,[20] 9 CFR 121,[21] and 42 CFR 73.[19] This form consists of several sections targeted to provide the regulatory agency with critical information on the biocontainment facility, safety, security, personnel, training, and research plans using SAT.

The entity is physically inspected by the FSAP following submission of the completed APHIS/CDC Form 1. The primary focus of this inspection is compliance with applicable federal regulations governing BSAT (7 CFR 331,[20] 9 CFR 121,[21] and 42 CFR 73[19]). During this visit, the inspectors verify the information provided in the submitted APHIS/CDC Form 1; evaluate personnel training, including mentorship programs; conduct interviews of personnel to identify issues related to biosafety, biosecurity, and training programs; check the engineering controls supporting the containment suites; and corroborate the commissioning or service records of all supporting machinery, including air-handling units, breathing-air systems, validation data for autoclaves, and all inactivation procedures to ensure that proper parameters are met and the methods used are determined to be efficacious with respect to producing nonviable waste. Ideally, entity registration is granted for 3 years after all inspection observations are satisfactorily resolved. However, a "conditional" registration may be granted under special circumstances (eg, during the interim when the entity needs to be operational to generate the data to satisfy a requirement). The FSAP inspectors ensure that the workers, communities, and the environment are not harmed by the operation of a containment or high containment laboratory.

APHIS/CDC Form 1 is also used to request changes to an approved registration. The entity must submit a letter to the FSAP requesting amendment to its registration and furnish the revised sections of the APHIS/CDC Form 1 related to the modifications. Most common amendments to registration involve addition and removal of personnel, name changes, addition or removal of agents or toxins, and changes in statement of work, including changes in project design, agent strains, animal models, modes of agent administration, and new laboratory projects.

EXHIBIT 31-2

ANIMAL AND PLANT HEALTH INSPECTION SERVICE/CENTERS FOR DISEASE CONTROL AND PREVENTION FORMS

- APHIS/CDC Form 1: Application for Registration for Possession, Use, and Transfer of Select Agents and Toxins
- APHIS/CDC Form 2: Request to Transfer Select Agents and Toxins
- APHIS/CDC Form 3: Report of Theft, Loss, or Release of Select Agents or Toxins
- APHIS/CDC Form 4: Report of the Identification of a Select Agent or Toxin
- APHIS/CDC Form 5: Request for Exemption of Select Agents and Toxins for an Investigational Product

APHIS: Animal and Plant Health Inspection Services
CDC: Centers for Disease Control and Prevention
Reproduced from: Centers for Disease Control and Prevention; Animal and Plant Health Inspection Services. Forms. 13 August 2013. http://www.selectagents.gov/Forms.html. Accessed June 25, 2014.

Security Risk Assessment

Security risk assessment (SRA) is the method used to approve an individual for access to select agents or toxins in accordance with the USA PATRIOT Act of 2001 and the Public Health Security and Bioterrorism Preparedness and Response Act of 2002. The Federal Bureau of Investigation Criminal Justice Information Services division determines if an individual who has been identified by a registered entity as having a legitimate need to access a select agent or toxin meets one of the statutory restrictors that would restrict access.

A "restricted person" under 18 USC 175b (USA PATRIOT Act) is an individual[26] who:

- is under indictment for a crime punishable by imprisonment for a term exceeding 1 year or who has been convicted in any court of a crime punishable by imprisonment for a term exceeding 1 year;
- is a fugitive from justice;
- is an unlawful user of any controlled substance;
- is an alien illegally or unlawfully in the United States;
- has been adjudicated as a mental defective or has been committed to any mental institution;
- is an alien (other than an alien lawfully admitted for permanent residence) who is a national of a country as to which the secretary of state has made a determination (that remains in effect) that such country has repeatedly provided support for acts of international terrorism; or
- has been discharged from the armed services of the United States under dishonorable conditions.

All individuals, including the RO, AROs, laboratory research staff, and animal-care workers requesting unescorted access to CDC- or APHIS-registered spaces containing BSAT require an approved SRA. Escorted individuals, such as inspectors and visitors with no access to BSAT, do not require an approved SRA. FSAP works closely with the Federal Bureau of Investigation Criminal Justice Information Services division to identify individuals who are prohibited to access BSAT based on the restrictions identified in the USA PATRIOT Act of 2001.[15] This process involves submitting an amendment to the lead agency (CDC or APHIS) and adding the individual to the entity registration to obtain a unique Department of Justice number, which is recorded on a Bioterrorism Security Risk Assessment Form (FD-961). The completed FD-961 is reviewed, certified by the RO, and submitted to CJIS with two sets of fingerprints.[26] The FSAP authorizes individual access to BSAT based on the results of the SRA. The SRA is renewed every 3 years. All individuals with approved SRA undergo a general initial training, which provides site-specific information on biosafety, security, incident response, and insider threat awareness. Refresher training is provided annually to all SRA-approved individuals.

Biological Select Agents and Toxins Inventory and Accountability

FSAP regulations require complete, current, and accurate inventory of all long-term (LT) BSAT. Materials that contain or have been exposed to infectious select agents, including (but not limited to) laboratory cultures, animals, animal tissues, confirmed clinical specimens, plants, and plant tissues, are subject to FSAP regulations. Select toxins and recombinant or synthetic nucleic acids encoding functional forms of select toxins are also regulated. Animals inoculated with select toxins and their tissues are exempt from FSAP regulations. Inventory records are not required for BSAT that the FSAP has excluded from the provisions of the Select Agent Regulations, nor for inactivated BSAT materials as long as an approved method for inactivation is used.

CDC-DSAT defines LT storage as placement in a system designed to ensure viability for future use. As a rule, LT BSAT materials are not part of an ongoing experiment and have not been accessed for a significant period of time (eg, 30 calendar days).[27] SAT are considered working stock (WS) if the materials are: (*a*) a part of an ongoing experiment, (*b*) accessed frequently, or (*c*) not stored for an extended period of time. FSAP regulations do not require inventory records for BSAT classified as WS; however, all WS must be kept and used in secure locations by approved individuals (ie, those with current SRAs enrolled in a suitability program, if accessing Tier 1 agents). The DA's interim guidance on BSAT inventory management allows BSAT to remain in WS status for up to 180 days; however, the DA guidance document requires individuals to maintain detailed records of all BSAT WS materials at all times.

Significant amounts of BSAT WS can be generated in a containment laboratory on any given day. Accounting for these materials can be challenging, as they are continuously used or consumed in various experiments. Entities with large BSAT inventories must establish procedures to retain only "valuable" BSAT. Establishing peer-reviewed and accepted criteria for retention and destruction of LT BSAT materials can be

beneficial to the investigators and the host entity. An example of criteria developed for retention and destruction of LT BSAT materials is shown in Exhibit 31-3.

Specimen boxes containing LT BSAT materials can be wrapped with tamper-evident materials after verification by two BPRP-certified individuals. Follow-up tube-by-tube inventory is not needed as long as the tamper-evident seals remain intact. Reducing access and repeated contact with LT BSAT materials will preserve specimen integrity and will also allow for accurate real-time inventory of these materials. Additionally, uniform labeling of LT BSAT specimens should remain a priority for research staff in order to have well-labeled research materials for all current and future investigations. Advances in labeling technologies permit for human-readable information, barcodes, and radiofrequency identification tags to be incorporated on any size of specimen labels. Specimen tags that adhere to frozen tubes are also available, making it possible to label archival materials.

