Chapter 5

Environmental, Health, and Safety (EHS)

Objectives

This chapter will provide an introduction to the role that Environmental, Health, and Safety (EHS/SHE/HSE) programs play in the operation of a biomanufacturing facility. The foundational elements of EHS are examined; however, the chapter is not intended to serve as a comprehensive study of EHS.

After completing this chapter the student will be able to:

- Explain the importance of effective EHS processes in biomanufacturing.
- Describe EHS regulatory and non-regulatory requirements related to biomanufacturing.
- Describe the role of these regulations and requirements in EHS efforts.
- List general types of hazards associated with biomanufacturing operations and processes.
- Define qualitative and/or quantitative hazard analytical methods used to analyze biomanufacturing systems and processes, including:
  - Root Cause Analysis (RCA)
  - Failure Mode and Effects Analysis (FMEA)
  - Hazard and Operability studies (HAZOP)
  - risk assessment
- Identify the basic biomanufacturing hazard control strategies, applications, and limitations, including elimination, substitution, engineering, administrative, and Personal Protective Equipment (PPE).
- Describe the major components of an EHS program and their purpose in preventing injuries in a biomanufacturing setting.

Terms

Administrative controls: EHS control intended to modify human behavior so that exposure to hazards are either minimized or managed

Agent: chemical agents (solid, liquid, or gas phase) and biological hazards that can potentially cause harm to humans and other living organisms, property, and the environment

Biological hazard: living organism or non-living agent that can cause harm to humans and other living organisms and the environment; examples include bacteria, viruses, allergens, toxins, etc.

Centers for Disease Control and Prevention (CDC): a United States government agency whose mission is to protect health and promote quality of life through the prevention and control of disease, injury, and disability

Chemical hazard: substances in either a solid, liquid, or gas form that can cause health problems, death, and/or environmental pollution; examples include acids, solvents, cleaning agents, etc.

Engineering control: EHS control intended to either eliminate the need for human interaction or physically impede human exposure to a hazard by employing a facility or equipment design; engineering controls include barrier guards, shielding, ventilation, etc.

Environmental Protection Agency (EPA): a United States government agency whose mission is to protect human health and the environment

Ergonomic hazard: stresses created on the human body by repetitive tasks, improperly designed or adjusted workspaces, incorrect use of tools/equipment, etc.; also referred to as a biophysical hazard

Safety Data Sheet (SDS): a vital document that provides information about the properties of a particular chemical, describing details about associated hazards such as first aid measures, accidental measures, exposure controls and personal protection, toxicological information, ecological information, etc.

Occupational Safety and Health Administration (OSHA): a United States government agency whose mission is to assure safe and healthful working conditions for working men and women

Physical hazard: environmental factors such as temperature, pressure, noise, trips/falls, Electromagnetic Radiation (EMR), mechanical forces, and motive forces (electricity, pneumatics); OSHA defines a physical hazard as one that relates to a chemical for which there is valid evidence that it is a combustible liquid, compressed gas, or oxidizers such as organic peroxides, as well as explosive, flammable, pyrophoric (liable to spontaneously ignite in air), unstable (reactive), or water-reactive substances

Personal Protective Equipment (PPE): EHS control intended to provide protection to a worker against potential hazards; PPE consists of specialized clothing and gear, such as lab coats, aprons, gloves, safety goggles, respirators, etc.

Environmental, Health, and Safety Programs in Biomanufacturing

Workers at a biomanufacturing facility can be exposed to a variety of hazards as they perform their daily tasks. Hazards are actions, materials, or situations that can harm or kill people, destroy products, equipment, buildings, threaten a nearby community, and/or impact the environment. Organizations will institute an Environmental, Health, and Safety (EHS) program in order to eliminate or reduce these hazards; the program name may also be referred to as Safety, Health, Environment (SHE) or Health, Safety, and Environment (HSE).

Potential hazards fall into one of the following categories:

- chemical: substances in either a solid, liquid, or gas form that can cause health problems, death, and/or environmental pollution (e.g. acids, bases, solvents, cleaning agents, etc.)
- biological: living or dead organisms that can cause health problems, death, and/or environmental pollution (e.g., bacteria, viruses, allergens, toxins, etc.)
- physical: environmental factors such as temperature, pressure, noise, trips/falls, electricity, etc.
- ergonomic: stresses created on the human body by repetitive tasks, improperly designed or adjusted workspaces, incorrect use of tools/equipment, etc.

Government agencies such as the **Occupational Safety and Health Administration (OSHA)** and the **Environmental Protection Agency (EPA)** enforce regulations related to workplace safety and health and the environment. Thus the requirement to create a safe and healthful environmentally responsible workplace is a key tenet for organizations.

