

Chapter 23

BIOSURETY

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INTRODUCTION

The influence of infectious disease on the course of history has been continuous. Endemic diseases such as malaria and human immunodeficiency virus have contributed to the endemic poverty of many Third World countries. Although humans have coexisted with infectious diseases for centuries, their potential for use as weapons against humans has become a matter of particular concern. Use of infectious diseases against enemies is not a new idea. Throughout history there have been well-documented and deliberate attempts to use noxious agents to influence battles, assassinate individuals, and terrorize the masses. South American aboriginal hunters often use arrow tips dipped in curare and amphibian-derived toxins. Additionally, there are reports from antiquity that crude wastes and animal carcasses were catapulted over castle walls and dropped into wells and other bodies of water to contaminate water sources of opposing forces and civilian populations. These practices precede written records but demonstrate the human race's long involvement in the use of biological weapons. One of the earliest well-documented cases of using infectious agents in warfare dates back to the 14th century siege of Kaffa (now Feodosia, Ukraine). During the attack, the Tartan forces experienced a plague outbreak. Turning their misfortune into advantage, they began to hurl the cadavers of the deceased into Kaffa using a catapult. Defending forces retreated in fear of contracting the plague. The abandoned city was easily taken by the Tartan forces, and the hasty retreat from Kaffa resulted in the spread of the plague epidemic to Constantinople, Genoa, Venice, and other Mediterranean port cities where the retreating forces found safe harbor.¹⁻³

Tactics such as these, and the understanding that disease, or even fear of disease, can be as detrimental to fighting forces as bullets, led military leaders to seek ways in which they could prevent disease among their soldiers as well as use it against their enemies. Although the first vaccine for smallpox was not used until 1796, variolation was practiced long before that time and provided lifelong immunity. Variolation was the procedure of deliberately inoculating people using scabs from smallpox infections either blown into the nose or rubbed into a puncture on the skin. General George Washington ordered the variolation of all soldiers in 1777. Because they were able to protect their own forces, commanders were free to use infectious disease in more deliberate ways. The British military reportedly used smallpox as a weapon against the Delaware Indians when General Jeffery Amherst ordered that blankets and handkerchiefs from smallpox-infected patients at Fort Pitt's infirmary be presented to them during a peace meeting.^{1,2,4,5}

During the 19th century there were many advances in the understanding of bacterial agents. For the first time bacteria were isolated from diseased individuals and animals and grown in artificial culture outside the body using various growth media. Armed with these new methods of growing large volumes of bacteria, German scientists and officers began a large biological campaign against the Allied Forces during World War I. Instead of targeting the soldiers in this campaign, they targeted the livestock that were destined for shipment to the Allied Forces with the agents causing anthrax and glanders. Large numbers of horses and mules were reported to have died from these infections.^{1,2,6,7} These biological campaigns are considered to have had a negligible effect on the outcome of the war. The Germans were far more successful in their campaigns with chemical agents.

The devastating effects of German chemical warfare efforts led to the drafting of the Protocol for the Prohibition of the Use in War of Asphyxiating, Poisonous or Other Gases and of Bacteriological Methods of Warfare, signed at Geneva, Switzerland, on June 17, 1925.^{8,9} This treaty prohibited the use of both biological and chemical agents in warfare but did not provide for any inspections to verify compliance. Nor did the treaty prohibit the use of biological or chemical agents in research, production of agents, or possession of biological weapons. Many countries agreed to the measure in 1925 with the stipulation that they had the right to retaliate against biological or chemical weapon attacks with their own arsenals. Many countries proceeded to work with both biological and chemical weapons, and 50 years passed before any agreement on biological and toxin weapons was ratified by the US Senate. The Japanese aggressively advanced biowarfare in World War II by using Chinese prisoners to study the effects of anthrax, cholera, typhoid, and plague. More than 10,000 people were killed from the use of these agents on both military prisoners and civilian populations.^{1,2,10} Despite their best efforts at the time, the Japanese never developed an effective means of infecting large numbers of persons using biological munitions.

By the end of World War II, the Americans and Soviets were investing heavily in the weaponization of biological agents. Advances in science and technology allowed researchers to develop efficient ways to disperse infectious agents, often using routes quite different from the way people normally contracted the disease. Infectious agents were placed in missiles, bombs, and aerosol delivery systems capable of targeting large numbers of people. The ability to create aerosol clouds of infectious disease agents and infect large numbers of people simultaneously changed the perceived risk

associated with biological agents. Scientists estimated that casualties caused by the release of agents from aircraft ranged from 400 to 95,000 dead and 35,000 to 125,000 incapacitated depending on the agents used.^{2,11} Agents that had been encountered only in manageable, naturally occurring outbreaks acquired the potential to kill or incapacitate large numbers of people.

The lethal and unpredictable nature of biological weapons and their ability to affect noncombatants galvanized the global community against their use in warfare, and led to over 100 nations, including the United States, Iraq, and the former Soviet Union, signing the 1972 Biological Weapons Convention.^{9,12} This treaty prohibited the use of biological agents as weapons but stopped short of ending defensive research. The ability of some countries to continue aggressive weapons development programs despite having signed the convention demonstrated its ineffectiveness as a means of controlling the proliferation of biological and chemical weapons. During the 1990s an attempt was made to strengthen the Biological Weapons Convention by adding a verification regime referred to as the Biological Weapons Convention Protocol. This protocol would have added to the original agreement the ability to inspect both declared and suspected sites for biological weapons manufacture. This would have meant that a significant number of facilities that could be considered "Dual Use" (eg, vaccine production facilities, university research centers, and beer brewing plants) would now be subject to inspection from international weapons inspection teams. The Bush administration eventually rejected the protocol in 2001 because it felt that the inspection of these potential "Dual Use" facilities would not assist in uncovering illicit activity and create an undue burden on US commercial facilities.