Centralized Management of Long-Term Biological Select Agents and Toxins

Maintaining accurate and current inventory of LT BSAT materials at all times can be burdensome to principal investigators (PIs) and research staff who are focused on meeting timelines for deliverables and project goals. BSAT inventory discrepancies identified during internal audits or announced and unannounced inspections by regulatory agencies can result in serious consequences to the registered entity with respect to continuation of research and loss of public trust. One proposed solution to this dilemma is to establish centralized management of LT BSAT materials under the care of the RO and the AROs to alleviate considerable inventory and accountability burden from the PIs and research staff (Exhibit 31-4). Under this model, LT BSAT materials that have been verified by a third party would be labeled with PI-specific information, wrapped with tamper-evident materials, and centrally stored within the registered laboratory space in dedicated storage containers with restricted access.

Centralized LT BSAT inventory management would enhance readiness for unannounced regulatory compliance inspections that include BSAT inventory verification, and would simplify the transition of BSAT inventory when a PI retires or leaves the institution. Verification of LT BSAT inventory by the PI or researcher and a third party would also allow for identification of archival specimens requiring new uniform labels. The PI or researcher will identify BSAT specimens no longer needed for current and future investigations, including potentially contaminated specimens, specimens with reduced or no bioactivity, and excess specimens.

Biological Select Agents and Toxins Inventory Audits

Registered entities are required to conduct complete inventory audits of a PI's BSAT holdings in LT storage during physical relocation of a collection or inventory upon the departure of a registered PI with BSAT holdings, or in the event of a theft or loss of BSAT. In addition to the FSAP requirements, Army Regulation (AR) 50-1 requires annual 100% physical inventory of all BSAT holdings by each PI.[28] If the LT BSAT materials are verified and wrapped, the inventory burden is dramatically reduced, as long as the tamper-evident seals are intact. Army regulation also requires BSAT inventory audits of each registered PI at least once annually by the biological surety program staff. These

EXHIBIT 31-3

SAMPLE CRITERIA FOR RETAINING OR DESTROYING BIOLOGICAL SELECT AGENTS OR TOXINS

Retention Criteria

1. Unique materials (serotypes, strains, etc)
2. Support ongoing research activities and all existing agreements
3. High scientific value for future scientific investigations
4. Deemed evidence material by law enforcement
5. Materials retained from published studies

Destruction Criteria

1. Potentially contaminated and/or degraded materials (eg, samples that have been subjected to multiple freeze/thaw cycles)
2. Excess quantities from a specific microbe or toxin
3. No anticipated future scientific value with the understanding that projected future mission requirements can be difficult
4. Materials that lack expected bioactivity

EXHIBIT 31-4

CENTRALIZED BIOLOGICAL SELECT AGENTS AND TOXINS INVENTORY MANAGEMENT CONSIDERATIONS

Reduce inventory burden on PI/researcher
- Transfer long-term BSAT accountability responsibility to RO/ARO and dedicated biological surety staff (select agent managers)
- Limit principal investigator/researcher responsibility to working stock BSAT materials

Enhance accountability and security
- Manage long-term BSAT materials with dedicated staff
  - 100% long-term BSAT inventory verification and tamper-evident wrapping
  - Long-term BSAT consolidated within registered space
  - Eliminate variability in record keeping from multiple PIs/researchers
- Enhance security of BSAT materials
  - Long-term BSAT in dedicated and locked freezers within registered spaces
  - Limit physical access to long-term BSAT materials

Manageable process with economy of space and personnel
- Enhance real-time inventory awareness for long-term BSAT
- Consolidate long-term BSAT within containment spaces

Maintain mission capability with enhanced flexibility
- Retain all unique and critical BSAT materials
- Capture all essential characterization and experimental data (eg, DoD BSAT database)
- Prepared to receive or send BSAT to other DoD entities at all times

Inventory reduction
- Assist PIs in identifying and destroying BSAT with no current or future scientific value
- Encourage sharing of BSAT among PIs within the institute

ARO: alternate responsible individual; BSAT: biological select agents and toxins; DoD: Department of Defense; PI: principal investigator; RO: responsible official

inventory audits include inspection of laboratory records of BSAT usage, physical inventory verification of both LT storage and WS BSAT, verification of the SAP registration of the PIs, BSAT transfer documentation, and BSAT destruction records. The annual BSAT inventory audits provide a great opportunity to interact with the registered PI and his or her technical staff and to identify areas where additional training may be warranted.

Biological Select Agent and Toxin Transfers

The Select Agent Regulations require entities to develop provisions and policies for shipping, receiving, and storing SAT, including documented procedures for receiving, monitoring, and shipping all SAT. There are primarily two types of BSAT transfers: intraentity and interentity. BSAT material must be packaged by individuals approved by the HHS secretary or APHIS administrator for access to SAT. If the transfer involves Tier 1 BSAT, the approved individuals must be certified in the entity's suitability program or personnel reliability program.

Intraentity transfers of SAT are performed between two registered PIs with a complete chain of custody document. The sender and receiver must be registered with the SAP for the BSAT being transferred. These transfers are physically performed by approved individuals in accordance with entity-specific standard operating procedures. An approved APHIS/CDC Form 2 is not required for intraentity transfer of BSAT materials.

Interentity transfers of SAT require an approved APHIS/CDC Form 2 prior to physical transfer of these materials. Once issued, an approved APHIS/CDC Form 2 is valid for 30 days. These transfers are governed by the US Department of Transportation Hazardous Material Regulations found in 49 CFR, parts 100 to 185.[29] The approved individual packaging SAT must ensure compliance with all applicable laws concerning packaging and shipping. DA uses approved BSP personnel trained and certified in shipping

procedures to verify the contents of the SAT shipments inside the containment laboratories prior to packaging. A completed chain of custody form is retained with copies of shipping documents for at least 5 years (DoD standard). The individual who witnesses packaging inside the containment laboratory also verifies the approved APHIS/CDC Form 2 and the shipping documents. The FSAP has amended the select agent regulations to accept and promote the recommendation of the report of the Defense Science Board Task Force, DoD Biological Safety and Security Program,[30] regarding the "lost in crowd" approach for all SAT shipments. However, registered DoD laboratories are currently required to use a carrier that maintains positive control, ensures chain of custody, is certified to handle HAZMAT (hazardous materials) standards 6.1 (poisons) and 6.2 (infectious substances), and requires two qualified drivers possessing current secret clearance, with at least one driver in the truck or within 25 feet of the truck at all times. Harmonization of DoD regulations with the FSAP is being discussed to standardize the select agent and toxin shipping practices.