Designing and successfully implementing an EHS program that will achieve the desired vision can prove to be challenging on a number of fronts. While biomanufacturing sectors have a common ground in the specific biologic being synthesized, the sectors themselves have differing, innate hazards depending on scope, scale, and function. In addition, there are differing views that have emerged relative to EHS strategies and there is no consensus on a unified strategy. Therefore each organization selects and implements the strategy that best matches the prevalent culture in that particular environment.

One of the most widely accepted EHS strategies relies on behavior-based programs to identify and control unsafe acts. This strategy is based primarily on an EHS theory published by H.W. Heinrich in 1931. Known as the “safety triangle” or “safety pyramid,” this theory of the cause of accidents attempted to establish an association between the number of unsafe acts that ultimately lead to minor injuries and, over time, to major injuries or fatalities. The safety triangle proposes that for every 300 unsafe acts there are 29 minor injuries and one major injury (Figure 5-1).

Figure 5-1. Safety triangle

Heinrich's theory has been predominant for many decades and has been the basis for many behavior-based EHS programs. These programs attempt to measure unsafe acts and encourage employees to report unsafe conditions. However, the theory itself has problems. While controlling unsafe behaviors has merit, a behavior-centric focus fails to recognize the difficulty associated with identifying and monitoring unsafe behaviors. Oftentimes an unsafe behavior is not recognized as being unsafe until an incident occurs or the potential for one emerges. Ultimately, most safety measurement programs are retrospective, that is, they tally unsafe conditions and incidences after they have presented an exposure to the business.

A more recent EHS strategy centers on risk management. The risk-based approach to developing an EHS program begins with hazard identification and is based on the fundamental rationale that it is the hazard that causes the harm. Through hazard identification and analysis, the true nature of a hazard may be understood. Hazard analysis techniques include:

- Hazard and Operability studies (HAZOP)
- Fault-Tree Analysis (FTA)
- Failure Modes and Effects Analysis (FMEA)
- Root Cause Analysis (RCA)

These techniques can help determine the way in which a hazard manifests, the conditions that can create exposure to the hazard, and the nature of the harm that might result. The proactive nature of this approach permits predictive analyses to determine the probability and severity potential associated with the hazard. These concepts will be explored more comprehensively later in this chapter.

The more complete understanding of how a hazard could present itself and how injuries could occur provides a better opportunity to design an EHS program that best addresses the hazard itself. It is important to note that risk-based strategies do not ignore the correlation between unsafe behaviors and undesired EHS performance. Risk-based models embrace behavior-based models as one of several underlying causes and attempt to rationalize the stimulus that initiates the unsafe behavior.

Despite the varying perspective associated with EHS philosophy, four concepts exist that are fairly consistent among and within all EHS programs:

- Senior management commitment and leadership: EHS success must begin with engagement at the senior-most leadership positions. The first step is to establish a believable EHS vision. More importantly, the leadership must be engaged and active. This means being visible, leading by example, and inspiring others to do the same.
- Line leadership and ownership: While senior management may be responsible for setting the EHS tone, it is the line managers and supervisors who establish and reinforce the culture needed to achieve EHS success. Line managers and supervisors must make EHS their first priority. All business and operational meetings must begin with EHS topics. Emerging EHS issues must take precedence over ongoing operational issues.
- Meaningful employee involvement: Having a trained, committed, and empowered workforce is requisite to achieving EHS success. When employees have the ability to identify EHS issues and the support from their leadership to invoke lasting changes, sustained EHS performance can be achieved.
- Engagement of EHS professionals: EHS specialists play a key support role, providing critical expertise, knowledge, and skills to help achieve EHS objectives. Their involvement in all facets of the EHS strategy can help to assure that the desired performance objectives are achieved.

Along with these concepts, an EHS culture can be achieved by ensuring that the EHS strategy includes the following vital elements:

- Clear roles and responsibilities: Defining the EHS expectations at all levels, from operational personnel up to and including the senior-most leadership, provides direction. Establishing and publishing these expectations sets the EHS tone and drives the culture.
- Hazard identification and analysis: All biomanufacturing sectors must understand the nature of the hazards specific to their respective workplace and institute strategies relative to these hazards that achieve the EHS mission.
- Focus on Continuous Improvement (CI): EHS strategies are, by nature, dynamic; they change in response to the continually-changing workplace. Most successful EHS strategies are rooted in this understanding and seek to continuously improve. One way to do this is to employ what is called the Plan-Do-Check-Act (PDCA) cycle (Deming). This cycle iteratively calls for the creation of a plan (Plan), execution of the plan (Do), observing the results (Check), and adjusting as necessary (Act). Routinely applying Plan-Do-Check-Act methodologies can help to test the efficacy of the existing EHS strategy and identify areas requiring improvement.
- Effective two-way communication: Creating a culture of open communication between personnel on the operational floor and the leadership must be promoted to ensure that

early detection and intervention can be achieved. Effective two-way communication can also serve to demonstrate management's commitment to the EHS mission objective.