President Richard M Nixon ordered the dismantling of the US offensive biological weapons program and diverted its funding to other vital efforts such as cancer research in 1969. Although the United States and Great Britain were busy destroying their weapon stockpiles, other countries and extremist organizations continued to develop and use both biological and chemical weapons. In the 1970s the Soviet Union and its allies were suspected of having used "yellow rain" (trichothecene mycotoxins) during campaigns in Laos, Cambodia, and Afghanistan.¹ An accidental release of *Bacillus anthracis* spores (the causative agent of anthrax) from a Soviet weapons facility in Sverdlovsk killed at least 66 people in 1979.¹³⁻¹⁵ After the Persian Gulf War and United Nations Special Commission inspections, Iraq disclosed that it had bombs, Scud missiles, 122-mm rockets, and artillery shells armed with botulinum toxin, *B anthracis* spores, and aflatoxin. According to a 2002 report from the Center for Nonproliferation

Studies, six countries (Iran, Iraq, Libya, North Korea, Russia, and Syria) were known to possess biological or toxin weapons based on clear evidence of a weaponization program. An additional 11 nations (Algeria, China, Cuba, Egypt, Ethiopia, Israel, Myanmar, Pakistan, Sudan, Taiwan, and Vietnam) were suspected of having biological weapons programs with varying certainty. This list includes nations that also had former weapons programs.¹⁶ Because of the lack of verification in any of the international agreements, it is difficult to determine whether the massive quantities of agents produced by those nations have been destroyed. Although the Biological Weapons Convention attempted to restrain nations in the biological weapons race, other events make it clear that the greater threat may now come from extremist organizations that exploit political instability worldwide to gain access to the agents and technologies that will further their agendas.

Extremist organizations have used biological agents to further their agendas since the 1980s. Food and water contamination may be a highly effective means to deliver a chemical or biological attack. Over 750 people were infected with *Salmonella typhimurium* through contamination of restaurant salad bars in Oregon by followers of the Bhagwan Shree Rajneesh in 1984.^{1,2,17} A Japanese sect of the Aum Shinrikyo cult attempted an aerosolized release of the anthrax agent from Tokyo building tops in 1994.^{1,2,18} This cult also unsuccessfully attempted to obtain Ebola virus during an outbreak in Africa during the 1990s, and it released sarin nerve gas into a subway system in Tokyo. Several national and international groups have been found in possession of ricin toxin with the intent to disperse the toxin in an attack.^{1,2} The anthrax mailings sent in October 2001 in the United States demonstrated that individuals were able to use biological agents as bioterrorism experts had warned for more than two decades. Although the anthrax attacks were not successful in causing large numbers of casualties and fatalities, they did have a significant economic and emotional impact. The Centers for Disease Control and Prevention (CDC) reported the effects of this one attack included 5 fatalities, 17 illnesses, a cost of \$23 million to decontaminate one Senate office building, \$2 billion in lost revenue to the US Postal Service, and as much as \$3 billion for the decontamination of the US Postal Service buildings and procurement of mail sanitizing equipment.¹⁹

As the potential use of these agents by extremist organizations and individuals came into the spotlight, congressional interest in regulating the research community increased. It was evident that a fundamental change in the US policy toward the regulation of these agents was required. The need for change was made apparent by the case of Larry Wayne Harris, microbiologist and suspected white supremacist, who was

arrested in 1995 after receiving freeze-dried cultures of *Yersinia pestis* (the agent that causes plague) from the American Type Culture Collection. Because it was not a crime to possess these materials, he was only able to be charged for mail fraud and sentenced to 18 months of probation and 200 hours of community service in spite of the fact that there was a clear intent to use these materials in a malicious manner. At the time that his crime was committed, it was not a federal offense or even illegal to be in possession of these agents.²⁰ In contrast, once the laws were changed, a professor in Texas who was conducting valid research without malicious intent was convicted and sentenced to 2 years in prison for improper handling of plague samples. The prosecutor in the case was seeking 10 years in prison and millions in fines; however, the sentence was reduced because of the great contributions that Thomas Butler had made to the scientific community. There was no indication that he planned on using these specimens for bioterrorism.^{21,22} Since that conviction, there has been concern in the scientific community regarding the risks of engaging in research that could put one in jail for relatively minor infractions of the law.

REGULATORY AGENCIES

After the Oklahoma City bombing, Congress passed the Anti-Terrorism Act of 1996. This act provides law enforcement activities with a broad range of new tools to be used in investigating and prosecuting potential acts of terrorism in the United States. With this act, Congress declared that the responsibility for developing regulations to control access to and possession of biowarfare threat agents would be the US Department of Health and Human Services (DHHS) and the US Department of Agriculture (USDA).

The first regulatory framework for working with and transferring select agents and toxins was published by the CDC in 1997. In these regulations the CDC had four goals:

1. identify the agents that are potentially hazardous to the public health;
2. create procedures for monitoring the acquisition and transfer of the restricted agents;
3. establish safeguards for the transportation of these infectious materials; and
4. create a system for alerting the proper authorities when an improper attempt is made to acquire a restricted agent.

In June 2002, the CDC convened an interagency working group with diverse representation, including Department of Defense (DoD) experts, to determine which infectious diseases and toxins should be listed

The US government and other nations have undertaken a variety of approaches to combat the extremist threat. Export controls on key precursor materials and equipment have been implemented since 2001. New technical sensors to detect and identify specific agents or categories of agents have been developed and deployed. These systems have been used during events where large populations have assembled such as the Olympic games and the Super Bowl. In direct response to the anthrax mailings of 2001, the US Postal Service has implemented a continuous surveillance of major distribution centers to protect both their workers and the general public from another attack. New systems to monitor public health, such as syndromic surveillance systems, have been developed. Syndromic surveillance assists in highlighting areas in which an epidemic or outbreak might occur so that a containment and treatment strategy can be developed. Finally, to prepare for situations in which detection and surveillance efforts fail to warn of an attack, agencies in the federal government are focusing efforts to develop, improve, and stockpile medical countermeasures to the recognized biowarfare threat agents.²³

as select agents requiring regulation.

