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CHAPTER

4

Biological Hazards and Select Agents

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1. INTRODUCTION

Just as the field of research in the biological and health sciences encompasses a broad set of initiatives ranging from in vitro experiments in the laboratory setting to in vivo research in laboratory animals and human clinical trials, the set of regulations and guidance documents that apply to research with biological hazards is both far reaching and complex. The development of early guidance documents for safe work with biological hazards was driven in part by the efforts of the life sciences community itself [1] and in part by federal agencies. The discussion of regulatory requirements and guidance documents that follows is not intended to be an exhaustive listing of all sources. Rather, it is intended to focus on the main guidance documents, standards, and regulations that apply to work with biological materials. It is the opinion of the authors that the development and implementation of programs based on these biosafety guidance documents and regulations will form a solid foundation for investigator and institutional compliance in research with biological materials.

2. HISTORICAL PERSPECTIVES

Cases of laboratory workers developing infections after exposure to microorganisms that were being handled in their research laboratories (e.g., laboratory acquired infections; LAIs) were documented with increasing frequency in the literature in the early twentieth century [2–10]. As the frequency of LAIs increased, so did the development of new work practices and equipment designed to reduce the risk of infection to laboratory workers. Many of the work practices, pieces of equipment, and facility design principles that form the foundation of safe work with biological agents were developed at the United States Army Biological Research Laboratories, under the direction of Arnold G. Wedum, the director of industrial health and safety from 1944 to 1969 [11–14]. Safe work with biological hazards is based on the following foundations:

1. The Principle of Containment: Biological safety is based on the principle of containment, which can be defined as use of a combination of equipment, facility design, work practices, and personal protective equipment (PPE) to protect laboratory workers, the

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public, and the environment from exposure to infectious microorganisms handled in the laboratory [14]. Containment is achieved through a combination of good microbiological work practices, use of appropriate safety equipment, and proper laboratory facility design and operation. The field of biosafety, including the regulations and guidelines that make up the current regulatory environment, is based on the principles of risk assessment and risk mitigation. These principles allow research to be performed with infectious microorganisms for the benefit of society and the environment, with a focus on protecting laboratory workers, the public, and the environment from the risks associated with release of infectious agents from the laboratory setting [14].

2. Development of National Guidelines: Work at the United States Army Medical Research Institute of Infectious Diseases in Fort Detrick, Maryland, laid the groundwork for future development of national biosafety guidelines [14], beginning with the publication by the Centers for Disease Control and Prevention (CDC) of the *Classification of Etiologic Agents on the Basis of Hazard* in 1974 [15].
   a. Classification of Etiologic Agents on the Basis of Hazard: This document represents one of the first uses of the concept of multiple levels of containment, each corresponding with increased work practice, engineering, and facility design controls developed to mitigate risks associated with handling specific categories of infectious microorganisms. Microorganisms with similar modes of transmission and which cause diseases with similar levels of severity in healthy, adult humans are placed in the same category in *Classification of Etiologic Agents on the Basis of Hazard* [15]. The *Classification of Etiologic Agents on the Basis of Hazard* describes four containment levels that serve as the basis for the biosafety levels in use today, biosafety levels one through 4 (BSL-1–BSL-4), as described in the CDC and National Institutes of Health (NIH) publication *Biosafety in Microbiological and Biomedical Laboratories* (BMBL) [14]. The *Classification of Etiologic Agents on the Basis of Hazard* also establishes a fifth classification of nonindigenous animal pathogens for which entry into the United States is restricted by the US Department of Agriculture (USDA) [15]. This fifth classification of infectious agents serves as a foundation for the groups of infectious agents that are currently regulated under the USDA's Animal and Plant Health Inspection Service (APHIS) veterinary services (VS) and plant protection and quarantine (PPQ) permitting processes [14].
   b. The NIH Guidelines for Research Involving Recombinant DNA (rDNA) Molecules: As a result of the emergence of recombinant methods for generating novel DNA molecules, the NIH developed the *NIH Guidelines for Research Involving Recombinant DNA Molecules* (NIH Guidelines), first published in 1976 [16]. The NIH Guidelines use the model developed by the CDC in *Classification of Etiologic Agents on the Basis of Hazard* to describe four ascending levels of work practice, equipment, and facility design safeguards corresponding to four levels of physical containment tailored to the potential hazard associated with the type of microorganism in use with emerging rDNA technology. Specific physical containment levels are described for work with rDNA materials in organisms within laboratories (biosafety levels one through four; BL1–BL4), plants (plant biosafety levels one through four; BL1P–BL4P), and animals (animal biosafety levels one through four; BL1N–BL4N) are described in NIH Guidelines Appendix G, P, and Q, respectively [16]. For clarity, readers should note

that biosafety levels are abbreviated as "BSL" in the BMBL and as "BL" in the NIH Guidelines. Throughout this chapter the abbreviation associated with the appropriate document will be used in each section. In 1978, the NIH published the *NIH Laboratory Safety Monograph* (NIH Monograph) as an expansion of the original NIH Guidelines Appendix D "Supplementary Information on Physical Containment" [17]. The NIH Monograph contains detailed recommendations for good microbiological work practices, personal hygiene, personal protective equipment (PPE), disinfection and disposal of laboratory wastes, containment equipment (e.g., biological safety cabinets), and facility design, all of which are designed to ensure containment of research involving rDNA [17]. While the scope of the original version of the NIH Guidelines was limited to rDNA molecules constructed using recombinant techniques, advances in synthetic biology resulted in addition of synthetic nucleic acid molecules to the scope of the NIH Guidelines. These changes, along with the addition of "Synthetic Nucleic Acid Molecules" to the title of the document, became effective on March 5, 2013.

c. Biosafety in Microbiological and Biomedical Laboratories: The first edition of the joint CDC/NIH guidance document BMBL was published in 1984 [14] and supplemented the information contained in the *Classification of Etiologic Agents on the Basis of Hazard* and the *NIH Monograph* with summary statements containing specific guidance for work with infectious microorganisms known to have caused LAIs. The BMBL has been updated several times and is currently in its fifth edition [14]

3. Development of Federal Regulations

a. The Bloodborne Pathogen Standard: The Occupational Safety and Health Administration (OSHA) bloodborne pathogen standard (BBP) was published in 1991 and describes regulatory requirements in 29 CFR §1910.1030 to protect employees from exposure to infectious microorganisms that can be transmitted via blood, body fluids, and other potentially infectious materials (OPIM) [18]. In November of 2000, the Needlestick Safety and Prevention Act was passed, requiring revision of the OSHA BBP to include language specifying the evaluation and use of sharps with engineered sharps injury protection (SESIPs) [19].

b. Development of the Federal Select Agent Program (FSAP): Prior to the mid-1980s, aside from facility inspections and permits required by USDA APHIS for transfer of regulated agricultural infectious agents, there were no regulations requiring registration, licensing, or reporting of transfer of human and zoonotic pathogens within the United States [20]. Enacted in 1996, the Antiterrorism and Effective Death Penalty Act required the Department of Health and Human Services (HHS) to identify biological agents that have the potential to pose a severe threat to public health and safety and to regulate their transfer, resulting in the designation of certain biological agents and toxins as "select agents" [21] (Table 1). The CDC was required to develop and implement regulations to control the possession, use, and transfer of these select agents, resulting in the creation of the CDC Select Agent Program [21,22]. In 2001, the Uniting and Strengthening America by Providing Appropriate Tools Required to Intercept and Obstruct Terrorism Act (USA PATRIOT Act) established penalties for unauthorized possession and or transfer of select agents and toxins and established criteria for restricting access

TABLE 1 Select Agents and Toxins List

HHS and USDA select agents and toxins 7 CFR Part 331, 9 CFR Part 121, and 42 CFR Part 73
HHS SELECT AGENTS AND TOXINS
Abrin
Botulinum neurotoxins[a]
Botulinum neurotoxin producing species of *Clostridium*[a]
Conotoxins (short, paralytic alpha conotoxins containing the following amino acid sequence $X_1CCX_2PACGX_3X_4X_5X_6CX_7$)[b]
Coxiella burnetii
Crimean-Congo hemorrhagic fever virus
Diacetoxyscirpenol
Eastern equine encephalitis virus[d]
Ebola virus[a]
Francisella tularensis[a]
Lassa fever virus
Lujo virus
Marburg virus[a]
Monkeypox virus[d]
Reconstructed replication competent forms of the 1918 pandemic influenza virus containing any portion of the coding regions of all 8 gene segments (reconstructed 1918 influenza virus)
Ricin
Rickettsia prowazekii
SARS-associated coronavirus (SARS-CoV)
Saxitoxin
South American hemorrhagic fever viruses: Chapare Guanarito Junin Machupo Sabia
Staphylococcal enterotoxins A, B, C, D, E subtypes
T-2 toxin
Tetrodotoxin
Tick-borne encephalitis complex (flavi) viruses: Far eastern subtype Siberian subtype

TABLE 1 Select Agents and Toxins List—cont'd

HHS and USDA select agents and toxins 7 CFR Part 331, 9 CFR Part 121, and 42 CFR Part 73
Kyasanur forest disease virus
Omsk hemorrhagic fever virus
Variola major virus (smallpox virus)[a]
Variola minor virus (Alastrim)[a]
Yersinia pestis[a]
OVERLAP SELECT AGENTS AND TOXINS
Bacillus anthracis[a]
B. anthracis Pasteur strain
Brucella abortus
Brucella melitensis
Brucella suis
Burkholderia pseudomallei[a]
Hendra virus
Nipah virus
Rift Valley fever virus
Venezuelan equine encephalitis virus[a]
USDA SELECT AGENTS AND TOXINS
African horse sickness virus
African swine fever virus
Avian influenza virus[d]
Classical swine fever virus
Foot-and-mouth disease virus[a]
Goat pox virus
Lumpy skin disease virus
Mycoplasma capricolum[d]
Mycoplasma mycoides[d]
Newcastle disease virus[c,d]
Peste de petits ruminants virus
Rinderpest virus[a]
Sheep pox virus
Swine vesicular disease virus

Continued

TABLE 1 Select Agents and Toxins List—cont'd

HHS and USDA select agents and toxins 7 CFR Part 331, 9 CFR Part 121, and 42 CFR Part 73
USDA PLANT PROTECTION AND QUARANTINE SELECT AGENTS AND TOXINS
Peronosclerospora philippinensis (Peronosclerospora sacchari)
Phoma glycinicola (formerly *Pyrenochaeta glycines*)
Ralstonia solanacearum
Rathayibacter toxicus
Sclerophthora rayssiae
Synchytrium endobioticum
Xanthomonas oryzae

This table is a listing of all select agents and toxins regulated by the Federal Select Agent Program as of April 3, 2013. Select agents and toxins regulated by HHS due to potential threat to human health are indicated as HHS select agents and toxins. Select agents and toxins regulated by HHS and the USDA due to potential threat to human and animal health are indicated as overlap select agents and toxins. Select agents and toxins regulated by the USDA due to potential threat to animal or plant health are listed as USDA select agents and toxins. Tier One select agents and toxins are indicated by [a] in the table and are subject to additional regulatory requirements due to their higher potential risk to the public as defined in the regulations.