- Active and visible EHS initiatives: An active EHS committee can serve as a means to directly engage operational personnel. Additionally, formal EHS committees can review the efficacy of the overarching EHS strategy and programs, ongoing challenges, countermeasure strategies, incident statistics, and causal factors and serve as a liaison between the employees and the leadership community. Frequent EHS inspections and audits can reinforce the importance placed on EHS programs and can also identify previously undetected hazards and hazardous situations. "Stand-downs" that temporarily suspend manufacturing operations in favor of EHS training, awareness, or incident investigations can also highlight the leadership commitment.

Incorporating these elements into the EHS program is the first step toward developing a complete EHS strategy. Once the program and strategy are developed, an understanding of the regulatory requirements of government agencies is vital.

Regulatory Requirements and Guidance

All EHS strategies have a common thread- the necessity to ensure regulatory compliance. A regulatory focused program can in many ways help frame the structure and content of the EHS program. Many of the requisite hazard control methodologies in the biomanufacturing industry are dictated by these regulations. To understand the goal behind regulatory compliance, it is helpful to first understand the origin of safety related regulations in the United States.

In the 19th century, the Industrial Revolution drove technological advancement at an unprecedented pace, and with that growth unforeseen hazards emerged that were inherent to manufacturing processes. Companies were driven by profit, with little concern about the safety of its workforce. The labor force at the time was primarily untrained and had little understanding of safety. The need to work and earn money outweighed any potential hazards on the job. As a result, a massive number of serious injuries and fatalities resulted. The National Safety Council has estimated that between 18,000 and 21,000 laborers died from work related injuries in 1912, and the Bureau of Labor Statistics recorded approximately 23,000 workplace deaths in 1913; at the time there were approximately 38 million active laborers working in United States industries. Using an Injury and Illness Incidence rate formula from the United States Department of Labor, 60 workers out of every 100,000 could expect to die at work each year (based on 100 employees working 40 hours per week across 50 weeks).

During subsequent decades, public demand, government intervention, and organization cultural changes led to the development of regulations and increased awareness of safety. Figure 5-2 illustrates the overall decrease in workplace fatalities during the late 20th and early 21st centuries.

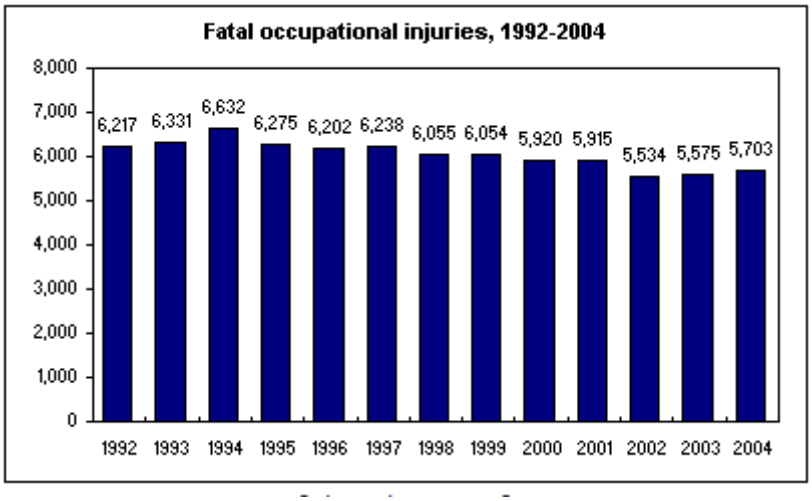

Figure 5-2. U.S. fatal occupational injuries showing an overall drop

Former Secretary of Labor Hilda Solis offered this sobering reminder of the need to remain vigilant and strive for continuous EHS improvement:

> "With every one of these fatalities, the lives of a worker's family members were shattered and forever changed. We can't forget that fact."

In 2008 the number of fatalities stood at 5,071. With a labor force of approximately 155 million, the fatality incident rate had fallen to 3.3 per 100,000 employees.

OSHA

The decline in occupational fatalities can be attributed to a variety of initiatives. In 1970 Congress enacted the Occupational Safety and Health (OSH) Act. This act was seen as an initiative to improve the welfare of the labor force and effectively called for industry to improve its collective health and safety performance. Perhaps the most important element of this act is contained in Section 5, widely referred as the "General Duty Clause." This clause sets forth responsibilities for all employers and employees as follows:

(a) each employer:

(1) "shall furnish to each of his employees employment and a place of employment which are free from recognized hazards that are causing or are likely to cause death or serious physical harm to his employees."

(2) "shall comply with occupational safety and health standards promulgated under this Act."

