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Research Compliance Professional's Handbook, Third Edition
4 Biosecurity, Biosafety, and Biorisk Management

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Introduction

Historically, the terms biosafety and biosecurity have had closely related and sometimes overlapping definitions. Today, a useful way to think about the two terms is that the goal of biosafety is to manage the risk of accidental release or unintended effects of potentially hazardous biological materials; whereas the goal of biosecurity is to manage the risk of intentional or malicious misuse of hazardous biological materials. Biosafety and biosecurity are important considerations in a broad range of endeavors from plant and animal agriculture to environmental protection; however this chapter is specifically focused on implications for human clinical research and human health.

At clinical research institutions, biosafety programs must be prepared to manage risks associated with several types of products, including:

- **Infectious agents and toxins from natural sources or clinical isolates;** this includes genetically unmodified microbial cultures used for research or diagnostic purposes, as well as human tissue samples.
- **Biological toxins manufactured for clinical or research purposes.** Examples include botulinum toxin used in the clinic (as Botox), as well as a wide variety of neurotoxins and immunotoxins used for basic laboratory research.
- **Recombinant and synthetic nucleic acid molecules.**
- **Genetically-modified microbes or animals** for use in preclinical or basic science laboratory research.
- **Human Gene Transfer products,** such as viral vectors made with recombinant DNA technology, intended for use in human gene transfer and gene therapy research and in clinical trials.

Every institution where these products are administered, handled or stored should have biosafety protocols in place, preferably as part of a formal biosafety program. At various institutions, the biosafety program may constitute an independent department, or may be incorporated into other departments such as Environmental Health and Safety, or Infection Control. Biosafety programs should be developed under the guidance of a **biosafety professional**—*i.e.*, a biosafety expert with significant training and experience. Some but not all biosafety professionals will have professional credentials certified by an organization such as the American Biological Safety Association (ABSA) International.[2] For institutions with complex biosafety needs, a key staff position is that of **Biological Safety Officer (BSO)**. The BSO is a biosafety professional who is familiar with the facilities, procedures and training at the institution and who provides advice and supervision related to safe handling and storage of biohazardous products. If an institution is subject to the NIH Guidelines For Research Involving Recombinant and Synthetic Nucleic Acid Molecules (NIH Guidelines), that institution is required to employ a BSO if the institution engages in research with Biosafety Level 3 or 4 containment (see below).

The primary goal of any well-designed biosafety program is to manage the risks associated with activities

involving biohazardous products. These activities include acquiring or manufacturing, tracking, transporting, labeling, storage, handling, and disposal of biological samples and biohazardous products. In the case of human gene transfer research, it also involves dosing and administration of the gene transfer product to the research subject. An important goal is to contain the biohazardous materials under conditions that minimize the risk to persons and the environment. To develop a biosafety protocol for each of these activities, it is necessary to assess the risk posed by accidental loss of containment, and by the relative potential for harm to persons or the environment by accidental exposure or release.

Implementing a biosafety protocol involves ensuring that packages containing biohazardous materials are properly labeled and that areas where these materials are handled have proper signage and security measures to prevent unauthorized persons from accidentally or intentionally interfering with biocontainment. Supervisors in charge of these areas must ensure that only trained personnel handle the biohazardous materials, and that personnel always use appropriate personal protective equipment (PPE). Depending on the product and activities under study, appropriate PPE may include, gloves, gown, shoe covers, eye protection, and a mask or respirator. The protocol must also describe the biohazard waste stream, including how all waste materials that have come into contact with biohazardous materials should be disposed of. Biohazard waste management requires coordination with the building facilities team and with appropriately certified waste haulers, as well as careful attention to local and national environmental regulations. Each protocol should also include emergency procedures in case of loss of containment. These include plans to provide first aid and medical care to exposed persons, spill cleanup, and coordination with first responders and emergency personnel.

For many biosafety protocols, a key piece of equipment is the **biosafety cabinet (BSC)**. A BSC provides a hood with a partially enclosed work area having directed airflow such that air is constantly pulled into the BSC and away from the researcher, who can sit or stand outside the BSC and manipulate experimental materials. The directed airflow ensures that most airborne contaminants are pulled away from the lab worker and into the hood for capture by a high-efficiency filter. BSCs are only useful if installed, maintained, and operated by properly trained personnel. BSCs are a key piece of equipment for most protocols at Biosafety Levels 2, 3, and 4.

In the US, there are several federal agencies that provide guidance and regulatory oversight affecting biosafety and research activities. The Department of Transportation (DOT) imposes a variety of rules regarding proper labeling and shipment of hazardous substances, including specific training requirements for persons who ship or receive such materials. The Occupational Health and Safety Administration (OSHA) sets standards for worker safety that can have a significant impact on design and implementation of biosafety programs. The two federal agencies that have the greatest day-to-day impact on biosafety programs at research institutions in the US are the Centers for Disease Control (CDC) in Atlanta, GA, and the National Institutes of Health (NIH) in Bethesda, MD. Between them, these two agencies publish the most important biosafety guidance documents for research: Biosafety in Microbiological and Biomedical Laboratories (BMBL),[3] a joint publication of CDC and the NIH; and the NIH Guidelines For Research Involving Recombinant and Synthetic Nucleic Acid Molecules (NIH Guidelines).[4]

The BMBL has been "the cornerstone of biosafety practice and policy in the United States" since the publication of the first edition in 1984. The BMBL is compiled by a team of dozens of scientific editors from government, academic, and industry settings and includes the work of hundreds of scientific contributors. The BMBL includes sections on topics such as risk assessment, principles of biosafety, and principles of laboratory biosecurity, as well as summary statements on specific considerations for handling of specific categories and species of agents (viruses, fungi, bacteria, parasites, biological toxins, etc). Appendices address issues such as biological safety cabinets (BSCs), decontamination, transportation, and pest management, among others.