On December 13, 2002, DHHS and the USDA each published interim regulations in the *Federal Register* that addressed the possession, use, and transfer of select biological agents and toxins (select agents). The final rule, which was published on March 18, 2005, is updated periodically to include emerging threats. The DHHS regulations are published in Title 42 Code of Federal Regulations (CFR) Part 73,¹⁹ and the USDA regulations are published in Title 7 CFR Part 331²⁴ and Title 9 CFR Part 121.²⁵ These rules apply to all academic institutions and biomedical centers; commercial manufacturing facilities; federal, state, and local laboratories; and research facilities. Regulated agents and toxins appear in Chapter 18, Laboratory Identification of Biological Threats, Exhibit 18-1.

The original list published in December 2002 remains largely unchanged in the regulation, which was published on March 18, 2005. The list is not limited to the infectious agent or toxin itself but also regulates the agents' genetic elements, recombinant nucleic acids, and recombinant organisms. If the DNA or RNA of an agent on the listing can be used to recreate the virus from which it was derived, then the genetic material is also subject to the regulation. Any organism that has been genetically altered must also be regulated. Finally, recombinant nucleic acids that encode for functional forms of toxins that can be expressed in vivo or in vitro are subject to regulation

to safeguard this material.

Some notable exceptions to the regulation allow for the unencumbered handling of diagnostic specimens by clinical laboratories. Title 42 CFR 73.5 states:

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

1. Unless directed otherwise by the HHS secretary, within 7 calendar days after identification, the select agent or toxin is transferred in accordance with 73.16 or destroyed on-site by a recognized sterilization or inactivation process.
2. The select agent or toxin is secured against theft, loss, or release during the period between identification of the select agent or toxin and transfer or destruction of such agent or toxin, and any theft loss or release of such agent or toxin is reported, and
3. The identification of the select agent or toxin is reported to the CDC or the Animal and Plant Health Inspection Service (APHIS) and to other appropriate authorities when required by federal state or local law.”¹⁹

The identification of certain agents in diagnostic specimens is of great concern to the CDC, and certain agents must be reported within 24 hours of identification. Exhibit 23-1 lists select agents and toxins with immediate reporting requirements, which is different from the reporting requirements for public health activities.

Additional variances are granted to the clinical laboratory to allow handling proficiency testing materials.

As with diagnostic testing, the recipient of these materials must safeguard them from theft, loss, or release; transfer or destroy the testing materials within 90 calendar days of receipt; and report identification of the agent or toxin within 90 calendar days. Both of these exceptions are important in that they allow exemption of clinical laboratories that may only handle such agents for short periods of time during diagnostics or proficiency testing periods. These laboratories, which are already registered and inspected by the College of American Pathologists, generally only handle small quantities of agent at any given time.

In addition to the specific allowances provided for clinical labs, there are guidelines for agents with general exclusions as follows:

- Any select agent or toxin that is in its naturally occurring environment provided it has not been intentionally introduced, cultivated, collected, or otherwise extracted from its natural source.
- Nonviable select agent organisms or nonfunctional toxins.
- Formalin-fixed tissues.
- Agents that have been granted exception as a result of their proven attenuations.

Attenuated virus and bacteria strains are listed on the CDC Web site. This is not a general exclusion for all “attenuated strains” of viruses or bacteria. If researchers want exemption from the provisions for a particular strain, a written request for exclusion with supporting scientific information on the nature of the attenuation must be submitted. Agents that have already received exclusion are listed in Table 23-1.

EXHIBIT 23-1	
IMMEDIATE REPORTING REQUIREMENTS FOR SELECT AGENTS	
DHHS Select Agents and Toxins	Overlap Select Agents and Toxins*
Ebola viruses	<i>Bacillus anthracis</i>
Lassa fever virus	Botulinum neurotoxins
Marburg virus	<i>Brucella melitensis</i>
South American hemorrhagic fever viruses (Junin, Machupo, Sabia, Flexal, Guanarito)	<i>Francisella tularensis</i>
Variola major virus (Smallpox virus)	Hendra virus
Variola minor (Alastrim)	Nipah virus
<i>Yersinia pestis</i>	Rift Valley fever virus
	Venezuelan equine encephalitis virus

DHHS: Department of Health and Human Services
 * Biological agents and toxins that affect both humans and livestock are termed overlap agents.