[a]*Tier One select agents and toxins requiring compliance with additional, specific regulatory components for biological materials determined to pose higher risk to public.*

[b]*C = Cysteine residues are all present as disulfides, with the first and third cysteine, and the second and fourth systeine forming specific disulfide bridges; the consensus sequence includes known toxins α-MI and α-GI as well as α-GIA, Ac1.1a, α-CnlB; X_1 = any amino acid(s) or Des-X; X_2 = Asparagine or Histidine; P = Proline, A = Alanine; G = Glycine; X_3 = Arginine or Lysine; X_4 = Asparagine, Histidine, Lysine, Arginine, Tyrosine, Phenylalanine, or Tryptophan; X_5 = Tyrosine, Phenylalanine, or Tryptophan; X_6 = Serine, Threonine, Glutamate, Aspartate, Glutamine, or Asparagine; X_7 = Any amino acid(s) or Des X and; "Des X" = "an amino acid does not have to be present at this position; " e.g., in a peptide sequence XCCHPA, a related peptide CCHPA would be designated as Des-X.*

[c]*A virulent Newcastle disease virus (avian paramyxovirus serotype 2) has an intracerebral pathogenicity index in day-old chicks (*Gallus gallus*) of 0.7 or greater or has an amino acid sequence at the fusion (F) protein cleavage site that is not consistent with virulent strains of Newcastle disease virus. A failure to detect a cleavage site that is consistent with virulent strains does not confirm the absence of a virulent virus.*

[d]*Select agents that meet any of the following criteria are excluded from the requirements of this part: Any low pathogenic strains of avian influenza virus, South American genotype of eastern equine encephalitis virus, West African clade of monkeypox viruses, any strain of Newcastle disease virus which does not meet the criteria for virulent Newcastle disease virus, all subspecies* M. capricolum *except subspecies* capripneumoniae *(contagious caprine pleuropneumonia), all subspecies* M. mycoides *except subspecies* mycoides *small colony (Mmm SC; contagious bovine pleuropheumonia), any subtypes of Venezuelan equine encephalitis except for subtypes IAB or IC, and vesicular stomatitis virus (exotic): Indiana subtypes VSV-IN2, VSV-IN3, provided that the individual or entity can verify that the agent is within the exclusion category.*

of certain individuals to listed select agents and toxins [21,23]. In 2002, the Public Health Security and Bioterrorism Preparedness and Response Act (Bioterrorism Response Act) required promulgation of additional regulations to expand control of possession and transfer of biological agents and toxins that have the potential to pose a severe threat to public health and safety and biological agents and toxins that have the potential to pose a severe threat to animal or plant health or to animal or plant products by creating the HHS CDC Select Agent Program and the USDA APHIS Select Agent Program [21,24]. As a result, in 2002, the CDC Division of Select Agents and Toxins and USDA APHIS established the joint FSAP as an interagency program to regulate safety and security practices of individuals and institutions in possession of select agents and toxins [21].

3. RELEVANT REGULATORY/OVERSIGHT AGENCIES, REGULATIONS, AND GUIDANCE DOCUMENTS

3.1 Department of Health and Human Services

1. Biosafety in Microbiological and Biomedical Laboratories
   a. The CDC and the NIH jointly published the BMBL, which is the main guidance resource for biological safety in the United States [14]. The BMBL contains valuable guidance for researchers working with biological hazards, including information on risk assessment for biological agents, guiding principles of laboratory biosafety and biosecurity, and agent summary statements for many pathogens used in research laboratories. The BMBL describes sets of work practices, safety equipment, and facility design features that together can be used to mitigate risks associated with research involving human pathogens posing increasing levels of risk to human health on potential exposure [14]. Agent summary statements describing the routes of infection, infectious dose, recommendations for safe work in research laboratories, and any specialized occupational health or regulatory issues are provided for a variety of pathogens that may be used in biological research. While agent summaries are provided for a variety of bacterial, fungal, parasitic, rickettsial, and viral agents, it is important for investigators to realize that failure to list a particular biological agent in the BMBL does not indicate that there are no risks associated with the agent in question [14]. In particular, the fifth edition of the BMBL was revised to include additional information regarding occupational health and immunizations for personnel working with biological agents, decontamination and sterilization methods, requirements for agriculture pathogen safety (BSL-3 (Ag)), and updated information on safe work practices for biological toxins [14].
2. Guidelines for Safe Work Practices in Human and Animal Medical Diagnostic Laboratories
   a. In 2008, the CDC convened a Blue Ribbon Panel of laboratory experts to develop an additional guidance document to specifically address safety issues encountered in the daily operations of clinical diagnostic laboratories for human and animal patients. These additional recommendations were published in January of 2012 as the *Guidelines for Safe Work Practices in Human and Animal Medical Diagnostic Laboratories* [25] (Diagnostic Laboratories Guidelines) and are a valuable addition to the recommendations contained in the BMBL. The Diagnostic Laboratories Guidelines contain detailed safety recommendations for specific pieces of laboratory equipment (e.g., ultra-low temperature freezers, centrifuges and cytocentrifuges, ELISA plate washers, etc.) and procedures that are of value to personnel working in both clinical and nonclinical microbiological laboratories [25].
3. NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules
   a. The NIH publishes the *NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules* [16] (NIH Guidelines), which provide guidance for proper review, oversight, and containment for procedures involving the construction and/or use of recombinant nucleic acid molecules, synthetic nucleic acid molecules, and cells, organisms, and viruses containing these molecules (Section I-A) [16].

4. CDC and USDA FSAP
   a. The CDC is tasked with developing regulations to apply to all entities that possess, use, transfer, or store infectious agents and toxins that "have the potential to pose a severe threat to public health and safety" [22], while USDA APHIS is tasked with regulation of infectious agents and toxin that "have the potential to pose a severe threat to plant health or plant products" [26] and those that "have the potential to pose a severe threat to animal health, or animal products" [27]. The CDC and APHIS have defined these agents as select agents [22,26,27]. Certain select agents and toxins that pose a severe threat to both human and animal health and animal products are designated as overlap select agents and are subject to regulation by both APHIS and CDC [22,26,27].
5. CDC Etiologic Agent Import Permit Program
   a. Import of etiological agents, hosts, and/or vectors of human disease into the United States requires an approved permit under the CDC Etiologic Agent Import Permit Program (IPP) (42 CFR §71.54). Under the regulation, etiologic agents include microorganisms and microbial toxins that can cause disease in humans, and the importation of bats, arthropods, snails, and nonhuman primate trophies.
6. USDA APHIS Import Permit Programs (IPPs)
   a. Import of a biological product as defined by USDA APHIS in 9 CFR §101 requires an individual to hold an approved US Veterinary Service Biological Product Permit (9 CFR §104.1). USDA APHIS also regulates the importation and/or interstate transfer of organisms that may be infectious to animals (including poultry) and animal vectors that have been intentionally infected with organisms or are known to be infected with or have been exposed to any contagious, infectious, or communicable disease of animals or poultry (9 CFR §122.1 (d) and (e)). Permits for importation of plant pathogens must be approved by the USDA APHIS PPQ division (7 CFR §330.2)
7. Regulations and Standards Applicable to the Proper Packaging and Shipment of Biological Agents: Dangerous Goods Regulations
   a. There are many guidelines and regulations, both internationally and within the United States, that impact the proper packaging, documentation, and shipment of dangerous goods (Table 2). In the United States, the most relevant regulations are the International Air Transport Association (IATA) Dangerous Goods Regulations (DGR) and the Department of Transportation (DOT) Federal Hazardous Materials Regulations (FHMR). Because the IATA DGR are the most restrictive of the regulations, they are usually the main source for compliance information, with specific sections being augmented by additional requirements under the DOT FHMR. Dangerous goods are defined in similar general terms in both the IATA DGR and DOT FHMR as substances that pose a risk to health, safety, and property when they are transported and which are specifically listed in applicable sections of each regulation (IATA DGR §1.0, 49 CFR §105.5) [28,29]. In research with biological materials, shipments that are known or reasonably suspected to contain pathogens, cultures of pathogens, patient specimens, biological products derived from living organisms, and that are known or reasonably believed to contain pathogens, genetically modified organisms, patient specimens, and/or shipments that contain dry ice are subject to regulation under the IATA DGR and/or the DOT FHMR [28,29].

TABLE 2 Dangerous Goods Shipping Regulations

Organization	Regulation or standard	Brief description of regulation or standard
INTERNATIONAL REGULATIONS		
The United Nations (UN)	UN recommendations on the transport of dangerous goods model regulations	Used as international model regulations by other organizations and associations to develop more specific regulations that apply to specific modes of transportation
International Civil Aviation Organization (ICAO)	Technical instructions for the safe transport of dangerous goods by air (ICAO TI)	All international flights must comply with the ICAO TI
International Air Transport Association (IATA)	IATA dangerous goods regulations (IATA DGR)	Membership includes most of the world's major airlines, and the IATA DGR is harmonized with the ICAO TI for compliance
International Maritime Organization (IMO)	International Maritime dangerous goods code (IMDG Code)	Required for all parties to the international convention for the safety of life at sea, including the United States (http://www.imo.org/About/Conventions/StatusOfConventions/Documents/status-x.xls; accessed 22.02.14)
Universal Postal Union (UPU)	The Letter Post Manual	Uses ICAO as the basis for provisions for safe shipments via post
US REGULATIONS		
US Department of Transportation (US DOT)	Federal hazardous materials regulations (DOT FHMR; 49 CFR 100–185)	Pertains to the shipment of all dangerous goods shipped in the U.S. by any mode of transportation including air, road, rail, and sea

International and US Regulations and Standards for Shipment of Dangerous Goods, including biological agents, are described [28,49,50].

8. Department of Labor OSHA
   a. The General Duty Clause: OSHA is responsible for promulgating general workplace safety regulations. In addition to regulations related to specific workplace hazards, all employers must comply with the OSHA general duty clause, which requires employers to provide employment and a place of employment free from recognized hazards that are likely to cause death or serious physical harm to employees (Section 5 (a)(1)) [30]. If serious workplace hazards are identified, the employer must implement mitigation measures that can include hazard assessment, exposure monitoring, medical surveillance, engineering and work practice controls, and the use of PPE.
   b. The BBP Standard: Compliance with the OSHA BBP Standard is required for "all occupational exposure to blood or other potentially infectious materials" (29 CFR §1910.1030a) [18]. Bloodborne pathogens are defined in the regulation as "pathogenic microorganisms that are present in human blood and can cause disease in humans" [18]. Bloodborne pathogens include the hepatitis viruses (hepatitis A, B, C, or D) and human immunodeficiency virus (HIV), but many entities choose to expand their interpretation of the regulatory definition to include other common microorganisms that may be used in research by interpreting these agents as falling under the category of OPIM.

According to the regulation, OPIM include human body fluids such as semen, vaginal secretions, cerebrospinal, synovial, pleural, pericardial, peritoneal, and/or amniotic fluids as well as saliva in dental procedures [18]. In addition, unfixed human tissues or organs, HIV-infected cell cultures, culture medium, or other solutions, or blood, organs, or other tissues from animals infected with HIV or hepatitis B virus (HBV) are considered to be OPIM. Other bodily fluids, such as urine or feces, are not considered to be OPIM unless they are visibly contaminated with blood. Many entities choose to include samples from research animals infected with other known human pathogens in their definition of bloodborne pathogens.