Exempt quantity (permissible amount) transfers of select toxins (Table 31-2) are not regulated by the FSAP.[31] The "toxin due diligence" provision was developed by FSAP to address concern that someone might stockpile toxins by receiving multiple orders below the excluded amount. It requires a person transferring toxins in amounts which would otherwise be excluded from the provisions to: (*a*) use due diligence to ensure that the recipient has a legitimate need to handle or use such toxins; and (*b*) report to FSAP if they detect a known or suspected violation of federal law or become aware of suspicious activity related to the toxin.[32]

Most "exempt" toxin transfers are to a nonregistered PI or a collaborator who demonstrates a legitimate need to handle or use the toxin being transferred. Due diligence must precede the transfer to ensure that the recipient does not exceed the exempt quantity limit established by the FSAP with any existing remnant quantities in their laboratories from previous investigations. The person initiating the transfer can require the recipient to complete documentation stating the intended use of the toxins and a statement indicating that receiving the requested amount of the toxin will not put them over the limits established for the select toxins by the FSAP. Tracking "exempt" select toxin transfers (sending and receiving) and monitoring their use must be an integral part of a due diligence effort at the entity level to avoid investigators accumulating quantities of select toxins above the permissible amounts at any time.

TABLE 31-2

PERMISSIBLE TOXIN AMOUNTS

Health and Human Services Toxins	Amount
Abrin	100 mg
Botulinum neurotoxins	0.5 mg
Short, paralytic alpha conotoxins	100 mg
Diacetoxyscirpenol	1,000 mg
Ricin	100 mg
Saxitoxin	100 mg
Staphylococcal enterotoxins (subtypes A, B, C, D, and E)	5 mg
T-2 toxin	1,000 mg
Tetrodotoxin	100 mg

Centers for Disease Control and Prevention; Animal and Plant Health Inspection Services. Permissible Toxin Amounts. 5 October 2012. http://www.selectagents.gov/Permissible%20Toxin%20Amounts.html. Accessed June 25, 2014.

Reporting Theft, Loss, or Release of Biological Select Agents and Toxins

FSAP requires an entity to immediately notify CDC or APHIS and appropriate federal, state, or local law enforcement agencies (by e-mail, facsimile, or telephone) of incidents involving theft, loss, or release (occupational exposure or release of an agent or toxin outside of the primary barriers of the bio-containment area) of SAT.[33] Thefts or losses also must be reported even if the SAT is subsequently recovered or the responsible parties are identified. A completed APHIS/CDC Form 3 must be submitted within 7 calendar days.

A BSAT inventory deficiency investigation may involve: (*a*) immediate notification to the physical security office; (*b*) 100% physical inventory of all of the registered PI's BSAT holdings by the RO or ARO; (*c*) complete inspection of the PI's BSAT usage records (laboratory notes); and (*d*) a complete database records check of the BSAT inventory holdings of the PI. If theft of BSAT is suspected, appropriate law enforcement agencies must be informed.

Release of BSAT from "primary containment" or release resulting in "potential exposure" to individuals requires immediate notification to the FSAP. Spills of SAT in biological safety level (BSL)-4 laboratories (sealed laboratories with personnel wearing positive pressure encapsulated suits) can be safely cleaned up without potential human exposure; no FSAP reporting is necessary because the entire BSL-4 laboratory

is considered "primary containment." However, if an individual experiences a breach in his or her positive pressure encapsulating suit at the same time as a spill or work done with animals outside of primary containment, initial notification to FSAP reporting is required, followed by the completion of APHIS/CDC Form 3. In contrast, SAT spills in BSL-2 and BSL-3 laboratories (unsealed directional airflow laboratories with personnel not wearing positive pressure encapsulated suits) outside of a functioning biological safety cabinet are reportable to FSAP, as these laboratory spaces are considered "secondary containment." The data collected and analyzed by the CDC on theft, loss, or release reporting from 2004 to 2010 indicate that the risk of exposure from BSAT managed by US laboratories to the general population is low.[34]

Identifying Select Agents and Toxins

Identifying BSAT as a result of diagnosis, verification, and proficiency testing, and final disposition of the identified agent or toxin must be reported to FSAP within 7 calendar days by completing APHIS/CDC Form 4. Identifying Tier 1 BSAT (see Exhibit 31-2) from diagnostic samples requires immediate (ie, within 24 hours) reporting to FSAP via e-mail, facsimile, or telephone. BSAT identified from proficiency testing specimens must be reported within 90 days of receipt of the sample. Any amount of select toxin identified must be reported to FSAP. Entities not registered with the FSAP are also required to report BSAT that have been identified from diagnostic specimens. Unregistered entities have 7 calendar days to transfer to a registered entity or destroy the identified SAT to remain in compliance with current federal regulations.

Restricted Experiments

An individual or an entity approved by the FSAP may not conduct restricted experiments without prior approval by the HHS secretary or APHIS administrator. Restricted experiments are: (*a*) experiments that involve the deliberate transfer of, or selection for, a drug resistance trait to select agents that are not known to acquire the trait naturally, if such acquisition could compromise the control of disease agents in humans, veterinary medicine, or agriculture; and (*b*) experiments involving the deliberate formation of synthetic or recombinant nucleic acids containing genes for the biosynthesis of select toxin lethal for vertebrates at an LD_{50} (the amount necessary to kill 50% of the subject population) that is less than 100 ng/kg body weight.[19] Additional guidance on restricted experiments involving recombinant or synthetic nucleic acids is outlined in the NIH's *Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules*.[35] This guidance is mandated for research that is conducted at or sponsored by an entity that receives any support for recombinant or synthetic nucleic acid research from the NIH, including research performed directly by the NIH.

Most registered entities designate the responsibility of identifying, reviewing, and approving restricted experiments to their Institutional Biosafety Committee (IBC). The biosafety officer and the RO are members of the IBC. Entity-specific IBC-approved research proposals with restricted experiments are forwarded to FSAP for review and approval. Restricted experiments containing HHS and overlap select agents will be further reviewed by the Intragovernmental Select Agents and Toxins Technical Advisory Committee. Restricted experiments involving USDA select agents will be further reviewed by subject matter experts from APHIS.

A typical request to FSAP to review a restricted experiment includes, but is not limited to, description of:

- the proposed experiment, including intended objectives,
- nucleic acid insert and the intended biological characteristics of the recombinant gene product,
- cloning/expression vector,
- host organism used for molecular cloning,
- selection methods (recombinant or passive),
- antimicrobial markers use,
- BSL considerations,
- estimated amount of toxin (recombinant or synthetic) to be produced (if applicable), and
- any planned animal or plant experiments.[36]

Restricted experiments using recombinant and passive selection methods and all select agent products resulting from these experiments are also subject to FSAP regulations. Transfer of any products of restricted experiments must be coordinated through the FSAP. The DA and the DoD require all of their research laboratories to remain in full compliance with all federal regulations governing BSAT.