TABLE 23-1
ATTENUATED STRAINS EXEMPTED FROM REGULATION

Agent	Qualifier	Effective Date of Exclusion
Avian influenza (highly pathogenic) virus	Recombinant vaccine reference strains—H5N1 and H5N3 subtypes	5/7/2003
<i>Bacillus anthracis</i>	Devoid of both plasmids pX01 ⁺ and pX02	2/27/2003
<i>Bacillus anthracis</i>	Devoid of pX02 (<i>Bacillus anthracis</i> Sterne, pX01 ⁺ ,pX02 ⁻)	2/27/2003
<i>Brucella abortus</i>	Strain RB51 (vaccine strain)	5/7/2003
<i>Brucella abortus</i>	Strain 19	6/12/2003
<i>Coccidioides posadasii</i>	□ chs5 strain + □cts/□ard1/□cts3 strain	10/14/2003
Conotoxin	Specially excluded are the class of sodium channel antagonist U-conotoxins, including GIIIA; the class of calcium channel antagonist w-conotoxins, including GVIA, GVII, MVIIA, MVIIC, and their analogs or synthetic derivatives; the class of NMDA-antagonist conantokins, including con-G, con-R, con-T and their analogs or synthetic derivatives; and the putative neurotensin agonist, contulakin-G and its synthetic derivatives	4/29/2003
<i>Coxiella burnetii</i>	Phase II, Nine Mile Strain, plaque purified clone 4	10/15/2003
Junin virus vaccine strain	Candid 1	2/7/2003
<i>Francisella tularensis</i> subspecies <i>novicida</i>	Utah 112 (ATCC 15482)	2/27/2003
<i>Francisella tularensis</i> subspecies <i>holoartica</i>	Live vaccine strains, includes NDBR 101 lots, TSI-GSD lots, and ATCC 29684	2/27/2003
<i>Francisella tularensis</i>	ATCC 6223, also known as strain B38	4/14/2003
Japanese encephalitis virus	SA 14-14-2	3/12/2003
Rift Valley fever virus	MP-12	3/16/2004
Venezuelan equine encephalitis virus	V3526 (virus vaccine candidate strain)	5/5/2003
Venezuelan equine encephalitis virus	TC-83	3/13/2003
<i>Yersinia pestis</i>	Strains that are pgm ⁻ due to a deletion of a 102-kb region of the chromosome termed the pgm locus. This includes strain EV or various substrains such as EV 76	3/14/2003
<i>Yersinia pestis</i>	Strains devoid of the 75 kb low-calcium response virulence plasmid such as Tjiwidej S and CDC A1122	2/27/2003

ATCC: American Type Culture Collection
NMDA: N-methyl-D-aspartate

In addition to the exclusions for specific strains of viruses or bacteria, certain amounts of toxin are not considered to pose a significant risk to human health or agriculture. Therefore, the requirement for registration depends on the amount of toxin possessed. The

toxins listed in Table 23-2 (in the purified form or in combinations of pure and impure forms) are exempt from regulation if the aggregate amount under the control of a principal investigator does not, at any time, exceed the amount specified.

CENTERS FOR DISEASE CONTROL AND PREVENTION SAFEGUARDS

The CDC regulations require entities handling select agents to register and meet the following criteria:

- The entity must appoint an individual to represent it in its dealings with the CDC (this person is called the Responsible Official).

TABLE 23-2
REGULATED AMOUNTS OF TOXINS*

Toxin	Amount (mg)
Abrin	100
Botulinum neurotoxins	0.5
Conotoxins	100
Diacetoxyscirpenol	1,000
Ricin	100
Saxitoxin	100
Shiga-like ribosome-inactivating proteins	100
Staphylococcal enterotoxins	5
Tetrodotoxin	100

*Current information can be obtained from the Centers for Disease Control and Prevention Web site: <http://www.cdc.gov/od/sap/sap/exclusion.htm>.

- The entity must define what agents are being used and for what purposes.
- The entity must provide the names of persons having access to agents.
- The entity must implement plans for the bio-safety, security, and emergency management.
- Each person having access to those agents must have a security risk assessment. This assessment ensures that restricted persons (per Title 18 United States Code 175b)²⁶ are denied access to any select agent or toxin.

The Attorney General defines a restricted person²⁶ as someone who:

- is under indictment for a crime punishable by imprisonment for a term exceeding 1 year;
- 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 (as defined in section 102 of the Controlled Substances Act [21 United States Code 802]²⁷);
- is an alien illegally or unlawfully in the United States;
- has been adjudicated as a mental defect 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 which the Secretary of State has determined to have repeatedly provided support for acts of international terrorism (if the determination remains in effect); or
- has been discharged from the Armed Forces of the United States under dishonorable conditions.

Once an entity is registered, the CDC may inspect its facilities at any time to ensure that handling of select agents is in accordance with the regulation. If at any time an entity is not in substantial compliance, the certificate of registration may be revoked, and all research involving select agents must cease until the entity can again demonstrate compliance with the regulations. Oversight by the CDC/USDA and the requirement for registration of both facilities and personnel represent a significant step in increasing the security of select agents and toxins that have the capacity to adversely impact human health and agricultural activities.

US ARMY BIOSURETY

To adapt to the post-9/11 world, the US Army began to develop its own policies involving select agents and toxins. Although the CDC's policies focused on limiting access to select agent stocks, the Army Biosurety Program focused on the reliability of personnel who had been granted full access to select agents to ensure that they were qualified. The biosurety program is based on the military experience with surety programs for both nuclear and chemical weapons. The goals of the chemical and nuclear surety program are to ensure that operations with these hazardous materials are performed safely and securely. The intent of the biological surety program is the same, but its policies also consider the unique aspects of biological agents.

Review of the DoD biological research, development, test, and evaluation programs revealed a need to heighten security and implement more stringent procedures for controlling access to infectious agents.²⁸ In light of the

newly identified threats to the public health, emphasis and funding were provided to address these concerns. In addition to increased security and control measures, the Department of the Army (DA) inspector general advocated the immediate implementation of a biosurety program. Work on the program began quickly with a series of interim guidance messages (beginning in December 2001) to the DoD biological defense research community. The first message defined the general guidelines for the Army's Biosurety Program. The second and third messages addressed biological personnel reliability programs (BPRPs), contractor personnel, and facilities. The policies set forth in the interim messages were formalized with the implementation of the draft Army Regulation (AR) 50-X, *Army Biological Surety Program* (current version dated December 28, 2004),²⁹ which established the DA's corporate approach for the safe, secure, and authorized use of biological select agents and toxins (BSATs) and

identified the procedures for the BPRP. In January 2005 all agencies throughout the Army that handled select agents were directed to comply with the draft AR 50-X as of May 5, 2005. This compliance requirement represented a major effort in a comparatively short period of time for all Army agencies handling BSATs.