- Individual institutions may choose to interpret the BBP standard to exclude characterized, well-established human cell lines in culture. However, in an OSHA interpretation letter issued to biological safety professionals of the American Biological Safety Association, even well-characterized and tested human cell lines cannot be tested for every known human pathogen, and as such may be considered to fall under the BBP standard [31]. Many entities choose to extend the use of universal precautions (in which all human blood and body fluids as well as OPIM are treated as if they are known to be infected with HBV, HIV, or other pathogens) to all use of human cell lines in culture.

c. The OSHA PPE Standard

- The OSHA PPE standard requires employers to provide and pay for PPE and ensure that it is used whenever employees may be exposed to hazards that may cause injury via absorption, inhalation, or physical contact (29 CFR §1910.132) [32].

9. The Environmental Protection Agency

a. The Federal Insecticide, Fungicide, and Rodenticide Act [33] charges the Environmental Protection Agency (EPA) with regulation of the sale, distribution, and use of antimicrobial pesticides (e.g., sanitizers, disinfectants, and sterilants; 40 CFR §150–189) [34]. Disinfectants and chemical sterilants that are used routinely in hospitals, veterinary clinics, and research laboratories to decontaminate infectious materials and surfaces are registered with the EPA. The registration process requires a disinfectant manufacturer to provide safety and, more importantly, efficacy data for inactivation of specific microorganisms to the EPA to receive registration or a license [35]. Use of an EPA-registered disinfectant in accordance with its EPA-approved use instructions as provided on the product label ensures that a registered antimicrobial will be effective against its target microorganisms. Due to the requirement of rigorous efficacy testing as part of the EPA registration process of disinfectants and sterilants, it is the opinion of the author that investigators and institutions should use EPA-registered products in cleaning, sanitizing, disinfection, and decontamination whenever possible. While non-EPA-registered disinfectants such as 70% ethanol can effectively inactivate some microorganisms, standardized efficacy testing and product use instructions similar to those required for registered disinfectants are not available. Use of EPA-registered disinfectants in accordance with product label instructions provides an institution with assurance that the products in use are effective and increases confidence in inactivation procedures for infectious microorganisms. Ultimately, it is the opinion of the author that this will lead to a higher level of assurance that the health of the public and the environment are being ensured by preventing a release of pathogens to the environment.

10. Medical/Infectious Waste Handling
    a. Medical and infectious waste handling regulations are promulgated at the state level. State-specific information may be found on the EPA website [36]. It is important to note that under no circumstances should medical or infectious waste be disposed of in the normal refuse stream and that a common factor in all medical waste handling regulations is the requirement for decontamination by methods specified in each local or state regulation prior to final disposal of medical waste.

4. KEY REGULATORY MANDATES

4.1 The NIH Guidelines: Recombinant and Synthetic Nucleic Acid Oversight

1. The NIH Guidelines define recombinant and synthetic nucleic acids as follows (Section I-B) [16]. Recombinant nucleic acids are molecules that are constructed by joining nucleic acid molecules and that can replicate in a living cell. Synthetic nucleic acids are molecules that are synthesized or amplified by chemical or other means, including those that are chemically or otherwise modified, but can still pair with naturally occurring nucleic acids. Any molecules that result from the replication of recombinant or synthetic nucleic acids as defined above also fall under the scope of the NIH Guidelines.
2. While technically not a regulation, any research with recombinant or synthetic nucleic acids that is either performed or sponsored by an institution that receives any support from the NIH must comply with the NIH Guidelines. This includes all research with recombinant or synthetic nucleic acids performed at the institution, even if the individual investigator performing the research does not receive NIH support (Section I-C) [16]. The NIH Guidelines also apply to any clinical trials or testing of materials containing recombinant or synthetic nucleic acids in humans (Section I-C-1-a-(2)) [16]. Failure to comply with the NIH Guidelines could result in suspension, limitation, or termination of NIH funds for the individual noncompliant research project or suspension, limitation, or termination of NIH funds for all recombinant or synthetic nucleic acid research at the institution. Therefore the NIH Guidelines are discussed in this section as a key mandate. The NIH also reserves the right to require prior approval by the NIH of any or all projects involving recombinant or synthetic nucleic acids at an institution (Section I-D-1; Section I-D-2) [16]. While entities performing research involving recombinant or synthetic nucleic acids that do not receive funding from the NIH are not required to comply with the NIH Guidelines, many entities choose to voluntarily follow the best practices described in the document [37].
3. The NIH Guidelines describe six general categories of experiments with recombinant or synthetic nucleic acids that fall under the purview of the NIH.
    a. Major Actions: Major actions under the NIH Guidelines involve the deliberate transfer of a drug resistance trait that could compromise the control or treatment of disease in humans, veterinary medicine, or agriculture (Section III-A-1) [16]. If the drug resistance trait proposed for use in the study would confer resistance to the primary drug available for treatment in the general population and/or in a specific subpopulation (e.g., pregnant women or children), then the experiment must be approved by the NIH director, the NIH Recombinant DNA Advisory Committee (RAC), and the local institutional biosafety committee (IBC) before initiation (Section III-A-1) [16].

b. Use of Toxin Genes: Experiments that involve deliberate formation of recombinant or synthetic nucleic acid molecules containing genes that encode toxins that are lethal for vertebrates at an LD50 of less than 100 ng per kilogram of body weight must be approved by both the NIH Office of Biotechnology Activities (OBA) and the local IBC before initiation (Section III-B-1) [16]. NIH OBA also reserves the right to determine from an investigator's application whether a proposed experiment is equivalent to an experiment previously approved as a major action, as described above. If no significant differences are present and if no information has emerged that would change the biosafety or public health recommendations for the proposed experiments, then NIH OBA may approve the similar experiment without NIH director or RAC review (Section III-B-2) [16].

c. Human Research: Any proposed experiments that involve deliberate transfer of recombinant or synthetic nucleic acid molecules into human research participants (defined in the NIH Guidelines as human gene transfer) [16] must be reviewed by the RAC, the local institutional review board (IRB), and the local IBC prior to enrollment of any research participant (Section III-C) [16].

d. IBC Approval Required Prior to Beginning Work: Often, an investigator's proposed research with recombinant or synthetic nucleic acids will fall under the category of experiments that require IBC approval prior to beginning work as defined in Section III-D of the NIH Guidelines [16]. An investigator is required to submit a registration document to the IBC describing the source of the nucleic acids, the nature of the inserted nucleic acid sequences, the host and vector to be used, whether a foreign gene will be expressed, and the containment level specified by the NIH Guidelines (Section III-D) [16]. Several categories of experiments are captured under this section of the NIH Guidelines:

- Experiments using biological agents in risk groups 2–4 or biological agents that require a USDA APHIS permit due to their regulated status as plant or animal pathogens as host-vector systems (Section III-D-1) [16].
- Experiments in which nucleic acids from risk group 2–4 or USDA APHIS-regulated plant or animal pathogens are cloned into nonpathogenic or lower eukaryotic host–vector systems (Section III-D-2) [16].
- Experiments that involve the use of infectious DNA or RNA viruses or replication-deficient DNA or RNA viruses in combination with helper viruses in in vitro or tissue culture systems (Section III-D-3) [16].
- Experiments involving whole animals in which the animal's genome has been altered by stable insertion of recombinant or synthetic nucleic acid molecules into the germ-line and experiments in which microorganisms that have been modified with recombinant or synthetic nucleic acids are introduced into whole animals (Section III-D-4) [16].
- Experiments involving genetic engineering of plants via introduction of recombinant or synthetic nucleic acid molecules, propagation of such plants, and/or use of plants with microorganisms or insects containing recombinant or synthetic nucleic acid molecules (Section III-D-5) [16].
- Large-scale experiments, which are defined as any experiment involving more than 10 L of culture (Section III-D-6) [16].

- Experiments involving influenza viruses (Section III-D-7) [16]. It should be noted that the NIH Guidelines specifically detail additional work practice, PPE and/or facility enhancements for work with certain risk group 3 influenza viruses, including strains containing the hemagglutinin segment from human H2N2 influenza strains isolated between 1957 and 1968, certain highly pathogenic avian influenza H5N1 strains, and research with any portion of the reconstructed 1918H1N1 strain (Section III-D-7 and Appendix G-II-C-5, BL-3 enhanced for research involving risk group 3 influenza viruses) [16].

e. Notification of IBC Simultaneously with Initiation of Work: Certain categories of experiments, including those involving the formation of recombinant or synthetic nucleic acid molecules containing no more than two-thirds of the genome of any eukaryotic virus, specific types of low-risk research with whole plants, and experiments that strictly involve generation of transgenic rodents that may be handled and housed appropriately at BL-1, require that the local IBC be notified simultaneously with initiation of experiments by an investigator (Section III-E) [16].

f. NIH Exempt Research: Finally, certain types of recombinant or synthetic nucleic acid molecules are exempt from the NIH Guidelines [16]:

- Those that cannot replicate and that cannot generate nucleic acids that can replicate in any living cell, such as oligonucleotides that do not contain an origin of replication, cannot integrate into DNA, do not result in production of a toxin that is lethal for vertebrates with an LD50 less than 100 ng/kg of body weight, and are not transferred into a human research subject (Section III-F-1) [16].
- Recombinant or synthetic nucleic acids that are not in organisms, cells, or viruses and that have not been manipulated to facilitate penetration of cellular membranes (Section III-F-2) [16].
- Recombinant or synthetic nucleic acids that only consist of the exact nucleic acid sequence from a single source that exists contemporaneously in nature (Section III-F-3) [16].
- Recombinant or synthetic nucleic acids from a prokaryotic host (including any indigenous plasmids or viruses) when only propagated in that same host (or a closely related strain of the same species), or when the nucleic acids are transferred to another host by well-established physiological means (Section III-F-4) [16].
- Recombinant or synthetic nucleic acids from a eukaryotic host (including chloroplasts, mitochondria, or plasmids, but specifically excluding viruses) when propagated only in that same host (or a closely related strain of the same species) (Section III-F-5) [16].
- Recombinant or synthetic nucleic acids consisting entirely of DNA segments from different species that are known to exchange DNA through physiological processes (e.g., known natural exchangers as defined in appendices A-I through A-IV of the NIH Guidelines; Section III-F-6) [16].
- Genomic DNA molecules that have acquired a transposable element as long as the transposable element does not contain any recombinant or synthetic DNA (Section III-F-7) [16].
- Experiments described in Appendix C of the NIH Guidelines, which the NIH director, with advice from the RAC and an opportunity for public comment, has determined not to pose a significant risk to health or the environment (Section III-F-8) [16].