Biosafety

Biosafety in microbiological and biomedical laboratories is based on two key principles: "containment" and "risk assessment." Core concepts of containment include microbiological practices, safety equipment, and facility safeguards that protect laboratory workers, the environment, and the public from exposure to infectious organisms. Risk assessment is a process that enables the appropriate selection of microbiological

practices, safety equipment, and facility safeguards that can prevent laboratory-associated infections. Modern biosafety practices described in the 5th edition of *Biosafety in Microbiological and Biomedical Laboratories*[37] are accepted as standards of practice by all CDC-registered entities to conduct work with SAT. The DA mandates the use of the current version of the manual and DA pamphlet 385-69, *Safety Standards for Microbiological and Biomedical Laboratories*,[38] in all US Army activities and facilities in which infectious agents or toxins are used, produced, stored, handled, transported, transferred, or disposed of, including the Army National Guard, the US Army Reserve, and contractors and consultants conducting microbiological and biomedical activities for the Army. The detailed principles and practices of biosafety are covered in a separate chapter of this textbook.

It is critically important to thoroughly train individuals in biosafety practices prior to providing access to the containment laboratories to handle, manipulate, and store BSAT. Training must include:

- microbiological laboratory techniques;
- use of personal protective equipment (PPE), safety equipment, and containment laboratory equipment;
- information on bloodborne pathogens;
- an entity-specific chemical hygiene plan;
- BSAT-specific information;
- emergency exit operations;
- immediate first aid; and
- reporting requirements for potential exposures to infectious agents and toxins.

Some of this initial training can be structured into mentorship programs in which individuals approved as mentors ensure new laboratory workers are able to work safely within the containment laboratories before they are granted independent access. In addition to project-specific training, the worker requesting access to the containment laboratories with BSAT is trained to recognize biohazards, understand potential health risks associated with exposures, provide appropriate first aid, and carry out follow-up reporting procedures.

FSAP regulations require individuals with access to Tier 1 BSAT to be enrolled in an occupational health program.[19–21] AR 50-1[28] also requires commanders and directors of the entities with a biological surety mission to establish and implement an occupational health program. Core elements of an occupational health program include: (*a*) risk assessment, (*b*) medical surveillance, (*c*) access to clinical occupational health services and management, and (*d*) hazard communication. Select agent risk assessments should consider:

- route of exposure,
- infectious dose,
- agent virulence,
- incubation period,
- environmental stability,
- communicability,
- genetic modification,
- available resources for pre- and post-exposure prophylaxis,
- available vaccine options,
- PPE use, and
- biocontainment requirements.[39]

Occupational health plans are required to comply with US Department of Labor and Occupational Safety and Health Administration regulations, as well as patient confidentiality laws. Promoting a safe and healthy work environment requires limiting exposures to infectious agents and toxins, promptly detecting and treating exposures, and using information gained from incidents to further improve safety measures and worker training. Occupational health and safety is a shared responsibility among the individual workers, their supervisors, PIs, biosafety specialists, healthcare providers, and the employer.

Personnel Reliability

Personnel reliability programs existed for decades in the US military. The BPRP, modeled after the military's nuclear and chemical personnel reliability programs, ensures that individuals with access to BSAT meet the highest standards of reliability.[18,40–42] The concept of personnel reliability was implemented over a decade ago in DoD laboratories working with BSAT.[43] AR 50-1, *Biological Surety*, outlines the BPRP described herein.[28]

Individuals with access to BSAT in DA and DoD laboratories are required to be enrolled in a BPRP. The FSAP added the "suitability" requirement for individuals with access to Tier 1 BSAT in October 2012. The FSAP's suitability assessment of personnel is based in part on the DoD's personnel reliability programs. The BPRP and the suitability assessment of personnel are primarily designed to reduce the risk of SAT misuse by an individual who has access to these agents (insider threat). The intent of the US Army's BPRP[18] and the FSAP's suitability assessment of personnel[44] is the same; however, there are significant differences between the two programs.

The commander or director is the head of the organization's BPRP and can serve as the reviewing official. The reviewing official appoints certifying officials (COs) who determine the reliability and suitability of individuals requiring access to SAT and ensure they

are appropriately qualified and trained to perform their duties. Commanders and directors may appoint BPRP monitors to assist COs in administering day-to-day activities; however, COs are responsible for continuous monitoring of individuals enrolled in the personnel reliability program. The reviewing official monitors the CO's decisions to disqualify individuals and may overturn them when procedures are unfair, inconsistent, or incorrectly applied. AR 50-1 requires the reviewing official to review all individual disqualification actions submitted by the CO.[28] The FSAP recommends suitability decisions on individuals requesting access to Tier 1 BSAT be a combined decision of the CO, RO, and the entity leadership (eg, commander, director, or reviewing official).[44]

To begin enrollment in the BPRP, supervisors of individuals who need to access BSAT in the CDC-registered containment spaces contact the designated CO. The CO is the gatekeeper for access to BSAT, ensuring that persons requesting access have met all the qualifying conditions. FSAP ensures that restricted persons do not have access to BSAT through the SRA process (see section above); the Army's BPRP further ensures that persons with access to BSAT are:

- trustworthy,
- mentally and emotionally stable,
- physically competent,
- free of unstable medical conditions,
- able to exercise sound judgment,
- willing to accept responsibility,
- able to adapt to changing work environments,
- free from drug and alcohol abuse,
- willing to participate in random drug testing, and
- willing to comply with all training requirements.

Enrollment in the Army's BPRP involves:

- initial interview,
- personnel records review,
- personnel security investigation,
- medical evaluation,
- drug testing, and
- CO's final evaluation and briefing.

The order of steps in the process is discretionary; nevertheless, each step must take place and be fully documented.

Initial Interview

The CO is required to conduct a personal interview of a potential enrollee in the BPRP to assess suitability and reliability. The CO must inform the candidate of the Privacy Act of 1974[45] and the Health Insurance Portability and Accountability Act[46] to obtain consent to proceed with the screening process. Although not required by the regulations, the initial interview may also include a written questionnaire. The candidate is asked questions that will allow the CO to determine whether he or she has engaged in any activities that would be either mandatory or potentially disqualifying factors. Mandatory disqualifying factors are those that are beyond the discretion of the CO for deciding reliability and suitability. If extenuating circumstances exist, the reviewing official may request an exception for the individual's enrollment through command channels. The following are mandatory disqualifying factors:

- current substance or alcohol dependence;
- drug or substance abuse within 5 years prior to the initial interview;
- trafficking, cultivating, processing, or manufacturing illegal or controlled drugs within the past 15 years;
- drug or substance abuse while enrolled in BPRP;
- inability to meet safety requirements; or
- meeting the criteria of a restricted person as defined by 18 USC § 175b.[47]

Other potentially disqualifying factors include:

- alcohol-related incidents or alcohol abuse;
- drug or substance abuse more than 5 years prior to initial interview; or
- mental or physical medical condition, medication usage, or medical treatment that may result in:
  - altered state of consciousness,
  - impaired judgment or concentration,
  - increased risk of impairment if exposed to BSAT,
  - impaired ability to wear PPE,
  - inability to meet physical requirements, or
  - inappropriate attitude, conduct, or behavior.

The CO must inform the candidate that he or she will be subject to random, unannounced drug testing as part of continuous monitoring; an initial negative test is required prior to certification in the BPRP. The CO must also explain to the candidate about: (*a*) continuous monitoring, (*b*) the requirement for self-reporting, and (*c*) use of prescription drugs. The initial interview is a good opportunity for the CO to get to know the candidate and to begin a relationship based on mutual trust and respect.