Surety Program Concepts

Biosurety is defined as the combination of four basic areas or pillars: (1) physical security, (2) biosafety, (3) agent accountability, and (4) personnel reliability.³⁰ The careful integration of these factors yields policies and procedures to mitigate the risks of conducting research with these agents. Physical security defines the actions that secure select agents and deny access to select agents for subversive purposes. Multiple layers of integrated levels of security can use a variety of means to detect intrusion and prevent theft or misuse of select agents. Biosafety, a term that has been used for many years and with various definitions, is best defined as the procedures used in the laboratory or facility to ensure that pathogenic microbes are safely handled. The procedures and facility design requirements defined in the *Biosafety in Microbiological and Biomedical Laboratories (BMBL)*, 5th edition, are the standard for the safe handling of all infectious agents.³¹ Agent accountability means keeping accurate inventory records and establishing an audit to ensure that stocks are not missing. Personnel reliability is the final pillar in ensuring that those who are granted access to agents are stable, trustworthy, and competent to perform the tasks assigned to them. Although the screening procedures for the CDC's security risk assessment are designed to exclude restricted persons, the DoD policy uses methods to assess a person's reliability. Every person having access to select agents submits

to initial screenings followed by continuous health monitoring, random drug tests, and periodic evaluation by the supervisor to ensure that each employee maintains the highest standards of personal conduct. All of these programs contribute in important ways to the mission of biosurety. Table 23-3 shows the pillars and contributing factors of biosurety. The foundation for the pillars is training: continuous training in all of these areas helps ensure that personnel understand the mission and conduct research safely and securely.

Physical Security

One of the important factors in establishing a dynamic biosurety program is security. Developing a security plan begins by identifying areas containing select agents and toxins and limiting access to those areas. Typically this is done by establishing restricted areas and using automated access control systems. These systems provide detailed information, record access to restricted areas, and can even be tied into closed-circuit television cameras to allow positive identification of personnel before they are allowed entry. A combination of increasingly restrictive security measures can help to establish layers of security perimeters commensurate with the risk related to the agents used. For example, card readers can be used to limit and identify progress thorough corridors of restricted areas, whereas locks activated by personal identification number key pads allow entry into specific rooms. Laboratories containing high-risk agents, such as Ebola virus and botulinum neurotoxins, may have additional measures such as biometric readers and intrusion detection systems. Specific requirements for access may include clearly defined and visible markings on security badges. Everyone in the facility should be aware of the ways that restricted areas are

TABLE 23-3
PILLARS OF BIOSURETY AND PILLAR COMPONENTS

Physical Security	Safety	Personnel Reliability	Agent Accountability
Limited access to biological restricted areas	Safety training and mentorship	Background investigations	Agent inventory noting locations of agents
Internal and external monitoring	Risk management	Medical screening	Access to stocks limited
Intrusion detection systems	Environmental surveillance	Employment records screening	Accurate and current inventory of historical and working stocks
Random search and inspection	Occupational health screening	Urinalysis	Auditable records system

marked and who is allowed access to those areas to identify intruders. Persons who are allowed access to the restricted areas must have completed all training required for the safe conduct of laboratory procedures. Training should be evaluated through testing, or preferably, a period of mentorship within the containment. A mentorship program allows the trainee to experience the working conditions and ask questions under close supervision. The time required for mentorship periods depends on the level of experience of the person entering containment. The trainee should not be allowed unescorted access to a containment area until the trainer is satisfied that he or she can perform a variety of tasks safely and securely.

Biosafety

The guidelines regarding the safe handling of infectious agents and toxins and for laboratory design are defined in the *BMBL*.³¹ Before the establishment of these guidelines, it was not uncommon to have laboratory workers become infected with the agents that they were handling. Sulkin and Pike conducted a series of studies from 1949 until 1976 documenting and characterizing laboratory-acquired infections.³²⁻³⁵ These studies helped to identify problems with common laboratory procedures of the time (mouth pipetting, needle and syringe use, and generally poor techniques) that contributed to the rate of laboratory infection. Although many laboratory-acquired infections occurred with *Brucella*, *Salmonella*, *Francisella tularensis*, *Mycobacterium tuberculosis*, hepatitis virus, and Venezuelan equine encephalitis virus, less than 20% were associated with a "laboratory accident." Also, the infected laboratory workers were not considered a threat to the public health because of the low incidence of agent transmission to contacts.

In 1979 Pike concluded in a review that "the knowledge, the techniques and the equipment to prevent most laboratory-acquired infections are available."³⁶ However, it was not until 1984 that the CDC/National Institutes of Health published the first edition of the *BMBL*, which described combinations of standard and special microbiological practices, safety equipment, and facilities that constituted biosafety levels 1 through 4. This publication also defined for the first time which agents should be handled in which laboratory safety level. The implementation of these guidelines around the country has significantly reduced the occurrence of laboratory-acquired infections.³¹ Under 42 CFR Part 73, the entity is required to develop a biosafety plan that identifies the agents used and procedures for their safe handling and containment.¹⁹

The *BMBL* describes three areas necessary to establish containment: (1) laboratory practices and techniques, (2) safety equipment, and (3) facility design/construction. The combination of laboratory practices and primary and secondary barriers reduces the chances of exposure for laboratory personnel, other persons, and the outside environment to hazardous biological agents. In developing the laboratory-specific procedures and practices, it is important to integrate all aspects of these barrier protections. In addition to the procedures specific to their research protocol, all persons operating in containment laboratories should understand the operation of the safety equipment that serves as the primary barrier for containment. Examples of primary barriers include biological safety cabinets, glove boxes, safety centrifuge cups, or any other type of enclosure or engineering control that limits the worker's exposure to the agent. Secondary barriers are facility and design construction features that contribute to the worker's protection and also protect those outside of the laboratory from contact with or exposure to agents inside the containment facility. Examples of secondary barriers include physical separation of laboratory areas from areas that are accessible to the general public, hand-washing facilities in close proximity to exits, and specialized ventilation systems that provide directional flow of air and high-efficiency particulate air filtration prior to exhaust. Training for the performed protocols and laboratory-specific operations should be clearly defined and well documented. Depending on the risk of the activities being conducted in the containment laboratory, it is not sufficient to read a manual or receive a briefing to ensure proper training. In many cases, a method to assess the person's understanding and ability to perform these tasks should be used.