4. The main regulatory mandate of the NIH Guidelines is to provide a framework for the proper assessment of risk, containment, and review and approval of certain classifications of experiments with recombinant and synthetic nucleic acids as defined above [16].
   a. Risk Assessment and Containment: The process of risk assessment begins with the investigator's initial assignment of a biosafety level appropriate for the research that will be performed. The NIH Guidelines provide tools to aid the investigator in the initial risk assessment by classifying biological agents into risk groups according to their potential to cause disease in a healthy adult (Appendix B) [16]. Biological agents are assigned to risk groups 1 through 4, with agents that are not associated with disease in healthy adults assigned to risk group 1, and with each successive risk group 2–4 posing a greater risk to human health. It is important to note that the listing of biological agents in the NIH Guidelines is not comprehensive, and that an investigator should not assume that biological agents not specifically listed are properly classified as a risk group 1 agent. Once an initial risk group assignment has been made by the investigator, the NIH Guidelines describe appropriate containment levels for:
      - In vitro work in the laboratory and work in small animals that are of a size that is conducive to housing in cages that provide containment of biological agents, most often laboratory rodents (Appendix G) [16],
      - Work with large animals that are of a size at which caging to provide containment of biological agents is not available and where the room itself provides containment (Appendix N) [16],
      - Work with plants (Appendix P) [16], and
      - Work with large volumes of biological agents in production facilities (Appendix K) [16].
   b. Each containment level, defined as a BL, consists of a combination of appropriate microbiological work practices, containment equipment, and facility design features. Each BL, a combination of the above risk-mitigation strategies, is developed to ensure safe research with biological agents that pose a greater risk to human health requiring progressively more complex containment practices and facilities (e.g., BL1 through BL4, BL1N-BLN4, BL1P-BL4P, good large-scale practice (GLSP), BL1-LS-BL3-LS) [16].
5. The NIH Guidelines require each institution to establish an IBC, which is responsible for reviewing research with recombinant and synthetic nucleic acids at the institution and ensuring that all such research is performed in compliance with the NIH Guidelines (Section IV-B-2) [16]. The composition of the IBC is specified in the NIH Guidelines to ensure that the committee includes members with adequate expertise to fully evaluate all research with recombinant and synthetic nucleic acids performed at an institution. For example, institutions performing recombinant or synthetic nucleic acid work in plants, animals, or human subjects are required to have at least one plant, animal, or human subject research expert as a committee member (Sections IV-B-4, IV-B-5, and IV-B-6, respectively) [16]. Similarly, any institution performing large-scale research or research at BL3 or BL4 must appoint a biological safety officer (BSO) who must serve as a member of the committee (Section IV-B-2(a-(1)) [16]. The NIH Guidelines also require at least two members of the IBC to be unaffiliated with the institution to represent the interest of the surrounding community (Section IV-B-2(a-(1)) [16]. Other recommendations for committee membership may be found in the NIH Guidelines, Section IV-B-2-a [16]. The specific review of functions of the IBC and the BSO shall be discussed later in this chapter.

4.2 The Federal Select Agent and Toxin Program

1. The select agent regulations [22,26,27] describe a strict set of requirements that apply to all entities, public or private, that possess, use, transfer, or store select agents and toxins.
   - **a.** Each entity must be registered with the CDC and/or USDA APHIS (42 CFR §73.7; 7 CFR §331.7; 9 CFR §121.7) [22,26,27], and must designate a responsible official (RO) as defined in the regulation (42 CFR §73.9; 7 CFR §331.9; 9 CFR §121.9) [22,26,27]. All personnel who will have access to select agents at an entity must undergo a security risk assessment (SRA) performed by the Department of Justice's Federal Bureau of Investigation Criminal Justice Information System to identify any persons who may fall into the category of "restricted persons" as defined by the regulation (42 CFR §73.10; 7 CFR §331.10; 9 CFR §121.10) [22,26,27].
   - **b.** The regulations detail specific security requirements to prevent unauthorized access to and/or theft, loss, or release of select agents and toxins, including the requirement for development of a written security plan describing physical and information security procedures, as well as inventory control measures (42 CFR §73.11; 7 CFR §331.11; 9 CFR §121.11) [22,26,27].
   - **c.** A written biosafety plan is required and must be based on the best practices described in the CDC/NIH BMBL, the OSHA Hazard Communication (29 CFR §1910.1200) [38], and Occupational Exposure to Hazardous Chemicals in the Laboratory (29 CFR §1910.1450) [39] Standards, as well as the NIH Guidelines (42 CFR §73.12; 7 CFR §331.12; 9 CFR §121.12) [22,26,27].
   - **d.** The regulations prohibit conduct of research involving or possession of products of a restricted experiment with a select agent or toxin unless the select agent program's review body, the Intragovernmental Select Agents and Toxins Technical Advisory Committee, provides prior review and approval. Restricted experiments include:
     - Deliberate transfer of or selection for a drug resistance trait in a select agent that does not naturally acquire such resistance if the trait confers resistance to a drug commonly used to treat disease in humans, veterinary medicine, or agriculture, or
     - Deliberate formation of recombinant or synthetic nucleic acids encoding genes for biosynthesis of select agent toxins with an LD50 of less than 100 ng per kilogram of body weight in vertebrates (42 CFR §73.13; 7 CFR §331.13; 9 CFR §121.13) [22,26,27].
   - **e.** A written incident response plan based on a site-specific risk assessment must describe "the response procedures for theft, loss, or release of a select agent or toxin; inventory discrepancies; security breaches (including information systems); severe weather and other natural disasters; workplace violence; bomb threats and suspicious packages; and emergencies such as fire, gas leak, explosion, power outage, and other natural and man-made events" (42 CFR §73.14; 7 CFR §331.14; 9 CFR §121.14) [22,26,27].
   - **f.** Entities are required to provide extensive training to all individuals who are approved for access to select agents and toxins (42 CFR §73.15; 7 CFR §331.15; 9 CFR §121.15) and select agents and toxins may only be transferred to another individual or entity that is registered with the CDC or APHIS to possess, use, or transfer that specific select agent or toxin, and then, only after review and approval from the CDC or APHIS (42 CFR §73.16; 7 CFR §331.16; 9 CFR §121.16) [22,26,27].

g. Detailed records of all aspects of an entity's select agent program are required (42 CFR §73.17; 7 CFR §331.17; 9 CFR §121.17), including notification of the CDC or APHIS in the event of a theft, loss, or release of select agents and toxins (42 CFR §73.19; 7 CFR §331.19; 9 CFR §121.19), and entities are subject to both announced and unannounced inspections by the CDC and/or APHIS (42 CFR §73.18; 7 CFR §331.18; 9 CFR §121.18) [22,26,27].

h. The most recent revision of the Federal Select Agent Regulations created a subset of select agents and toxins designated as "tier one select agents and toxins" due to the "greatest risk of deliberate misuse with significant potential for mass casualties or devastating effect to the economy, critical infrastructure, or public confidence, and pose a severe threat to public health and safety" [40]. Tier One select agents and toxins are indicated in Table 1 and require adherence to specific regulatory requirements in addition to those required for non-Tier One select agents and toxins. Some of the major changes associated with Tier One select agents and toxins are summarized below, but individuals seeking more information regarding Tier One requirements are strongly urged to consult the *Resource Manual for the Responsible Official* [41], which contains guidance on compliance with the Select Agent and Toxin Regulations.

- Enhanced Security Plan Requirements for Tier One Select Agents and Toxins: Many of the enhancements required for entities possessing Tier One select agents and toxins are related to increased physical and information security requirements 42 CFR §73.11(f); 7 CFR §331.11(f); 9 CFR §121.11(f)) [22,26,27]. The requirement for entities to develop a preaccess suitability assessment program for personnel with access to Tier One select agents and toxins has posed a particular challenge for many entities. Entities are also required to develop an ongoing suitability assessment program to ensure that all workers with access to Tier One select agents and toxins continue to meet institution-specific requirements throughout their employment. Entities are also required to develop a program to ensure self- and/or peer-reporting of incidents or conditions that could affect an individual's ability to work with or have access to Tier One select agents and toxins.
- Enhanced Incident Response Plan Requirements for Tier One Select Agents and Toxins: Entities in possession of Tier One select agents and toxins are required to detail response procedures for failure of intrusion detection systems and a process for notification of federal, state, or local law enforcement agencies of any suspicious or suspected criminal activity at the entity in their mandated incident response plan (42 CFR §73.14(e); 7 CFR §331.14(e); 9 CFR §121.14(e)) [22,26,27].
- Occupational Health and Training Enhancements for Tier One Select Agents and Toxins: In addition to mandated annual biosafety, security, and incident response training, entities in possession of Tier One select agents and toxins are required to develop annual insider threat awareness training for all personnel with access to Tier One select agents and toxins (42 CFR §73.15(b); 7 CFR §331.15(b); 9 CFR §121.15(b)) [22,26,27]. Finally, an occupational health program, while strongly recommended for all entities in the opinion of the authors, is required for entities in possession of Tier One select agents and toxins (42 CFR §73.12(d); 7 CFR §331.12(d); 9 CFR §121.12(d)) [22,26,27].

TABLE 3 Penalties Associated with Failure to Follow Federal Regulations for the Possession, Use, and Transfer of Select Agents and Toxins

ADMINISTRATIVE PENALTIES	
Entity	Deny, suspend, or revoke registration
Individual	Deny, suspend, or revoke access to select agents and toxins
CIVIL PENALTIES	
Entity knowingly violates any provision of the select agent regulations	Up to $500,000 fine
Individual knowingly violates any provision of the select agent regulations	Up to $250,000 fine
CRIMINAL PENALTIES	
Restricted person possesses or transfers a select agent or toxin in interstate or foreign commerce	Criminal fine, imprisonment of up to 10 years, or both
Transfer of a select agent or toxin to a person who is known or reasonably believed not to be registered with the federal select agent program	Criminal fine, imprisonment of up to 5 years, or both
A person who knowingly possesses a select agent or toxin without registration with the federal select agent program	Criminal fine, imprisonment for up to 5 years, or both

Failure to comply with the requirements of the Federal Select Agent Program can lead to administrative, civil, and/or criminal penalties, both for the entity and for individuals in possession of select agents and toxins.

i. Failure to comply with the regulations will result in potential administrative, civil, and/or criminal penalties for entities and/or individuals (Table 3) [22,26,27].

4.3 The CDC Import Permit Program: Importation of Human Pathogens

1. The CDC promulgates regulations designed to prevent the introduction, transmission, and spread of communicable human disease resulting from importation of various animal hosts or vectors or other etiological agents from foreign countries into the United States as part of the Foreign Quarantine Program (42 CFR §71.50–71.56) [42]. The CDC IPP is responsible for enforcement of the requirements for importation of infectious biological agents, as well as animals (e.g., cats, dogs, turtles, tortoises, terrapins, and nonhuman primates), animal products, and vectors capable of causing communicable disease in humans (42 CFR §71.51–71.54) [42]. An approved import permit (IP) must be obtained by an investigator prior to importation of any materials that may be infectious to humans from a foreign country [43], and approval of an IP may be accompanied by requirements and conditions, including an inspection by the CDC IPP to ensure that:
   a. The importer has implemented proper biosafety measures, and
   b. The importer ensures that the shipper meets all legal requirements regarding packaging, labeling, and shipment of infectious substances.

In some cases, the IP requires that the CDC approve an additional IP for any subsequent transfer of permitted infectious substances within the United States.

2. The Foreign Quarantine Program was modified in April of 2013 to include the provision that an approved IP is no longer required for import of a biological select agent listed in 42 CFR Part 73 [22] if the import has been approved by the FSAP under the form two transfer process described in 42 CFR 73.16 (HHS Select Agents) or 9 CFR 121.6 (Overlap Select Agents) [22,27].