Personnel Records Screening

Once the CO has completed the initial interview and found the candidate to be suitable for enrollment, the applicant's personnel records are screened by a supporting personnel officer. The screening official will determine the individual's citizenship and identify it to the CO. Any potentially disqualifying information (PDI) discovered during the screening process is immediately communicated to the CO. Individuals with extended federal government service may have information in their personnel records from the inception of their employment. In contrast, information in contract employees' personnel records may be limited to the length of their employment with that company. Anything that may indicate unsatisfactory employment history or dereliction of duty, such as job applications, enlistment contracts, and any other available pertinent record should be reviewed for PDI. The CO acts on any PDI discovered during the personnel records screening; however, the CO does not retain any records of this information.

Personnel Security Records Screening

The current minimum personnel security investigation (PSI) requirement for unescorted access to BSAT within DoD is a favorably adjudicated single-scope background investigation. This level of PSI is conducted to confer top secret clearance. However, a security clearance is not required for BPRP enrollment. The personnel security manager will request a copy of the PSI from the Office of Personnel Management on behalf of the CO. The personnel security officer will expeditiously provide any adverse information to the CO, ensuring Privacy Act requirements are not violated. Personnel scheduled for initial assignment to BPRP positions must have the appropriate and favorably adjudicated PSI completed within the 5 years preceding certification to the BPRP. PSI files contain sensitive information and should only be retained for the time necessary to determine suitability and reliability. The CO will review the results of the personnel security investigation to determine if the individual meets the suitability and reliability requirements of the BPRP.[48] The FSAP is not prescriptive, with respect to PSI, above what is required to obtain an SRA for suitability assessment of individuals with access to Tier 1 BSAT.

Medical Evaluation

The competent medical authority (CMA) medically evaluates the candidate to ensure that the individual seeking enrollment in the BPRP is physically, mentally, and emotionally stable; alert; competent; dependable; and free of unstable medical conditions that may impact BPRP duties.[18] The CMA meets with the candidate and reviews the individual's medical records to identify any PDI. Medical PDI includes any medical condition, medication use, or medical treatment that may result in an altered level of consciousness, impaired judgment or concentration, impaired ability to safely wear required PPE, or impaired ability to perform the physical requirements of the BPRP position, as substantiated by the medical authority to the CO. The candidate may also provide the CMA copies of medical records from a personal healthcare provider. If medical records are incomplete or inadequate, the CMA will conduct the appropriate medical evaluation. This may include a mental health evaluation if the CMA determines such an evaluation is prudent or upon request by the CO.[18] Medical PDI is reported to the CO with recommendations regarding the person's fitness for assignment to these duties or limitations in duties or reasonable accommodations that might allow the individual to perform his or her duties without compromising worker safety.

Drug Testing

All candidates for BPRP must complete drug testing within 6 months prior to initial certification. All drug test results will be provided to the CO before the individual is certified in the BPRP. Positive drug test results indicating illegal drug use will result in disqualification.

Certifying Official's Final Evaluation and Briefing

After the candidate has completed all phases of the screening, the CO conducts a final evaluation of all the information received during the screening process and conducts a final interview. During the final interview, the candidate will have an opportunity to review and discuss any BPRP-relevant issues, including PDI discovered during the screening process and the circumstances surrounding such an event, and before the CO's decision on the candidate's suitability and reliability for the program. During this time the CO:

- reviews the duties and responsibilities of the individual's BPRP position, including required PPE use;
- discusses the expectations for continuous monitoring;
- reviews disqualifying factors, including any incidents or medical issues that may have occurred since the initial interview;

- reminds the individual that prescription drug use must be under the supervision of a health-care provider; and
- reviews the self-reporting requirements of the BPRP.

At the end of the interview, the CO should inform the candidate whether he or she is suitable for the program, and the individual signs DA Form 3180 indicating his or her understanding of the program and willingness to comply with the requirements. If the candidate is determined to be eligible, the CO ensures that the candidate has completed all the core safety, security, and emergency training. The CO will notify the RO immediately after the individual is certified in the BPRP.[18]

Individuals certified in the BPRP are subject to continuous monitoring. Continuous evaluation includes, but is not limited to:

- self-reporting,
- peer and supervisor observation and reporting,
- periodic unannounced drug testing,
- periodic personnel security investigations,
- periodic medical evaluations by the CMA, and
- CO observation and evaluation.

The FSAP recommends the RO's involvement in the development, implementation, and administration of the Tier 1 BSAT suitability assessment program. The RO must ensure that access to Tier 1 BSAT is limited to individuals in the suitability program with the entity's ongoing suitability monitoring, and have current FSAP approval to access SAT. Ongoing efforts to harmonize the DoD regulations governing BSAT with the FSAP are expected to clarify the role of the RO in the BPRP or suitability assessment program.

Biosecurity

Safeguarding BSAT is a high priority for the DoD[41,43] and the FSAP.[49] According to the Office of Science and Technology Policy, the term "biosecurity" refers to the protection, control of, and accountability for high-consequence biological agents and toxins and critically relevant biological materials and information within laboratories to prevent unauthorized possession, loss, theft, misuse, diversion, or intentional release.[50] AR 190-17, *Biological Select Agents and Toxins Security Program*[51] prescribes the policy, responsibilities, procedures, and minimum standards for safeguarding BSAT. Biosecurity plans are based on risk assessments, are entity specific, and constitute sensitive information. A site-specific security plan based on risk assessments must be developed by all CDC-registered entities with BSAT. An effective site-specific security plan will have initial and continuous input from and interactions with:

- security personnel,
- commanders or directors,
- subject matter experts,
- local law enforcement officers,
- ROs and AROs,
- biosafety officers,
- occupational health CMAs,
- facilities management personnel, and
- information security management personnel.

An effective biosecurity plan is based on operational processes, accounts for all BSAT from creation or acquisition to destruction, does not violate any laws, weighs both primary and secondary affects, and is reviewed and updated at least annually.

The biosecurity program for CDC-registered entities with BSAT can be broadly divided into at least five major components: (1) BSAT security, (2) physical security, (3) personnel security, (4) operational security, and (5) information security.

Biological Select Agents and Toxins Security

There are a number of factors that contribute to the challenge of effective BSAT inventory and accountability within containment laboratories. Temperature-sensitive microbes, confined spaces, sharing of limited freezer space by multiple investigators, co-existence of both LT and WS BSAT, multiple users, and illegible specimen labels can all contribute to ineffective BSAT inventory and accountability. Uniform labels with human-readable information and barcodes, inventory verification and wrapping of all LT BSAT with tamper-evident materials, centralized storage of wrapped LT BSAT within the containment laboratory, and controlled access to LT BSAT materials can preserve the integrity of the stored specimens and provide an accurate real-time inventory of these materials. These LT BSAT management strategies can be instituted without affecting ongoing research. Entities must establish standard operating procedures for incoming, outgoing, and intraentity BSAT transfer. All transfers must be conducted with chain-of-custody documentation, which is retained and verified with BSAT inventory databases. BSAT destruction documents should be confirmed with the BSAT databases. BSAT inventory audit should include review of laboratory notes and verification of BSAT WS materials. All BSAT materials

must be maintained in CDC-registered laboratory spaces with restricted access to prevent theft, loss, or release of these materials. All personnel with access to BSAT must be trained in FSAP regulations, including reporting requirements. Entities must also conduct a complete inventory audit of a PI: (*a*) when the PI with BSAT holdings leaves the entity; (*b*) in the event of a theft or loss of BSAT; and (*c*) upon physical relocation of a collection of BSAT materials. These practices will also prepare the entity for any unannounced inspections. Effective BSAT inventory and accountability practices will preserve the integrity of the specimens and increase research efficiency within the containment laboratories.