Biological Personnel Reliability Program

The purpose of the BPRP is to ensure that persons with access to potentially dangerous infectious agents and toxins are reliable. The program as defined in AR 50-X chapter 2 (Biological Surety) goes far beyond the CDC requirements for access to select agents. Although the CDC ensures that restricted persons do not have access to select agents, the BPRP further requires that persons with access to select agents are "mentally alert, mentally and emotionally stable, trustworthy, and physically competent." To this end, personnel undergo an initial screening process and then submit to continuous monitoring for the duration of their duties accessing select agents. This is the most detailed chapter in the biosurety regulation, and the program

requires dedicated efforts of many persons to ensure that it is executed fairly and coordinated with all of the screening partners.

The first step in the establishment of the program is to identify personnel who must be enrolled. AR 50-X identifies four categories of persons who must be enrolled:

1. personnel who have a legitimate need to handle or use BSATs;
2. personnel whose duties afford direct access to storage and work areas, storage containers, and equipment containing BSATs, including persons with responsibility for access control systems such that they could provide themselves direct access to storage and work areas, storage containers, and equipment containing BSATs;
3. armed security guards inside the facility, as identified in biological security guidance to be published by the Office of the Provost Marshall General; and
4. personnel authorized to escort visitors to areas containing BSATs.

The requirements for enrollment, therefore, are not restricted to researchers who use BSATs daily but may extend to people who receive shipments at the warehouse or service equipment within the containment laboratories. They are also not limited to a particular job series (Government Schedule [GS]) of a government employee but are instead related to the specific duties. For example, in one division, there may be two employees who are both GS-403 series DA civilians performing tasks as microbiologists, but only one microbiologist may be required to have access to select agents. Therefore, enrollment in the BPRP is required only for the employee who must access the agents. This requirement has created some difficulty in implementing the BPRP because persons with access to select agents may have little incentive to endure the rigorous screening process and continuous intrusive monitoring if they can perform similar research with nonselect agents or perform select agent research in a non-DoD laboratory. The possibility of losing talented and well-trained researchers to other facilities and non-DoD agencies with less stringent programs, a continuing concern, may impact the ability of the Defense Threat Reduction Agency to provide research personnel to combat biological agent use in the United States by terrorist organizations.

The initial screening process for enrollment requires a six-step process:

1. initial interview
2. personnel records review
3. personnel security investigation

4. medical evaluation
5. drug testing and
6. final review.

The order of steps in the process is left to the discretion of the activity; however, each step must occur and be fully documented.

Initial Interview

The process begins with the initial interview conducted by the certifying official (CO). The CO is the gatekeeper for access to select agents and toxins, ensuring that persons requesting access have met all of the qualifying conditions. Typically, the CO supervises the worker or is otherwise in the supervisory chain. During the initial interview, the candidate grants consent for the screening and 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 suitability. If exceptional extenuating circumstances exist, reviewing officials may request an exception for the enrollment of the individual through their command channels. The following are mandatory disqualifying factors:

- Diagnosis as currently alcohol dependent based on a determination by an appropriate medical authority.
- Drug abuse in the circumstances listed below:
 - Individuals who have abused drugs in the 5 years before the initial BPRP interview. Isolated episodes of abuse of another person's prescribed drug will be evaluated.
 - Individuals who have ever illegally trafficked in illegal or controlled drugs.
 - Individuals who have abused drugs while enrolled in the BPRP, including abuse of another individual's prescribed drugs.
- Inability to meet safety requirements, such as the inability to correctly wear personal protective equipment required for the assigned position, other than temporary medical conditions. Questions regarding the duration of medical conditions will be referred to a competent medical authority.

The initial interview also determines whether any instances of potentially disqualifying activities exist. These are activities that the CO must consider when evaluating a person's reliability for access to BSATs. Potentially disqualifying factors are much broader and

are evaluated by the CO to establish a full picture of the person's character. The following excerpt from AR 50-X describes potentially disqualifying factors:

a. Alcohol-related incidents/abusing alcohol.

(1) Certifying officials will evaluate the circumstances of alcohol-related incidents that occurred in the 5 years before the initial interview and request a medical evaluation. An individual diagnosed through such medical evaluation as currently alcohol dependent will be disqualified per paragraph 2-7a, AR 50-X. Individuals diagnosed as abusing alcohol will be handled per paragraph (2) below. For an individual not diagnosed as a current alcohol dependent/abusing alcohol, including those individuals identified as recovering alcoholics, the CO will determine reliability based on results of the investigation, the medical evaluation, and any extenuating or mitigating circumstances (such as successful completion of a rehabilitation program). The CO will then qualify or disqualify the individual from the BPRP, as he or she deems appropriate.

(2) Individuals diagnosed as abusing alcohol but who are not alcohol dependent, shall at a minimum be suspended from BPRP processing pending completion of the rehabilitation program or treatment regimen prescribed by the medical authority. Before the individual is certified into the program, the CO will assess whether the individual has displayed positive changes in job reliability and lifestyle, and whether the individual has a favorable medical prognosis from the medical authority. Failure to satisfactorily meet these requirements shall result in disqualification.

b. Drug abuse.