4.4 USDA APHIS Biological Products, Organisms and Vectors, and Plant Pathogens Permitting Program: Import and Interstate Transfer of Agricultural Pathogens

1. Import of an animal product as defined by USDA APHIS in 9 CFR §101 requires an individual to hold an approved US Veterinary Animal Product Permit (9 CFR §104.1) [44]. Animal products under this definition include "vaccines, bacterins, allergens, antibodies, antitoxins, toxoids, immunostimulants, some cytokines, antigenic or immunizing components of live organisms, and diagnostic components, that are of natural or synthetic origin, or that are derived from synthesizing or altering various substances or components of substances such as microorganisms, genes or genetic sequences, carbohydrates, proteins, antigens, allergens, or antibodies" (9 CFR §104.2) as well as cell cultures (9 CFR §104.6) and seed organisms (9 CFR §104.7) [44]. There are several types of permits available for importing animal products, but the most common type required by individual researchers is the US Veterinary Permit to Import Cell Cultures and Their Products (USDA-APHIS VS 16-7) [45]. Application for a USDA-APHIS VS 16-7 requires an individual researcher to briefly describe the product, the method of propagation including composition of the medium and the species of animals or cell cultures involved, any inactivation or attenuation of the product, and the proposed plan for evaluation (9 CFR §104.4) [46].
2. USDA APHIS also regulates the importation and/or interstate transfer of organisms that may be infectious to animals (including poultry), animal vectors that have been intentionally infected with organisms or that are known to be infected with or to have been exposed to any contagious, infectious, or communicable disease of animals or poultry, or animal products and byproducts (9 CFR §122.1 (d) and (e)) [45]. A USDA APHIS VS 16-3 permit for the import or transport of controlled material or organisms or vectors is required and must be issued prior to shipment of organisms or vectors [47]. It is important to note that unlike the CDC IP, an approved USDA APHIS VS 16-3 permit is required both for importation of biological products, organisms, or vectors from foreign countries and for transfer of regulated agents from one state, US territory, or the District of Columbia to another (9 CFR §104.4 (b) (2); 9 CFR §122.2) [47].
3. USDA APHIS also requires investigators to apply for a PPQ Permit prior to importing soil, organisms, soil samples, or plants and plant products (7 CFR §330) [48].

4.5 Dangerous Goods Shipping Regulations: Transport of Biological Agents

1. IATA DGR and DOT FHMR regulations apply to any package containing dangerous goods that is presented for intrastate, interstate, or international shipment [28,29]. In most situations, investigators or their designees are identified as the shipper

of packages containing dangerous goods and as such, are responsible for proper classification of shipped materials, identification (by choosing a proper shipping name), selection of proper packaging materials, compliance with the proper packaging instruction while preparing the package for shipment, proper marking and labeling of packages with appropriate hazard labels, preparation of appropriate shipping documentation, and compliance with any other additional requirements (e.g., obtaining appropriate import and/or export permits) as described elsewhere in this chapter. Any individual who either prepares packages, or who presents prepared packages to a transporter (e.g., Federal Express or the United Parcel Service) must complete proper training prior to preparing or presenting the shipment. Under the IATA DGR, this training must be repeated every 24 months to ensure knowledge of the current regulations (IATA 1.5.0.3) [28], while the DOT FHMR require training to be repeated at least once every three years (49 CFR §172.704(c)(2)) [29]. Since the IATA DGR are the more stringent regulations with regard to training frequency, most institutions and/or employers choose to require that personnel who ship dangerous goods repeat training at least once every two years (24 months).

2. Classification of Dangerous Goods: Dangerous goods are divided into classes according to the type of hazard posed by the material. The individual preparing the package for shipment is responsible for correctly classifying the dangerous goods present in the shipment. While the exact list of dangerous goods varies between specific regulations, most dangerous goods associated with biological research will fall into either division 6.2 infectious substances or division 9 miscellaneous dangerous goods.
   a. Division 6.2 Infectious Substances: Any substance known or reasonably expected to contain pathogens such as bacteria, viruses, rickettsiae, parasites, fungi, and/or other agents such as prions that may cause disease in humans or animals is classified as a division 6.2 infectious substance under the IATA DGR (IATA 3.6.2.1.1) and must be packaged and shipped in accordance with the regulations for this division [28]. Cultures of pathogens must be classified as division 6.2 infectious substances, as well as patient specimens from humans or animals that are known or reasonably expected to contain pathogens. Infectious substances are further subdivided into either category A or category B substances. Category A infectious substances include those that are capable of causing permanent disability or life-threatening or fatal disease on exposure in otherwise healthy humans or animals (IATA 3.6.2.2.2.1) [28]. Infectious substances that do not meet the criteria for inclusion in category A are classified as category B infectious substances (IATA 3.6.2.2.2.2) [28].
   b. Division 9 Miscellaneous Dangerous Goods: Often biological materials, both those that may be infectious substances and those that do not meet the criteria for classification as an infectious substance, must be shipped below ambient temperatures to preserve viability. Any package presented for shipment that contains dry ice (solidified carbon dioxide) must be classified as division 9 miscellaneous dangerous goods (IATA 3.9.2.6) [28] and must be packaged and labeled in accordance with IATA DGR and DOT FHMR for this division [28,29]. Nonpathogenic, genetically modified organisms are classified as hazardous materials by the IATA DGR and must be classified as division 9 miscellaneous dangerous goods when shipped by air within the contiguous United States or when shipped by any method internationally and must be packaged and labeled in accordance with DGR (IATA 3.9.2.5.) [28]. However, it should also be noted

that nonpathogenic, genetically modified organisms that are shipped by ground within the contiguous United States are not considered to be hazardous materials by the DOT FHMR and therefore are not regulated [29].

3. Identification: Dangerous goods, once properly classified, must be assigned a proper shipping name. Each proper shipping name is associated with a specific United Nations (UN) number, which may be found in Table 4 (IATA 4) [28].
4. Packaging: The regulations provide specific requirements for proper packaging of each type of dangerous good [28]. These requirements are defined in the packing instruction associated with each category of dangerous goods and may have variable maximum net quantity limits that are dependent on the exact transportation mode (e.g., shipment via passenger versus cargo aircraft). Specific requirements for use of packaging materials tested and approved to meet UN specifications may apply to each packing instruction, and the number of primary and secondary containers and the presence and type of absorbent materials may also be specified in each packing instruction. Packing instructions may be found in the IATA DGR (IATA 5) [28].
5. Marking and Labeling: All DGR provide instructions regarding the specific type of hazard labels that are required to be attached to each package, including appropriate symbols, minimum dimensions, number of labels per package, and proper placement of markings and labels on each package [28,29].
6. Documentation: In most cases, shipment of dangerous goods requires the individual responsible for the shipment to prepare a legal document, referred to under the IATA DGR as the "Shipper's Declaration for Dangerous Goods" (IATA 8.1) [28]. The regulations contain detailed requirements for proper completion of the shipper's declaration and a requirement for retention of these records by both the shipper and the carrier for two years.

TABLE 4 IATA Proper Shipping Names

CATEGORY A INFECTIOUS SUBSTANCES	
UN 2814	Infectious substance, affecting humans
UN 2900	Infectious substance, affecting animals
CATEGORY B INFECTIOUS SUBSTANCES	
UN 3373	Biological substance, category B
GENETICALLY MODIFIED ORGANISMS OR MICRO-ORGANISMS	
UN 3245	Genetically modified organism
UN 3245	Genetically modified micro-organism
DRY ICE	
UN 1845	Dry ice
UN 1845	Carbon dioxide, solid

IATA DGR require all packages containing biological agents to be labeled with the proper UN identification number and shipping name. Identification numbers for category A and B infectious substances, genetically modified organisms or micro-organisms, and dry ice are listed in Table 4.

7. Special Considerations and Penalties for Violation:
   a. Transport of live infected animals by air without express authorization from the appropriate national authorities is prohibited under IATA regulations (IATA 3.6.2.6.1) [28].
   b. A technical name is required in addition to the proper shipping name for category A infectious agents in accordance with International Civil Aviation Organization (ICAO) special provision A140 [49]. The technical name consists of the genus and species of the pathogen located in parentheses following the proper shipping name and must be shown on the transport document, or shipper's declaration only. The technical name is not required to follow the proper shipping name on the outside of the package.
   c. Shipment of category A infectious substances via the US or other international postal systems *is prohibited under any circumstances* according to the Universal Postal Union (UPU; Article 132.2) [50], ICAO [49], and IATA [28] regulations.
   d. In the United States, violation of any hazardous materials regulations may result in a civil penalty of up to $50,000 for each violation, and in some cases, a criminal penalty of up to $500,000 and/or imprisonment for up to five years may apply (49 CFR §107.329 and §107.333) [29]. In cases in which the violation results in serious injury or death, penalties may be doubled [29].

4.6 OSHA BBP: Protection of Employees from Exposure to Bloodborne Pathogens

1. Under the BBP standard, any entity where employee(s) may have exposure to BBP must have a written exposure control plan (CFR §1910.1030, c), and this plan must be made accessible to employees [18]. The concept of universal precautions (i.e., treating all blood, body fluids, and in some cases, cultures, as infectious) is critical to compliance with the BBP standard.
2. In addition to development of an exposure control plan and adherence to universal precautions, engineering, and work practices controls must be implemented to eliminate or minimize employee exposures (CFR §1910.1030, d, (2)) [18]. Proper handwashing facilities, enforcement of proper handwashing practices following removal of gloves or other PPE, and provision of antiseptic hand sanitizers when handwashing facilities are not immediately available are required. Use of sharps in conjunction with BBPs is a high-risk activity, and the BBP standard details proper sharps handling and disposal practices (including use of approved sharps disposal containers) and prohibition of bending, recapping, or removal of contaminated sharps (unless part of a procedure specific-requirement or if no feasible alternative is available) [18]. Basic good laboratory practices, such as prohibiting mouth pipetting, eating, drinking, smoking, applying cosmetics, or handling contact lenses in work areas, storage of food and drink outside of work areas, and performing laboratory procedures carefully to minimize splashing, spraying, or generation of aerosol droplets of pathogens are also required. Laboratories where work with BBP is performed and potentially contaminated equipment and containers are used for transport of BBP must be appropriately signed and labeled [18].
3. PPE use is mandated whenever engineering and work practice controls cannot eliminate the risk of exposure to personnel [18]. Minimum PPE requirements include gloves, gowns or laboratory coats, face shields or masks, and eye protection, as well as mouthpieces,

resuscitation bags, or pocket masks or other ventilation devices. The BBP standard also requires employers to ensure that proper PPE is used by employees [18].

4.7 The OSHA PPE Standard

1. The PPE standard requires employers to provide training for all employees who are required to use PPE. The training must address when PPE is needed and what type, how to wear and care for PPE properly, and the limitations of PPE [32]. Specific requirements for eye and face protection (29 CFR 1910.133) [51], respiratory protection (29 CFR 1910.134) [52], and hand protection (29 CFR 1910.138) [53] are of importance for work with biological agents. In particular, respiratory protection is required for specific work with infectious agents known to be transmitted via respiratory exposure routes (work with animals and manipulations of risk group 3 pathogens and all risk group 4 pathogens). The respiratory protection standard includes requirements for medical screening prior to use of specific types of respiratory protection and requirements for proper fit testing of employees (29 CFR §1910.134(e); 29 CFR §1910.134(f), respectively) [52].