Physical Security

A physical security plan developed using site-specific risk assessment can detect, deter, or delay threat and provide sufficient time to respond to the threat. Security barriers such as perimeter fences, armed guards, walls, locked doors, secured laboratories, and locked freezers can deter intrusion and deny access to BSAT. FSAP regulations require:

- controls limiting access to CDC-registered spaces to approved individuals with access to BSAT,
- provisions to safeguard animals and plants infected with select agents,
- review and update of access logs to CDC-registered spaces,
- prevention of access credentials sharing,
- procedures for reporting loss of access credentials,
- procedures for personnel changes,
- three barriers (physical structures that are designed to prevent access to unauthorized individuals) to access Tier 1 BSAT,
- intrusion detection systems where Tier 1 BSAT is manipulated or stored,
- response time not exceeding 15 minutes for a force capable of interrupting a threat to Tier 1 BSAT manipulation and storage spaces, and
- procedures for access control in power failures.[19,49]

Personnel Security

The FSAP and DoD consider personnel security integral to detecting insider threat. The personnel security office at the entity level works with the RO to facilitate SRA documentation and fingerprinting for individuals requesting access to CDC-registered spaces. Personnel security also includes: verification of background information, security investigations, personnel dossier reviews, identifying violators of security and safety procedures, and identifying individuals who threaten or support those who threaten to do harm to others. The biosecurity plan should include personnel security measures based on a site-specific risk assessment. A robust "insider threat awareness" training program developed and continuously updated based on site-specific risk assessments is administered to individuals with access to Tier 1 BSAT. Insider threat awareness training is an annual requirement.[19]

Operational Security

Effective operational security posture builds on existing operational procedures and mitigates threats based on site-specific risk assessments.[49] Operational security measures for an entity with BSAT should include:

- training personnel on securing BSAT;
- monitoring individual access to areas containing SAT;
- monitoring BSAT activities inside containment suites through security closed-circuit television or by using an escort;
- control of after-hour and weekend access to containment laboratories with BSAT;
- screening visitors, packages, and delivery trucks at the entry point;
- procedures in place for immediate notification to the RO, commander or director, security forces, and law enforcement if theft or loss of SAT is suspected;
- training personnel to identify and report suspicious activities;
- prominently displayed identification badges on individuals within the entity;
- constant building security surveillance;
- intrusion detection systems;
- surveillance of backup power generators; and
- peer reporting procedures for any sudden changes in behavior among approved individuals with access to SAT.[49]

Information Security

FSAP regulations require registered entities to develop and implement procedures for information control and information security.[52] Information security procedures and protocols must:

- ensure all external connections to systems that manage security for the registered space are isolated or have controls that permit and monitor authorized and authenticated users;
- ensure authorized and authenticated users only access information necessary to fulfill their roles and responsibilities;
- prevent malicious code from compromising the confidentiality, integrity, or availability of information systems that control safety and emergency equipment, engineering controls for the containment laboratories, and access to registered space;
- include regular patching and updates to operating systems as well as to individual applications;
- protect network operating systems with security firewalls;
- protect hardware assets;
- include data encryption;
- ensure remote access capability;
- establish robust information backup systems in the event of primary system failure;
- establish procedures for purging electronic storage media prior to disposal; and
- establish procedures for shredding paper documents and computer disks.[52]

Incident Response and Emergency Management

A robust incident response plan and a knowledgeable and competent emergency management team are critical to an entity involved in developing medical countermeasures against dangerous pathogens and toxins. An incident is an occurrence, natural or human-made, that requires a response to prevent the theft, loss, or release of an SAT or to protect human life and animal and plant health.[53] FSAP, DA, and DoD regulations require entities with SAT to develop, exercise, and routinely update a comprehensive, site-specific incident response plan to ensure the security and safeguarding of BSAT in the event of human-made threats and natural disasters. A site-specific incident response plan protects human life before property, is focused on laboratories and not just the entire facility, is developed as a result of collaboration between research staff and leadership, includes responder participation and training, and addresses primary and secondary effects and the impact on workers at the facility.[53] Developing an incident response plan at the entity level should be a team effort involving (but not limited to) the RO, AROs, biosafety officer, facility engineers, PI or researcher, security manager, occupational health physician or CMA, and entity leadership, with input from local first responders (fire department, emergency medical and law enforcement).

Laboratory leadership, supervisors, biosafety specialists and subject matter experts within a registered entity with SAT should develop incident response information specific to the agents, toxins, and procedures conducted in that laboratory. Individuals working in the laboratory must be trained on how to respond to an incident with the materials they handle in the laboratory, emergency exit procedures, and the use of communication devices within the laboratory. Laboratory incident response information must also include decontamination protocols, first-aid, and reporting requirements.[19] Laboratory and facility incident response plans should be practiced via exercises with entity staff and external first responders (fire department, emergency medical and law enforcement); this practice is critical and will save lives and property in the event of a real incident.

The incident response plan should consider and mitigate vulnerability assessments specific to the laboratory and the facility. The incident response plan must include provisions for theft, loss, or release of SAT, inventory discrepancies, and security breaches.[19]

Theft, Loss or Release

Response to suspected theft or loss of SAT should include immediate notification to the entity RO and commander or director for an immediate investigation and verification of pertinent SAT inventory. An investigation should include physical inventory and reconciliation of all LT SAT with database records, review of laboratory usage records, transfer records, destruction records, and WS records. Once theft or loss has occurred, the investigation and recovery of SAT is a law enforcement function. Law enforcement, state, and federal agencies, including FSAP, must be notified of theft or loss of SAT; in terms of FSAP, initial notification is followed by a completed APHIS/CDC Form 3 within 7 days. The entity should be prepared to support law enforcement with all its recovery efforts.

Release of SAT from primary containment could occur during movement (breakage of specimen tubes), due to loss of engineering controls (eg, equipment malfunction, power outage), or as a result of an unforeseen event inside the containment laboratory. SAT release can pose a significant additional risk of exposure to workers if they are not adequately protected with PPE and if the release is not captured and neutralized. Workers potentially exposed to SAT should be immediately evaluated by occupational medicine staff, and appropriate follow-up care must be provided to the affected workers.

Local and state public health agencies and FSAP must be notified of SAT release, including potential exposures to workers. Theft, loss, or release of SAT is also reported to the chain of command in the DA and DoD laboratories.