The historical origins of the NIH Guidelines are rooted in the 1975 Asilomar Conference on Recombinant DNA,

organized in response to growing concern over potential implications of recombinant DNA technology. The NIH Guidelines were first issued in 1976 and subsequently amended many times. At presstime, new revisions due in the final months of 2018 had not been released.[5] The main body of the NIH Guidelines includes sections on scope, safety considerations, specific types of experiments, and roles and responsibilities of investigators, institutions, and the NIH. The guidelines also incorporate several appendices with technical information related to research with specific biological agents, plants and animals.[6]

All research involving recombinant and synthetic nucleic acid molecules is subject to NIH Guidelines if conducted at institutions that receive relevant NIH funding; furthermore all human gene transfer research involving relevant NIH funding is also subject to NIH Guidelines at every clinical trial site. Additionally, the NIH Guidelines recommend voluntary compliance for research involving recombinant and synthetic nucleic acid molecules even if NIH funding is not involved. Finally NIH Guidelines compliance may be required by local government regulations or by various funding agencies other than NIH itself.

The NIH Guidelines apply to many categories of basic science, preclinical, and clinical research involving microbes, plants, animals and human subjects. A notable research category defined by the NIH Guidelines, Section III-C[7] is **Human Gene Transfer (HGT)** research. HGT research is the deliberate transfer into a human research subject of an investigational product that includes genetically modified components including those derived from recombinant or synthetic DNA or RNA, with the exception of certain very short or molecularly inert nucleic acid molecules. Notably, HGT research includes "gene therapy", as well as a broad range of other applications using genetically modified probiotics, stem cells, vaccines, or viral vectors.

In the past, an NIH committee known as the **Recombinant DNA Advisory Committee (RAC)** played an important role in review and approval of HGT protocols; however in August 2018 the Director of the NIH announced that the role of the RAC would be greatly reduced, such that the RAC no longer has any routine oversight role for HGT research. [8]

For each institution subject to NIH Guidelines, a key component of compliance is registration of an **Institutional Biosafety Committee (IBC)** with the NIH. Currently there are over 1,200 IBCs registered with NIH. The IBC membership at each institution must include both scientific experts with relevant experience and also members of the public to serve as the voice of the local community. The primary roles of the IBC as mandated by the NIH Guidelines are to assure institutional compliance and approve research involving recombinant and synthetic DNA and RNA and genetically modified organisms and viruses. An especially high-profile aspect of this oversight is review and approval of clinical trials involving HGT research. Under the NIH Guidelines, HGT research at an institution must be approved by the IBC prior to enrollment of any subjects. The requirement for IBC approval is separate from and in addition to requirements for review by other entities such as the FDA and the Institutional Review Board (IRB).

Another important role of the IBC is to serve as an advisory body to the institution on all aspects of biological safety. Because of the expertise of the committee membership, many institutions choose to rely on their IBCs to approve a range of research activities that involve infectious agents or biohazards, even if the research does not include genetically modified agents (and thus falls outside of the NIH Guidelines mandate).

As a substitute for—or in addition to—administering its own IBC, an institution has the option of engaging an **externally-administered IBC**, which is operated on behalf of the research site by an external service provider. About a third of all IBCs registered with NIH are externally administered on behalf of research sites. For research such as multicenter clinical trials that extends to multiple sites and institutions, it is important to note that, in general, activities at each site must be approved by an IBC registered for that site. In other words, a clinical trial subject to the NIH Guidelines conducted at twelve clinical trial sites must have twelve IBC approvals. Many

clinical trial sponsors find that it is most efficient to work with a single provider of externally-administered IBC services at all twelve sites (importantly, it is up to each site to decide whether or not to defer to an externally-administered IBC).

Each new biosafety protocol should be designed in consultation with a biosafety expert, and at institutions subject to the NIH Guidelines the protocol must be approved by the IBC (except for certain minimal risk activities that are exempt). Among other considerations, each protocol will describe the containment measures required for safe handling of materials under study. This description will include assignment of a **Biological Safety Level (BSL)** on a scale of BSL-1 (lowest containment) to BSL-4 (highest containment). Research at BSL-1 usually requires simple PPE and usually does not usually require use of a BSC. Research at BSL-2 involves higher-risk infectious agents and generally involves use of a BSC, along with more stringent training. Research at BSL-3 and BSL-4 requires very complex and sophisticated containment facilities, training, and security as well as direct supervision by highly trained biosafety professionals.