(1) In situations not otherwise addressed in paragraph 2-7b, a CO may qualify or disqualify an individual who has abused drugs more than 5 years before the initial BPRP screening, or have isolated episodes of abuse of another's prescription drugs within 15 years of initial BPRP screening. In deciding whether to disqualify individuals in these cases, the CO will request medical evaluation and may consider extenuating or mitigating circumstances. To qualify the individual for the BPRP, the CO's memorandum of the potentially disqualifying information (PDI) must include an approval signed by the reviewing official. Ex-

amples of potential extenuating or mitigating circumstances include, but are not limited to:

- (a) Successful completion of a drug rehabilitation program.
- (b) Isolated experimental drug abuse.
- (c) Age at the time of the drug abuse ("youthful indiscretion").

(2) Certifying officials may qualify individuals whose isolated episodes of abuse of another's prescription drugs occurred 15 or more years before the initial BPRP screening without medical review or additional reviewing official approval. Certifying officials will consider such abuse in conjunction with other PDI in determining reliability of the individual.

c. Medical condition.

Any significant mental or physical medical condition substantiated medically and considered by the CO to be prejudicial to reliable performance of BPRP duties may be considered as grounds for disqualification from the BPRP. In addition, the medical authority will evaluate individuals and make a recommendation to the CO on their suitability for duty in the BPRP in the following circumstances:

- (1) Individuals currently under treatment with hypnotherapy.
- (2) Individuals that have attempted or threatened suicide before entry into the BPRP.
- (3) Individuals that have attempted or threatened suicide while enrolled in the BPRP. To qualify such an individual for the BPRP, the CO's memorandum of the PDI (paragraph 2-15a) must include an approval signed by the reviewing official.

d. Inappropriate attitude or behavior.²⁹

In determining reliability, the CO must conduct a careful and balanced evaluation of all aspects of an individual. Specific factors to consider include, but are not limited to:

- negligence or delinquency in performance of duty;
- conviction of, or involvement in, a serious incident indicating a contemptuous attitude toward the law, regulations, or other duly constituted authority. Serious incidents include, but are not limited to, assault, sexual misconduct, financial irresponsibility, contempt of court, making false official statements, habitual traffic offenses, and child or spouse abuse;

- poor attitude or lack of motivation. Poor attitude can include arrogance, inflexibility, suspiciousness, hostility, flippancy toward BPRP responsibilities, and extreme moods or mood swings;
- aberrant behavior such as impulsiveness or threats toward other individuals; and
- attempting to conceal PDI from CO through false or misleading statements.

Personnel Records Review

Once the CO has completed the initial interview and found the candidate to be suitable for enrollment, human resources personnel screen the candidate's official employment or service history records to identify any problematic areas of job performance. Anything that may indicate unsatisfactory employment history or dereliction of duty should be reported to the CO for consideration as PDI. Job applications, enlistment contracts, and any other record available to the personnel screener should be reviewed for PDI.

Personnel Security Investigation

Personnel security investigation dossiers are screened by the personnel security specialist for PDI. Personnel scheduled for initial assignment to BPRP positions must have the appropriate and favorably adjudicated personnel security investigation completed within the 5 years preceding certification to the BPRP. The minimum personnel security investigation required for military and contractor employees is the National Agency Check, Local Agency Check, and Credit Check. The minimum personnel security investigation for civilian employees is the Access National Agency Check with Written Inquiries; a National Agency Check, Local Agency Check, and Credit Check is also acceptable for civilian employees. Higher level investigations are acceptable provided they have been completed within the past 5 years.

Medical Evaluation

The medical evaluation ensures that the person being certified is physically, mentally, and emotionally stable; competent; alert; and dependable. A competent medical authority is charged with conducting a review of military health records and civilian occupational health records to assess the individual's health. If the medical record is not sufficiently complete for the medical authority to provide a recommendation to the CO, then a physical examination must be conducted. 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 personal protective equipment, or impaired ability to perform the physical requirements of the BPRP position, as substantiated by the medical authority to the CO. Medical PDI is reported to the CO with the recommendations regarding the person's fitness for assignment to these duties. The competent medical authority should again consider these factors when determining the scope and duties of personnel within containment research laboratories.

Drug Testing

The next step in the screening is to conduct a urinalysis. This screening must be done within a 6-month window of the final review and before being certified as reliable and suitable for assignment to duties requiring handling of BSATs. In most cases, military personnel are already performing a command-directed urinalysis. If they have had a negative test reported within 6 months, there is no additional testing required. However, if they have not been tested under the command randomized program within the past 6 months, arrangements must be made with the commander for a specially coded BPRP urinalysis. For DA civilians, the majority of research personnel have never been part of a testing designated pool. This testing must be completed according to DHHS standards as published in the Mandatory Guidelines for Federal Workplace Drug Testing programs. For most DA civilians, this will require that their position be a test-designated position, which then allows the Army to require urine drug testing. AR 600-85 is the Army regulation governing this program under the direction of the Army Substance Abuse program offices at every installation. This regulation is being revised to include biological BPRPs in the same sensitive position category as the nuclear and chemical BPRPs. The testing of contractor employees is the responsibility of the contractor; however, the biosurety officer must provide the oversight to the contractor to ensure that testing is being performed properly.

Final Review

After the candidate has completed all phases of the screening, the CO conducts a final review to inform the individual of any PDI disclosed to the CO during the screening process. The review provides an opportunity for discussing the circumstances in which the potentially disqualifying events took place before the CO's decision on the candidate's suitability for the program. At the end of the interview, the CO should inform the

candidates if they are suitable for the program and discuss the expectations for continuous monitoring. AR 50-X lists eight areas that must be briefed to the individual during the final interview:

1. The individual has been found suitable for the BPRP.
2. The duties and responsibilities of the individual's BPRP position.
3. Any hazards associated with the individual's assigned BPRP duties.
4. The current threat and physical security and operational security procedures used to counter this threat.
5. Each person's obligations under the continuing evaluation aspects of the BPRP.
6. A review of the disqualifying factors.
7. The use of all prescription drugs must be under the supervision of a healthcare provider. While in the BPRP, any use of any drugs prescribed for another person is considered drug abuse and will result in immediate disqualification.
8. Required training before the individual begins BPRP duties.