5. KEY PERSONNEL AND UNIVERSITY COMMITTEES DESIGNATED TO IMPLEMENT REGULATORY MANDATES

5.1 Research with Recombinant and Synthetic Nucleic Acids: The IBC

1. The IBC is responsible for ensuring that all work with recombinant and synthetic nucleic acids at an institution is performed in compliance with the NIH Guidelines. To achieve this function, the IBC reviews proposed research projects and assesses a variety of aspects of the research including:
   - **a.** assessment of the containment levels required for the research (Section IV-B-2-b-(1)) [16];
   - **b.** assessment of the facilities, procedures, practices, and training of personnel involved in the proposed project (Section IV-B-2-b-(1)) [16];
   - **c.** ensuring that all requirements for any human gene transfer research projects are met (Section IV-B-2-b-(1) and Appendix M) [16];
   - **d.** ensuring that no human research subject is enrolled in a human gene transfer experiment until the NIH RAC has reviewed the research, the project has been approved by both the IBC and IRB of the clinical trial site, and any other regulatory requirements have been met (Section IV-B-2-b-(1)) [16];
   - **e.** ensuring that approval of any human gene transfer experiments chosen for public review by the RAC take into consideration any issues raised and recommendations made as a result of the RAC review and any of the principal investigator's responses to the RAC (Section IV-B-2-b-(1)) [16];
   - **f.** ensuring that the RAC review process has been completed before granting final approval to a project (Section IV-B-2-b-(1)) [16]; and
   - **g.** ensuring that the institution complies with all surveillance, data reporting, and adverse event reporting requirements of the NIH Guidelines (Section IV-B-2-b-(1)) [16].

2. The IBC must notify the investigator of the results of its review (Section IV-B-2-b-(2)), is responsible for lowering containment levels for specific experiments (Section IV-B-2-b-(3)) and for setting containment levels for experiments involving animals or plants (Section IV-B-2-b-(4)) [16]. The IBC must periodically review research conducted at the institution to ensure compliance with the NIH Guidelines, and adopt emergency plans detailing the institution's response to accidental spills and contamination of personnel with recombinant or synthetic nucleic acid materials (Section IV-B-2-b-(6)) [16]. Any significant violations of the NIH Guidelines and any significant research-related accidents or illnesses must be reported by the IBC to appropriate institutional officials and NIH OBA within 30 days (Section IV-B-2-b-(7)) [16].

5.2 Research with Recombinant and Synthetic Nucleic Acids: The BSO

1. A BSO must be appointed by institutions that perform large-scale research or are involved in production activities that use viable organisms containing recombinant or synthetic nucleic acids, or that perform research with recombinant or synthetic nucleic acids at BL3 or BL4 (Sections IV-B-3-a and IV-B-3-b) [16]. The NIH Guidelines further define specific duties for the BSO that must include:
   a. periodic inspections of laboratories to ensure that laboratory safety standards are followed by investigators and research staff (Section IV-B-3-c-(1)) [16];
   b. reporting of any significant problems or violations of the NIH Guidelines and any significant research-related accidents or illnesses to the IBC and the appropriate institutional officials (Section IV-B-2-b-(2)) [16];
   c. development of emergency plans for appropriate response to spills and personnel contamination with recombinant or synthetic nucleic acid materials and investigation of laboratory accidents involving these materials (Section IV-B-2-b-(3)) [16];
   d. providing advice to principal investigators and the IBC on laboratory safety and security procedures (Sections IV-B-2-b-(4) and IV-B-2-b-(5)) [16].

5.3 Research with Recombinant and Synthetic Nucleic Acids: The Principal Investigator

1. Substantial responsibility lies with the principal investigator (PI) for compliance of his or her research with the requirements of the NIH Guidelines (Section IV-B-7) [16].
   a. General requirements include a responsibility not to initiate research with recombinant or synthetic nucleic acids until appropriate approval is granted as outlined in the NIH Guidelines and ensuring simultaneous notification of the IBC with initiation of experiments described in Section III-E of the NIH Guidelines [16].
   b. The PI is responsible for reporting of accidents, exposures or violations of the NIH Guidelines to the appropriate institutional official, in addition to being trained in good microbiological techniques, adhering to institutional emergency plans for response to accidental spills and personnel contamination, and ensuring that all shipping requirements are met in any transfers of recombinant or synthetic nucleic acid molecules. Specific details regarding information that the PI is required to submit to NIH OBA and the local IBC are detailed in Section IV-B-7-b and Section IV-B-7-c of the NIH Guidelines [16].

c. Perhaps most importantly, the NIH Guidelines place responsibility for ensuring that all personnel have adequate access to the protocols describing potential biohazards and precautions to be taken, training in the practices and techniques necessary to ensure personnel safety and proper accident response procedures, and information regarding appropriate medical surveillance programs assigned to the protocol such as vaccinations or serum collection with the PI (Section IV-B-7-d) [16]. Under the NIH Guidelines, the PI is also primarily responsible for supervision of the safety performance of the personnel in his or her laboratory and correction of any work errors or conditions that might lead to the release of recombinant or synthetic nucleic acid materials to the environment, including maintaining the integrity of physical containment devices such as biosafety cabinets and any biological containment methods (Section IV-B-7-e) [16].

d. The PI is also responsible for complying with all applicable reporting requirements including those pertaining to reporting of problems with implementation of containment practices and/or issues associated with human gene transfer experiments (Sections IV-B-7-e-(2) and IV-B-7-e-(5), respectively) [16].

5.4 Research with Select Agents and Toxins: The RO

1. Designation of a RO is required as part of an entity's registration with the Select Agent Program.

a. The RO is required to undergo the same security risk assessment process as all other personnel with access to select agents and must be given the authority and responsibility to act on behalf of the entity regarding all aspects of the Select Agent Program [22,26,27].

b. The RO is the primary point of contact between the entity and the CDC or APHIS and is responsible for ensuring that the entity's programs comply with all of the requirements set forth in the select agent regulations [22,26,27]. Individual investigators may not communicate with the FSAP. All communications regarding an entity's registration and program are required to be coordinated by the RO.

c. The RO is required to be physically present at the registered entity to oversee compliance and to respond to onsite incidents involving select agents and toxins, and must ensure that annual inspections are performed of each laboratory where select agents and toxins are stored or used [22,26,27]. Institutions may also designate one or more individuals to serve as alternate responsible officials (AROs), who act for the RO in his or her absence.

d. The entity is required to designate to the RO and the ARO the authority and control needed to ensure compliance with the Select Agent Regulations [41].

5.5 Environmental Compliance and Research Safety: The Department of Environmental Health and Safety

1. At most institutions, compliance with other regulatory requirements not mentioned above, in addition to local and state regulations and accepted best practices for work with biological hazards, is assigned to a specific department, such as the department of environmental health and safety. The placement of this department within the

institutional reporting structure may vary, but the department should play a key role in interactions with other institutional compliance bodies.

6. COMMON COMPLIANCE CHALLENGES

6.1 NIH Guidelines

1. It is the opinion of the authors that most compliance issues associated with the NIH Guidelines fall into a category representing failure by investigators to obtain appropriate approval from NIH OBA and/or the IBC prior to beginning work that is covered by the guidelines. This can be especially challenging, because a wide variety of products based on recombinant and synthetic nucleic acid materials and/or viral vector-based systems are available for purchase from commercial vendors. Introduction of commercial products involving viral vectors or commercially produced viral particles based on recombinant or synthetic nucleic acids into mammalian cells and/or animals represents research that must be approved by the IBC prior to commencement.
2. Transfer of drug resistance traits into microorganisms can be another challenging area of compliance with the NIH Guidelines. Use of many common antimicrobial resistance markers used in molecular cloning techniques (e.g., kanamycin, puromycin, ampicillin, etc.) do not require preapproval under the major action section of the NIH Guidelines (Section III-A-1) [16]. However, investigators must perform due diligence to ensure that a particular drug resistance trait will not confer resistance to a preferred treatment for use in medicine and/or agriculture. Investigators should pay particular attention to specific drugs that are no longer considered to be preferred treatment in most human or animal populations, but are still commonly used in the treatment of special populations (e.g., pregnant women, children, or immunocompromised patients; Section III-A-1-a) [16].
3. Incident reporting is another often-challenging area of compliance for institutions and investigators. In general, incidents that involve noncompliance with the guidelines must be reported to NIH OBA within 30 days [54]. This 30-day reporting deadline also applies to accidents or exposures involving low-risk materials (generally BL1). However, in cases of accidents or exposures to higher-risk materials, expedited reporting is required. Accidents or incidents that result in known exposure of personnel to recombinant or synthetic nucleic acids materials handled at BL2 must be reported to NIH OBA immediately [54]. The reporting requirement deadlines for work with recombinant or synthetic nucleic acid materials at BL3 or BL4 are also clearly defined. In the case of work in high or maximum containment (BL3 and BL4). Accidents, spills, or incidents that result in either a known or a potential personnel exposure must be reported to NIH OBA immediately [54].

6.2 The Federal Select Agent Program

1. Possession of Select Agents
   a. Clinical laboratories and research laboratories, particularly those with work that includes screening of samples to identify unknown biological agents, must be aware that the Select Agent Program requires entities that identify a select agent or toxin to notify the FSAP immediately and arrange to either transfer the agent to an entity

with a current registration for possession of the select agent or toxin identified or to document destruction of the samples within seven calendar days of identification [22,26,27].

b. Restricted persons
- All persons who have received Security Risk Assessment (SRA) approval for access to select agents and toxins are required to notify the RO of any change in personal status that could result in the loss of SRA approval. This includes any events that would cause an individual to fall into the category of a restricted person [55].

c. Security Issues
- Compliance with the inventory requirements of the Select Agent (SA) regulations can be particularly challenging. The regulations provide detailed requirements that specify the information that must be contained in an inventory record, retention of records, regular auditing of an entity's inventory, etc. [41,56]. Inventory discrepancies may result from a variety of situations, including miscounting or misplacement of regulated materials. Animals infected with select agents must be accounted for from the time of infection to final carcass destruction. Documentation of destruction of materials used in in vitro experiments is required as well. The most recent version of the regulations requires that investigators document information specifying the purpose of use, amount used, and other information each time an inventoried item is accessed [41,56].
- Access to select agents and toxins must be restricted to personnel who are SRA approved, with additional personnel screening requirements applying to individuals with access to Tier One select agents and toxins [41]. Any personnel, including both internal employees of the entity and external personnel such as contractors, manufacturer service representatives, etc., who have not received SRA approval and have not completed any additional requirements as part of an entity's registration must be treated as a visitor. Visitors must be escorted at all times by an SRA-approved individual. This can pose a significant burden on small programs, because the escort is not permitted to have any duties in addition to serving as an escort [41].
- An entity is required to have detailed procedures to detect and respond to breaches in physical and information security and to perform annual drills or exercises to ensure that these procedures are effective [41]. It is the opinion of the authors that, while most entities are in compliance with the obvious requirements for physical and information security (e.g., building security and access control measures, firewall protection of information systems, etc.), it is often challenging to deal with the more subtle implications of these security requirements. Some examples include failure to collect proximity cards, remove access levels associated with proximity cards, and terminate access to electronic inventory records and other regulated electronic information upon termination of an individual's employment with an entity.