Inventory Discrepancies

SAT inventory discrepancies (overage or shortage) should be immediately reported to the entity RO and AROs. The PI and research staff must conduct an investigation to resolve or confirm the inventory discrepancy. The memorandum of inventory discrepancy investigation should include:

- identity of the SAT,
- amount of discrepancy,
- date of last inventory and by whom,
- current or last known storage location,
- names of individuals who discovered the discrepancy,
- names of individuals who are notified of the discrepancy, and
- explanation or resolution, if available.

Theft and loss of BSAT must be reported to FSAP.[19]

Security Breaches

A security breach can occur due to a disruption in an established security network or failure to follow established security procedures and policies, or during active and deliberate intrusion from unauthorized sources (eg, intruders, enemy forces). The RO and the commander or director must be notified of all security breaches to restricted areas containing SAT. Security breaches may include:

- access to SAT by individuals not approved by the FSAP;
- individuals "piggy backing" into restricted areas;
- tampering of access controls, locks, and seals securing SAT;
- unauthorized access to SAT inventory databases;
- tampering of security badges, passcodes, or other entry credentials to restricted areas containing SAT;
- unauthorized removal of SAT from restricted areas;
- sharing of access credentials by workers;
- damage to building infrastructure resulting in easy access to SAT; and
- compromises due to hacking or deliberate manipulations in computer programing controlling containment access.

Lessons learned should be incorporated to enhance security systems and decrease security breaches.[56] The FSAP requires the RO to ensure that individuals with access to SAT are trained annually on entity incident response plans.

SUMMARY

The intent of the FSAP and the DoD's BSP is the same: to allow peaceful research to continue while restricting BSAT access to individuals and parties who intend to misuse them and do harm. Overall, current regulatory requirements promote laboratory safety and security of BSAT by requiring laboratory registration; prescreening of individuals requesting access to BSAT; personnel reliability or suitability assessments for individuals seeking access to Tier 1 BSAT; BSAT inventory management; preapproval and monitoring of BSAT transfers; reporting requirements for theft, loss, release, or identification of BSAT; preapproval for certain genetic alterations to BSAT (restricted experiments); and periodic onsite inspections by regulatory agencies. Regulatory burden on entities with BSAT can be significant; however, it is critical for the public to have confidence that work involving BSAT is conducted in a manner that prioritizes laboratory and public safety and protection of the environment.

Biological surety and security requirements to access BSAT in DoD laboratories currently meet or exceed that of the FSAP. DoD also imposes additional biological surety and security measures beyond those required by the FSAP, on contractors using DoD-owned BSAT. Having different eligibility standards to access and work with BSAT can have significant impact on collaborative research; harmonization of administrative policies and practices of facilities registered with FSAP is expected to promote increased collaboration among scientists. Currently, DoD is synchronizing its biological surety regulations with the FSAP regulations in accordance with Executive Order 13546.[22]

Scientific advances in synthetic biology are likely to challenge the current regulations governing BSAT; however, current US regulations governing BSAT are consistent with the broad international framework of agreements intended to prevent development and proliferation of chemical and biological weapons.

REFERENCES

1. Frischknecht F. The history of biological warfare. In: *Decontamination of Warfare Agents: Enzymatic Methods for the Removal of B/C Weapons*. Richardt A, Blum MM, eds. Wiley-VCH Verlag GmbH & Co. KGaA: Weinheim, Germany; 2008.

2. Frischknecht F. The history of biological warfare. Human experimentation, modern nightmares and lone madman in the twentieth century. *EMBO Rep*. 2003 Jun;4 Spec No:S47–S52.

3. Poupard JA, Miller LA. History of biological warfare: catapults to capsomeres. *Ann N Y Acad Sci*. 1992;666:9–20.

4. Noah DL, Huebner KD, Darling RG, Waeckerle JF. The history and threat of biological warfare and terrorism. *Emerg Med Clin North Am*. 2002;20:255–271.

5. Poupard JA, Miller LA, Granshaw L. The use of smallpox as a biological weapon in the French and Indian war of 1763. *ASM News*. 1989;55:122–124.

6. International Peace Conference, The Hague, 29 July 1899. Laws of War: Declaration on the Use of Projectiles the Object of Which Is the Diffusion of Asphyxiating or Deleterious Gases; July 29, 1899. http://avalon.law.yale.edu/19th_century/dec99-02.asp. Accessed August 15, 2014.

7. International Committee of the Red Cross. *Final Act of the Second Peace Conference. The Hague, 18 October 1907*. http://www.icrc.org/ihl.nsf/52d68d14de6160e0c12563da005fdb1b/4360cf9a132f97d7c125641e00372ed1?OpenDocument. Accessed June 25, 2014.

8. Wheelis ML. Biological sabotage in World War I, In:Geissler E, Moon JEvC, eds. *Biological and Toxin Weapons: Research, Development, and Use From the Middle Ages to 1945*. Oxford, UK: Oxford University Press; 1999.pp 35-62.

9. Rutecki GW. A revised time-line for biological agents: revisiting the early years of the germ theory of disease. *Med Hypothesis*. 2007;68(1):222–226.

10. Roffey R, Tegnell A, Elgh F. Biological warfare in a historical perspective. *Clin Microbiol Infect*. 2002; 8(8):450–454.

11. Harris S. Japanese biological warfare research on humans: a case study on microbiology and ethics. *Ann N Y Acad Sci*. 1992;666:21–52.

12. Harris S. The Japanese biological warfare programme: an overview, In: *Biological and Toxin Weapons: Research, Development and Use from the Middle Ages to 1945*. Edited by Geissler, E and Moon, J.E.v.C, 127-152. 1999. Stockholm International Peace Research Institute, Oxford University Press, Oxford, UK.

13. United Nations Office for Disarmament Affairs. Convention on the Prohibition of the Development, Production and Stockpiling of Bacteriological (Biological) and Toxin Weapons and on Their Destruction. http://www.un.org/disarmament/WMD/Bio. Accessed June 25, 2014.

14. Pub L 104-132. Antiterrorism and Effective Death Penalty Act of 1996. 24 April 1996. http://www.gpo.gov/fdsys/pkg/PLAW-104publ132/content-detail.html. Accessed June 25, 2014.

15. Pub L 107-56. Uniting and Strengthening America by Providing Appropriate Tools Required to Intercept and Obstruct Terrorism Act of 2001. 26 October 2001. http://www.gpo.gov/fdsys/pkg/PLAW-107publ56/content-detail.html. Accessed June 25, 2014.

16. Pub L 107-188. Public Health Security and Bioterrorism Preparedness and Response Act of 2002. 12 June 2002. http://www.gpo.gov/fdsys/pkg/PLAW-107publ188/pdf/PLAW-107publ188.pdf. Accessed June 25, 2014.

17. US Department of Agriculture Animal and Plant Health Inspection Service. Agricultural Select Agent Program. http://www.aphis.usda.gov/programs/ag_selectagent/. Accessed August 15, 2014.