At the end of the interview, the CO and the candidate sign DA Form 3180 indicating their understanding of the programs and their willingness to comply with the requirements. The person is then "certified" and subject to continuous monitoring.

Continuous Monitoring

During the continuous monitoring phase, BPRP personnel are required to self-report any changes in their status and observations of other BPRP employees. Any changes in medical status should be evaluated by the competent medical authority. Periodic reinvestigations should be conducted every 5 years, and urine drug testing should be conducted at least once every 12 months for military personnel and randomly for DA civilians and contractors. Medical monitoring and routine physical examinations should be conducted periodically depending on the type of containment work being performed.

Agent Accountability

Agent accountability in the research field presents a new challenge. Microbiological agents are replicating organisms; thus, the accounting for each and every microbe is meaningless over time. As an example, the recorded transfer showing the receipt of 1 mL of any

replicating agent and the subsequent shipment of 1 mL to a second researcher does not mean that the first researcher no longer holds stocks of that agent. The recipient researcher can use the original 1 mL of agent to create 50 more 1-mL vials of the same agent. In this sense, every researcher has the capability to be a small-scale production facility, which makes for a dynamic inventory environment requiring clear guidelines and meaningful documentation requirements to ensure a current and accurate record.

Title 42 CFR 73 states that an "entity required to register under this part must maintain complete records relating to the activities covered by this part" and specifies the data points that must be captured.

Such records must include: (1) accurate, current inventory for each select agent (including viral genetic elements, recombinant nucleic acids, and recombinant organisms) held in long-term storage (placement in a system designed to maintain viability for future use, such as a freezer or lyophilized materials), including: (i) the name and characteristics (eg, strain designation, GenBank accession number, etc); (ii) the quantity acquired from another individual or entity (eg, containers, vials, tubes, etc), date of acquisition, and the source; (iii) where stored (eg, building, room, and freezer); (iv) when moved from storage and by whom and when returned to storage and by whom; (v) the select agent used and purpose of use; (vi) records created under § 73.16 and 9 CFR 121.16 (transfers); (vii) for intra-entity transfers (sender and the recipient are covered by the same certificate of registration), the select agent, the quantity transferred, the date of transfer, the sender, and the recipient; and (viii) records created under § 73.19 and 9 CFR Part 121.19 (notification of theft, loss, or release). (2) Accurate, current inventory for each toxin held, including: (i) the name and characteristics; (ii) the quantity acquired from another individual or entity (eg, containers, vials, tubes, etc), date of acquisition, and the source; (iii) the initial and current quantity amount (eg, milligrams, milliliters, grams, etc); (iv) the toxin used and purpose of use, quantity, date(s) of the use and by whom; (v) where stored (eg, building, room, and freezer); (vi) when moved from storage and by whom and when returned to storage and by whom including quantity amount.¹⁹

With these criteria, it is possible to determine who accesses select agents, as well as when and where they were accessed. Although this may be rather easily accomplished in a facility where a limited number of persons has access to agents and uses them infrequently, it is more challenging in facilities with multiple storage sites, research areas, and principal investigators directing the activities of multiple investigators in shared laboratory suites.

AR 50-X gives the minimum requirements for site-specific standing operating procedures that address each entity's activities. The intent of AR 50-X is to have a clear audit trail of custody from receipt to destruction or transfer. Although laboratory notebooks may capture some aspects of the data, they do not provide a system that is sufficiently dynamic to meet the need for documentation and management of research stocks. Automation of these records will allow the retrieval of the information that is required for both researchers and those ensuring that the research is compliant with regulatory guidelines.

The draft AR 50-X limits entities that the Army can

transfer select agents to without further oversight. Requests to transfer Army BSATs must be approved by the assistant to the secretary of defense for nuclear and chemical and biological defense programs. Most requests to transfer must identify recipient information, name and quantity of the agent to be provided, purpose for which the BSATs will be used, and the rationale for providing the agent. In approving the request, the assistant to the secretary of defense may require conformance to biosurety measures for the recipient that are beyond those of the DHHS, USDA, and APHIS federal regulations.

SUMMARY

The programs securing select agents currently being implemented are detailed and complex. However, the intent of these programs remains simple: to keep biological agents that can cause catastrophic impact to humans, animals, and plants out of the hands of those who wish to use them for malicious intent. Although biological agents that remain in the environment often do not pose a threat to large populations, the quantities of agents produced and purified for research purposes could be used to incite panic, cause pandemic disease, and disrupt the industrial base of the United States. The procedures implemented by the DHHS and APHIS represent a significant step in securing these agents throughout the country. These agencies require entities to register and declare the agents in their possession, to ensure that the agents are handled under the appropriate safety and security controls, and to ensure that all persons who have ac-

cess to select agents have undergone a security risk assessment. These agencies also require that an entity develop emergency response plans, rehearse these plans with local and federal response teams, and keep accurate and current inventory records so that any loss or theft could be rapidly addressed. In addition to screening for restricted persons, the Army has taken a further step to ensure that personnel with access to select agents are trustworthy, physically able, mentally stable, and well trained for conducting research with these agents. Not only will persons who work with the agents within DoD institutes meet these standards, but also those with whom DoD shares research tools may be held to this higher standard. The immensity of this task cannot be overstated, but it is an important step in maintaining the public trust in performance of the vital research leading to effective countermeasures against biological threat agents.

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