d. Biosafety Issues
- The FSAP inspection process is based on compliance with best practices specified in the BMBL and the NIH Guidelines. During routine, scheduled, and unannounced inspection processes, FSAP inspectors use extensive checklists based on these

guidance documents [41]. One common challenge for entities involves the requirement in the most recent edition of the BMBL for annual reverification of ventilation controls under routine operational and failure scenarios to ensure that BSL-3 and BSL-4 facilities are capable of meeting performance standards required for containment of infectious agents.

e. Restricted Experiments
- It is critical that investigators understand and comply with the SA regulations pertaining to performance of restricted experiments. Investigators must be aware that introduction of or selection for drug resistance traits that could confer resistance to agents used to treat diseases caused by select agents or toxins in humans, veterinary medicine, or agriculture requires preapproval from the FSAP [41]. It is also crucial to note that possession of products of restricted experiments also requires preapproval from the FSAP [41]. If an investigator plans to obtain a strain of a select agent or toxin containing drug resistance traits from another investigator or commercial repository, the entity's RO must be notified well in advance so that the appropriate approvals can be obtained.

f. Release of Select Agents and Toxins
- The main regulatory mandate of the FSAP is to prevent the theft, loss, or release of select agents and toxins. It can be challenging for entities to determine whether a particular scenario constitutes a release of select agents and toxins that must be reported to the FSAP. Some scenarios that require mandatory reporting include known personnel exposures to select agents and toxins (e.g., failure of respiratory protection, percutaneous injury with contaminated sharps, etc.), a spill outside of a primary containment device, or failure of an engineering control (e.g., failure of ventilation system components resulting in a reversal of airflow in a containment facility, failure of effluent decontamination systems or autoclaves, etc.) [41].

g. Due Diligence Requirements for Research Involving Exempt Quantities of SA Toxins
- The most recent version of the Select Agent Regulations requires entities to develop programmatic controls to ensure that investigators working with exempt quantities of select agent toxins are in compliance with the quantity limits that allow work to proceed without registration with the FSAP [57].

6.3 CDC and USDA APHIS IPPs

1. The most obvious compliance issue in regard to the CDC and USDA permit programs is failure on the part of an investigator to obtain a permit prior to import of a biological agent controlled under these programs. There is a distinction between CDC IPP and the USDA APHIS IPP that is of particular importance for investigators. Unlike the CDC IPP, USDA APHIS import permits are required for both import from foreign countries into the United States and shipment of regulated biological materials between states within the United States [42,45,48].

2. It is also important for investigators to pay particular attention to any conditions that are associated with the approval of an import permit by the CDC or USDA APHIS. These conditions may consist of additional containment practices (e.g., anterooms, primary containment enclosures), specific enhancements to disinfection practices, or

facility enhancements required for possession of the biological agent. Another common condition of approval restricts transfer of the biological agent from the permitee to another individual without first requiring the receiver to obtain an approved CDC or USDA APHIS permit.

6.4 Dangerous Goods Shipping

1. In the opinions of the authors, one of the most common compliance challenges for institutions and investigators involved in the shipment of biological materials is failure to ensure proper training of personnel. All personnel involved in the preparation of the package and in presentation of the package to the shipper must have had adequate training in compliance with the dangerous goods shipping regulations [28,29]. In the case of shipment of biological research materials, both the laboratory or research personnel preparing the actual package and any administrative personnel who may present the package to the shipper (e.g., Federal Express, United Parcel Service, etc.) must have appropriate training, and documentation of this training must be maintained by the institution.
2. Compliance with all details of the package preparation, package labeling, and paperwork preparation must be observed [28,29]. It is common for packages to be returned to the originator or for the shipper to refuse to accept packages that are improperly labeled or presented for shipment with incomplete or improperly completed paperwork.
3. Another key area of importance for investigators involves proper classification of biological materials for shipment [28,29]. While the designation of category A infectious agents is relatively straightforward, the assignment of a particular sample to either category B or an exempt specimen classification is based on the professional opinion of the individual preparing the package for shipment. In the opinion of the authors, the key concept for investigators to consider in classification of biological materials is whether the sample is known or may be reasonably suspected to contain a pathogen. For example, it is the opinion of the authors that patient samples obtained from a population in which there is a known outbreak of an infectious disease (animal or human) would be best categorized as category A samples. Again, in the opinion of the authors, most human and or animal samples may be correctly categorized as category B or exempt, unless the investigator has a reason to suspect that the samples may be infectious.

6.5 Occupational Safety and Health Administration Bloodborne Pathogen Standard

1. PPE and Hygiene Challenges
   a. Specific types of PPE are addressed in the BBP standard, including use of gloves when employees may have hand contact with blood and OPIM, during phlebotomy procedures (except under certain defined situations in the regulation (CFR §1910.1030(3)(ix)(d)), and when handling contaminated items or in contact with contaminated surfaces [18]. Masks in combination with eye protection (e.g., goggles, glasses with side shields, or chin-length splash shields) must be worn whenever there is a reasonably anticipated risk of generation of splashes, spray, spatter, or droplets of

blood or OPIM (CFR §1910.1030(3)(x)), and protective clothing such as a lab gown, lab coat, or similar dedicated protective apparel is required (CFR §1910.1030(3)(xii)) [18].

b. The BBP standard also requires that PPE be removed before leaving the work area (CFR §1910.1030(3)(vii)) [18]. In the opinion of the authors, proper removal and storage of PPE is a commonly observed compliance issue in research and clinical settings. In addition to proper removal of PPE, hand hygiene practices are specified in the regulation. It is the responsibility of the employer to provide readily available handwashing facilities or, in areas where this is not feasible, to provide antiseptic hand cleansers or towelettes (BBP §1910.1030, d, (2), (iii and iv)) [18] for employee use. Similarly, it is the responsibility of the employer to ensure that employees wash hands as soon as possible after removing gloves and other PPE, or in the case of an area where a sink is not readily available, to sanitize hands and follow up with handwashing with soap and water as soon as possible (BBP §1910.1030, d, (2), (iii and v) [18].

c. In the opinion of the authors, failure of employers to provide a broad range of sizes and types of appropriate PPE in readily accessible areas can lead to reduced employee compliance with requirements for donning and doffing of PPE (BBP §1910.1030, d, (3), iii) [18]. For example, if gloves are ill fitting, dexterity can be adversely affected. Likewise, laboratory coats or coverall suits that are too large or too small for an employee can restrict movement and lead to reduced compliance. Providing employees with opportunities to evaluate different types and sizes of PPE (e.g., different types of face shields, safety glasses, gloves, etc.) can lead to increased compliance with PPE requirements.

2. Training and Documentation Challenges

a. The BBP standard requires annual training for all employees that incorporates a specified list of topics (BBP §1910.1030 (g)(2)) [18]. Ensuring that all employees complete training on an annual schedule can be difficult to manage and enforce.

b. In the section of the OSHA BBP standard pertaining to occupational health requirements, specific documentation requirements are listed (BBP §1910.1030 (h)(1)) along with specific documentation retention requirements [18].

c. The required Exposure Control Plan must be reviewed and updated annually (BBP §1910.1030(c)(1)(iv)) and must include [18]:

- review and addition of new tasks and procedures that may change occupational exposure classifications, and considerations of changes to employee positions that may change the exposure assessments defined in the plan; and
- identification and evaluation of new technology and safer medical devices designed to eliminate or minimize occupational exposures.

d. SESIP Challenges

- Employers are required to provide opportunities for employees directly performing work that may result in exposure to BBP or OPIM to participate in the identification, evaluation, and selection of engineering and work practice controls, including SESIPs (BBP §1910.1030(c)(1)(iv)) [18]. It is the opinion of the authors that this evaluation process often poses a challenge for personnel involved in laboratory and animal research. Because most SESIPs are engineered specifically for use in clinical applications with human patients, SESIPs are not always available

in needle gauges or configurations that lend themselves to research applications. In these cases, close communication between safety and research personnel can often result in development of additional work practice controls that mitigate the risks associated with the use of non-safety engineered sharps. It should be noted that documentation of the evaluation SESIPs in a particular procedure and specific language providing scientific rationale should be retained for experiments in which research personnel determine that use of SESIPs interferes with the research goal. Personal preference is not an acceptable rationale for noncompliance with the SESIPs provisions of the OSHA BBP standard.

- In addition to requiring evaluation and implementation of SESIPs, the OSHA BBP standard also contains provisions for proper disposal of sharps devices (BBP §1910.1030(d)(2)(vii)) [18]. Disposable, one-time use sharps devices should be disposed of in an approved sharps disposal container immediately after use. Needles should not be recapped, bent, broken, or otherwise handled prior to disposal. In cases in which there is a procedural requirement for recapping of needles, a one-handed technique or specially designed engineering control (e.g., needle recapping tray) must be used (BBP §1910.1030(d)(2)(vii)(B)) [18].

7. ADDRESSING NONCOMPLIANCE

7.1 Institutional Resources

1. Often, the same institutional resources that are appointed to ensure compliance with guidelines and/or regulations are the most useful resource for investigators. The personnel responsible for coordination of the IBC activities at a particular institution have a unique understanding of issues that are commonly experienced by investigators. Likewise, the institutional department charged with managing the health and safety program will be most familiar with the unique situations and regulatory environment consisting of local, state, and federal mandates. Often these institutional entities have established guidelines or guidance documents to assist investigators in compliance. In an ideal institutional environment, interactions between institutional departments and investigators can lead to the recognition of the need for development of improved or targeted training initiatives and guidance tools for investigators and research personnel.

References

[1] Berg P, Baltimore D, Brenner S, Roblink R, Singer M. Summary statement of the Asilomar conference on recombinant DNA molecules. Proc Natl Acad Sci USA 1975;72(6):1981–4.
[2] Harding L, Byers KB. Epidemiology of laboratory-associated infections. In: Fleming DO, Hunt DL, editors. Biological safety: principles and practices. 4th ed. Washington, DC: ASM Press; 2006.
[3] Pike RM. Laboratory-associated infections: summary and analysis of 3921 cases. Health Lab Sci 1976;13(2):105–14.
[4] Pike RM. Past and present hazards of working with infectious agents. Arch Pathol Lab Med 1978;102(7):333–6.
[5] Pike RM. Laboratory-associated infections: incidence, fatalities, causes, and prevention. Annu Rev Microbiol 1979;33:41–66.
[6] Pike RM, Sulkin SE. Laboratory-acquired infections in the United States. Tex Rep Biol Med 1951;9(2):346–7.
[7] Pike RM, Sulkin SE, Schulze ML. Continuing importance of laboratory-acquired infections. Am J Public Health Nations Health 1965;55:190–9.