18. US Department of the Army. *Biological Surety*. Washington, DC: DA; 2008. Army Regulation 50-1.

19. Select Agents and Toxins, 42 CFR Part 73 (2012).

20. Possession, Use, and Transfer of Select Agents and Toxins, 7 CFR Part 331 (2012).

21. Possession, Use, and Transfer of Select Agents and Toxins, 9 CFR Part 121 (2012).

22. Optimizing the Security of Biological Select Agents and Toxins in the United States. *Fed Regist*. 2010;75(130): 39439–39442. Executive Order 13546. http://www.gpo.gov/fdsys/pkg/FR-2010-07-08/pdf/2010-16864.pdf. Accessed June 25, 2014.

23. Centers for Disease Control and Prevention; Animal and Plant Health Inspection Services. List of Select Agents and Toxins. 12 September 2013. http://www.selectagents.gov/Select%20Agents%20and%20Toxins%20List.html. Accessed June 25, 2014.

24. Centers for Disease Control and Prevention; Animal and Plant Health Inspection Services. Forms. 13 August 2013. http://www.selectagents.gov/Forms.html. Accessed June 25, 2014.

25. Centers for Disease Control and Prevention; Animal and Plant Health Inspection Services. Registration for Possession, Use, and Transfer of Select Agents and Toxins. 22 October 2013. http://www.selectagents.gov/RegistrationForm.html. Accessed June 25, 2014.

26. Centers for Disease Control and Prevention; Animal and Plant Health Inspection Services. Security Risk Assessments. 25 March 2013. http://www.selectagents.gov/sra.html. Accessed June 25, 2014.

27. US Department of Health and Human Services (HHS), Centers for Disease Control and Prevention (CDC)/Division of Select Agents and Toxins and US Department of Agriculture (USDA), Animal and Plant Health Inspection Service (APHIS)/Agriculture Select Agent Program (ASAP). Guidance on the Inventory of Select Agents and Toxins. 20 June 2014. http://www.selectagents.gov/LongTermStorage.html. Accessed August 15, 2014.

28. US Department of the Army. *Nuclear and Chemical Weapons and Materiel: Biological Surety*. Washington, DC: DA; 2008. Army Regulation 50-1.

29. Transportation, 49 CFR, Parts 100–185 (1999).

30. US Department of Defense, Office of the Under Secretary of Defense for Acquisition, Technology, and Logistics. *Report of the Defense Science Board Taskforce on DoD Biological Safety and Security Program*. Washington, DC: Defense Science Board; 2008.

31. Centers for Disease Control and Prevention; Animal and Plant Health Inspection Services. *Permissible Toxin Amount*s. 5 October 2012. http://www.selectagents.gov/Permissible%20Toxin%20Amounts.html. Accessed June 25, 2014.

32. Centers for Disease Control and Prevention; Animal and Plant Health Inspection Services. *Federal Select Agent Program Policy Statement on Toxin Due Diligence Provision*. 3 May 2013. http://www.selectagents.gov/Toxin_Due_Diligence_Provision.html. Accessed June 25, 2014.

33. US Department of Health and Human Services Centers for Disease Control and Prevention and US Department of Agriculture Animal and Plant Health Inspection Service Agriculture Select Agent Services. *Select Agents and Toxins: Theft, Loss or Release Information Document*. Atlanta, GA: CDC; June 8, 2010.

34. Henkel RD, Miller T, Weyant RS. Monitoring select agent theft, loss and release reports in the United States, 2004–2010. *Applied Biosafety*. 2012;17(4):171–180.

35. US Department of Health and Human Services, National Institutes of Health, Office of Biotechnology Activities. *NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules*. Bethesda, MD: HHS/NIH; 2013.

36. Federal Select Agent Program, US Department of Agriculture/Animal and Plant Health Inspection Service; Department of Health and Human Services/Centers for Disease Control and Prevention. *Restricted Experiment Guidance Document*. Riverdale, MD, Atlanta, GA: USDA/APHIS, HHS/CDC; 2013.

37. US Department of Health and Human Services, Centers for Disease Control and Prevention, and National Institutes of Health. Chosewood LC, Wilson DE, eds. *Biosafety in Microbiological and Biomedical Laboratories*. 5th ed. Washington, DC: US Government Printing Office; 2009.

38. US Department of the Army. *Safety Standards for Microbiological and Biomedical Laboratories*. Washington, DC: DA; 2013. DA PAM 385-69, Rapid Action Revision.

39. US Department of Health and Human Services, Centers for Disease Control and Prevention/Division of Select Agents and Toxins; US Department of Agriculture/Animal and Plant Health Inspection Service Agriculture Select Agent Program. *Occupational Health Program Guidance Document for Working With Tier-1 Select Agents and Toxins*. Washington, DC: HHS; 5 July 2013.

40. US Department of Defense. *Nuclear Weapon Personnel Reliability Program (PRP)*. Washington, DC: DoD; 2012. DoD Instruction 5210.42.

41. US Department of Defense. *Minimum Security Standards for Safeguarding Chemical Agents*. Washington, DC: DoD; 2007. DoD Instruction 5210.65.

42. US Department of Defense. *Minimum Security Standards for Safeguarding Biological Select Agents and Toxins*. Washington, DC: DoD; 2006. DoD Instruction 5210.89.

43. Carr K, Henchal EA, Wilhelmsen C, Carr B. Implementation of biosurety systems in a Department of Defense medical research laboratory. *Biosecur Bioterror*. 2004;2(1):7–16.

44. US Department of Health and Human Services, Centers for Disease Control and Prevention/Division of Select Agents and Toxins; US Department of Agriculture/Animal and Plant Health Inspection Service. *Guidance for Suitability Assessments*. Washington, DC: HHS; 2013.

45. Privacy Act, 5 USC § 552a (1974).

46. Health Insurance Portability and Accountability Act, Pub L 104–191, 110 Stat 1936.

47. Crimes and Criminal Procedure, 18 USC § 175B (2011).

48. US Department of Defense. *Personnel Reliability Program—Personnel Security Investigations and Adjudications. Policy and Implementation Procedures for Personnel Security Investigations and Adjudications*. Washington, DC: DoD; 2012. Army Directive 2012-17.

49. US Department of Health and Human Services, Centers for Disease Control and Prevention/Division of Select Agents and Toxins; US Department of Agriculture/Animal and Plant Health Inspection Service/Agriculture Select Agent Program. *Security Guidance for Select Agent or Toxin Facilities*. Washington, DC: HHS; 2013.

50. The White House Office of Science and Technology Policy. Biosecurity website. http://www.whitehouse.gov/administration/eop/ostp/nstc/biosecurity. Accessed July 3, 2014.

51. US Department of the Army. *Biological Select Agents and Toxins Security Program*. Washington, DC: DA; 2009. Army Regulation 190-17.

52. US Department of Health and Human Services, Centers for Disease Control and Prevention/Division of Select Agents and Toxins; US Department of Agriculture/Animal and Plant Health Inspection Service/Agriculture Select Agent Program. *Information Systems Security Control Guidance Document*. Washington, DC: HHS; 2012.

53. US Department of Health and Human Services, Centers for Disease Control and Prevention/Division of Select Agents and Toxins; US Department of Agriculture/Animal and Plant Health Inspection Service/Agriculture Select Agent Program. *Incident Response Plan Guidance Document*. Washington, DC: HHS; 2013.