[8] Sulkin SE, Pike RM. Laboratory-acquired infections. J Am Med Assoc 1951;147(18):1740–5.
[9] Sulkin SE, Pike RM. Laboratory infections. Science 1951;114(2950):3.
[10] Sulkin SE, Pike RM. Survey of laboratory-acquired infections. Am J Public Health Nations Health 1951; 41(7):769–81.
[11] Reitman M, Wedum AG. Microbiological safety. Public Health Rep 1956;71(7):659–65.
[12] Wedum AG. Ii. Airborne infection in the laboratory. Am J Public Health Nations Health 1964;54:1669–73.
[13] Wedum AG. Laboratory safety in research with infectious aerosols. Public Health Rep 1964;79:619–33.
[14] U.S. Department of Health and Human Services: Centers for Disease Control and Prevention and National Institutes of Health. Biosafety in microbiological and biomedical laboratories. 5th ed. US Department of Health and Human Services; 2009.
[15] Ad Hoc Committee on the Safe Shipment and Handling of Etiologic Agents. Classification of etiologic agents on the basis of hazard. 4th ed. Atlanta, GA: U.S. Department of Health, Education, and Welfare, Public Health Service, Center for Disease Control, Office of Biosafety; 1974.
[16] National Institutes of Health. NIH guidelines for research involving recombinant or synthetic nucleic acid molecules. U.S. Department of Health and Human Services; 2013.
[17] National Institutes of Health Office of Research Safety NCI. National institutes of health laboratory safety monograph: a supplement to the NIH guidelines for recombinant DNA research. U.S. Department of Health, Education, and Welfare; 1978.
[18] Occupational Safety and Health Administration. Bloodborne pathogens. http://www.osha.gov/pls/oshaweb/owadisp.show_document?p_id=10051&p_table=STANDARDS [accessed 30.05.14].
[19] Needlestick safety and prevention act. 2000. http://www.osha.gov/needlesticks/needlefaq.html [accessed 30.05.14].
[20] Trans-Federal Task Force on Optimizing Biosafety and Biocontainment Oversight. Report of the Trans-Federal Task Force on Optimizing Biosafety and Biocontainment Oversight. 2009. http://www.ars.usda.gov/is/br/bbotaskforce/biosafety-FINAL-REPORT-092009.pdf. [accessed 30.05.14].
[21] Blaine JW. Establishing a national biological laboratory safety and security monitoring program. Biosecur Bioterror 2012;10(4):396–400.
[22] U.S. Department of Health and Human Services. Select agents and toxins. http://www.ecfr.gov/cgi-bin/retrieveECFR?gp=&SID=8a4be60456973b5ec6bef5dfeaffd49a&r=PART&n=42y1.0.1.6.61 [accessed 30.05.14].
[23] U.S. Congress. Uniting and strengthening America by Providing Appropriate Tools Required to Intercept and Obstruct Terrorism (USA PATRIOT) Act 2001. http://www.selectagents.gov/resources/USApatriotAct.pdf [accessed 30.05.14].
[24] U.S. Congress. Public Health Security and Bioterrorism Preparedness and Response Act. 2002. http://www.selectagents.gov/resources/PL107-188.pdf [accessed 30.05.14].
[25] Miller JM, Astles R, Baszler T, Chapin K, Carey R, Garcia L, et al. Guidelines for safe work practices in human and animal medical diagnostic laboratories. Recommendations of a CDC-convened, Biosafety Blue Ribbon Panel. Morbidity and Mortality Weekly Report Surveillance Summaries 2012;61(Suppl):1–102.
[26] U.S. Department of Agriculture Animal and Plant Health Inspection Service Plant Protection and Quarantine Programs. Possession, use, and transfer of select agents and toxins. http://www.ecfr.gov/cgi-bin/retrieveECFR?gp=&SID=8a4be60456973b5ec6bef5dfeaffd49a&r=PART&n=42y1.0.1.6.61 [accessed 30.05.14].
[27] U.S. Department of Agriculture Animal and Plant Health Inspection Service. Possession, use, and transfer of select agents and toxins. http://www.ecfr.gov/cgi-bin/retrieveECFR?gp=1&SID=b9126e9fba23e3e7933354a1d2630d72&ty=HTML&h=L&n=9y1.0.1.5.58&r=PART [accessed 30.05.14].
[28] International Air Transport Association. Dangerous goods regulations. 55th ed. International Air Transport Association; 2014.
[29] U.S. Department of Transportation. Hazardous materials and oil transportation. http://www.ecfr.gov/cgi-bin/text-idx?SID=3d06b55e9b6dc811cab4d69a32054382&c=ecfr&tpl=/ecfrbrowse/Title49/49cfrv2_02.tpl [accessed 30.05.14].
[30] U.S. Congress. Occupational safety and health act of 1970. 1970. http://www.osha.gov/pls/oshaweb/owadisp.show_document?p_table=OSHACT&p_id=2743 [accessed 30.05.14].
[31] McCully R.E. Letter of interpretation: applicability of the Occupational Safety and Health Administration's (OSHA) standard 29 CFR 1910.1030, "occupational exposure to bloodborne pathogens" to established human cell lines. 1994. http://www.osha.gov/pls/oshaweb/owadisp.show_document?p_table=INTERPRETATIONS&p_id=21519 [accessed 30.05.14].

[32] Occupational Safety and Health Administration. Personal protective equipment. http://www.osha.gov/pls/oshaweb/owadisp.show_document?p_table=STANDARDS&p_id=10118 [accessed 30.05.14].
[33] U.S. Environmental Protection Agency. Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA). http://www.epa.gov/oecaagct/lfra.html [accessed 30.05.14].
[34] U.S. Environmental Protection Agency. Pesticide programs. http://www.gpo.gov/fdsys/pkg/CFR-2003-title40-vol21/pdf/CFR-2003-title40-vol21-part152.pdf [accessed 30.05.14].
[35] U.S. Environmental Protection Agency. Selected EPA-registered disinfectants. http://www.epa.gov/oppad001/chemregindex.htm [accessed 30.05.14].
[36] U.S. Environmental Protection Agency. Wastes—where you live: state programs. http://www.epa.gov/oppad001/chemregindex.htm [accessed 30.05.14].
[37] National Institutes of Health Office of Biotechnology Activities. Frequently asked questions: NIH guidelines for research involving recombinant or synthetic nucleic acid molecules (NIH Guidelines). 2013. http://osp.od.nih.gov/sites/default/files/Synthetic_FAQs_April_2013.pdf. [accessed 24.05.14].
[38] Occupational Safety and Health Administration. Hazard communication. http://www.osha.gov/pls/oshaweb/owadisp.show_document?p_table=STANDARDS&p_id=10099 [accessed 30.05.14].
[39] Occupational Safety and Health Administration. Occupational exposure to hazardous chemicals in laboratories. http://www.osha.gov/pls/oshaweb/owadisp.show_document?p_table=STANDARDS&p_id=10106 [accessed 30.05.14].
[40] National Select Agent Registry. General FAQs about select agents and toxins. http://www.selectagents.gov/FAQ_General.html - sec1q11 [accessed 24.05.14].
[41] Federal Select Agent Program. Resource manual for the responsible official. 2013. http://www.selectagents.gov/resources/Resource_Manual_All.pdf. [accessed 03.06.14].
[42] Centers for Disease Control and Prevention. Import permit program (IPP). http://www.cdc.gov/od/eaipp/ [accessed 03.06.14].
[43] Centers for Disease Control and Prevention. Import permit program (IPP): applications. http://www.cdc.gov/od/eaipp/importApplication/ [accessed 03.06.14].
[44] U.S. Department of Agriculture Animal and Plant Health Inspection Service. Veterinary Biologics. http://www.aphis.usda.gov/wps/portal/footer/topicsofinterest/applyingforpermit?1dmy&urile=wcm%3apath%3a%2Faphis_content_library%2Fsa_our_focus%2Fsa_animal_health%2Fsa_vet_biologics%2Fct_vb_import_export_products [accessed 03.06.14].
[45] U.S. Department of Agriculture Animal and Plant Health Inspection Service. Animal health permits, http://www.aphis.usda.gov/wps/portal/footer/topicsofinterest/applyingforpermit?1dmy&urile=wcm%3apath%3a%2Faphis_content_library%2Fsa_our_focus%2Fsa_animal_health%2Fsa_import_into_us%2Fsa_apply_for_permits%2Fct_animal_health_permits_home [accessed 03.06.14].
[46] U.S. Department of Agriculture Animal and Plant Health Inspection Service. VS 16.7 permit to import cell cultures and their products. http://www.aphis.usda.gov/wps/portal/footer/topicsofinterest/applyingforpermit?1dmy&urile=wcm%3apath%3a%2Faphis_content_library%2Fsa_our_focus%2Fsa_animal_health%2Fsa_import_into_us%2Fsa_apply_for_permits%2Fct_animal_health_permits_home [accessed 03.06.14].
[47] U.S. Department of Agriculture Animal and Plant Health Inspection Service. Application for permit to import or transport controlled material or organisms or vectors. http://www.aphis.usda.gov/animal_health/permits/downloads/vs16_3.pdf [accessed 03.06.14].
[48] U.S. Department of Agriculture Animal and Plant Health Inspection Service Plant Protection and Quarantine. Plant health import information. http://www.aphis.usda.gov/wps/portal/aphis/ourfocus/planthealth?1dmy&urile=wcm%3apath%3a%2FAPHIS_Content_Library%2FSA_Our_Focus%2FSA_Plant_Health%2FSA_Import%2F [accessed 03.06.14].
[49] International Civil Aviation Organization. Technical instructions for the safe transport of dangerous goods by air: International Civil Aviation Organization. 2013.
[50] Universal Postal Union. Letter post manual. 2013. http://www.upu.int/uploads/tx_sbdownloader/actInFourVolumesLetterPostManualEn.pdf. [accessed 03.06.14].
[51] Occupational Safety and Health Administration. Eye and face protection. http://www.osha.gov/pls/oshaweb/owadisp.show_document?p_table=STANDARDS&p_id=9778 [accessed 30.05.14].
[52] Occupational Safety and Health Administration. Respiratory protection. http://www.osha.gov/pls/oshaweb/owadisp.show_document?p_table=STANDARDS&p_id=12716 [accessed 30.05.14].

[53] Occupational Safety and Health Administration. Hand protection. http://www.osha.gov/pls/oshaweb/owadisp.show_document?p_table=STANDARDS&p_id=9788 [accessed 30.05.14].
[54] National Institutes of Health Office of Biotechnology Activities. Frequently asked questions for labs conducting recombinant or synthetic nucleic acid research: reporting of incidents related to research subject to the NIH guidelines for research involving recombinant or synthetic nucleic acids to the National Institutes of Health (NIH) Office of Biotechnology Activities (OBA). 2013. http://osp.od.nih.gov/sites/default/files/FAQs_about_Incident_Reporting.pdf. [accessed 24.05.14].
[55] Federal Select Agent Program. Security risk assessment FAQs. National select agent registry [accessed 03.06.14].
[56] Federal Select Agent Program. Security guidance for select agent or toxin facilities. http://www.selectagents.gov/resources/Security_Guidance_v3-English.pdf [accessed 03.06.14].
[57] Federal Select Agent Program. Due diligence FAQs. http://www.selectagents.gov/FAQ_DueDiligence.html [accessed 03.06.14].