(b) each employee:

(1) "shall comply with occupational safety and health standards and all rules, regulations, and orders issued pursuant to this Act which are applicable to his own actions and conduct."

The OSH Act laid the groundwork for the establishment of the Occupational Safety and Health Administration. OSHA's stated mission is to prevent workplace related injuries, illnesses, and deaths. In order to accomplish this mission, OSHA:

- promulgates regulations (also referenced as standards)
- coordinates enforcement activities
- assists and encourages the states in their efforts to assure safe and healthful working conditions
- provides for research, information, education, and training in the field of occupational safety and health

There are no specific biomanufacturing regulations as of yet, but OSHA has many requirements that all industrial settings are obligated to meet. Examples include electrical safe work practices, confined spaces, bloodborne pathogens, hearing and eye protection, and the control of exposures to hazardous materials and agents (Figure 5-3). OSHA also addresses specific types of workplace environments with regulations such as the control of hazardous chemicals in laboratory environments.

Figure 5-3. Warning signs for hazardous conditions that OSHA regulates

EPA

Similar to the origin of workplace safety initiatives, public awareness regarding environmental pollution played an important role in driving action by the federal government. An enduring legacy of the Industrial Revolution, as well as massive industrial expansion resulting from two World Wars, created widespread contamination of soil, water, and air in the United States. At the time there were no regulatory restrictions placed on the discharge of industrial wastes by companies, and no serious regard for the cumulative effect on the environment was ever made.

In the summer of 1957 Rachel Carson, a biologist working with the United States Fish and Wildlife Service, received a letter from a friend in Massachusetts describing how the use of DDT to control mosquito populations had resulted in the death of songbirds. Carson investigated the situation and used her observations as the basis of a book, *Silent Spring*, which she published in an effort to bring the environmental situation fully into the spotlight of public opinion:

> "Over increasingly large areas of the United States spring now comes unheralded by the return of birds, and the early mornings are strangely silent where once they were filled with the beauty of bird song."
>
> *Silent Spring*, 1962

As public awareness increased, the federal government was compelled to take action. On December 2, 1970, Congress created the United States Environmental Protection Agency. The EPA was established to conduct research, monitoring, standard-setting, and enforcement activities in an effort to ensure environmental protection. The EPA enforces a myriad of regulations designed to improve environmental conditions, including the:

- Environmental Impact Statements required by the National Environmental Policy Act (1970)
- Resource Recovery Act (1970)
- Federal Water Pollution Control Amendments (1972)
- Regulation of Land Use (1972)

Over the years the EPA has strengthened its resolve to reduce environmental discharge and emissions. The agency revised water pollution legislation in 1972 by shifting emphasis from "water quality" to "effluent limitations" with a goal of "zero discharge." Additional examples of the EPA's efforts can be witnessed in the Resource Conservation and Recovery Act (1976), the Federal Insecticide, Fungicide, and Rodenticide Act (1988), and the Clean Air Act Amendments (1990). The EPA also focused on enforcement and remediation with the Superfund Amendments and Reauthorization Act (1986). These regulations and others like them introduced permit requirements for wastewater discharge, exhaust and stack emissions, and hazardous waste generation, accumulation, and disposal.

The cumulative effect of these collective regulations is difficult to quantify, but the sheer volume of regulations and the restriction of discharge and emissions have helped improve environmental conditions in the United States since their inception. The future focus on the environment may well be driven by the international community, as evidenced by worldwide initiatives intent on reducing greenhouse gas emissions.

Other guidance

Federally required regulations are not the only influence on an organization's EHS strategy and program. Local, state, and regional agencies can impose additional legal requirements, which are typically more restrictive than federal requirements. Special interest and environmental advocacy groups, customers, funding providers, and landlords may artificially impose EHS performance expectations by applying pressure directly (in contracts) or indirectly by attempting to influence the public perception.

Additionally, there are organizations that provide industry-wide recommendations. The principle objective of these additional sources of guidance is to provide a technical common ground for safeguarding workplaces, consumers, and the environment. The guidance can specifically serve as the basis for EHS legislation; facilitate fair trade practices between

countries; set social responsibility baselines; encourage safer, cleaner, and/or more efficient manufacturing methodologies; and illustrate industry advances and standardize practices between similar operations. A few examples relevant to biomanufacturing environments are described later in this chapter.

Centers for Disease Control and Prevention (CDC)

One of the most important sources of guidance for the biomanufacturing industry is the Centers for Disease Control and Prevention. The CDC, a government agency, actively works to identify and define preventable health problems. The CDC also leads many efforts focused on developing, testing, and publishing criteria specifically focused on disease prevention and control. Among the many publications offered by the CDC, there are two that have particular importance to the biomanufacturing industry: *Biosafety in Microbiological and Biomedical Laboratories* (BMBL) and *Primary Containment for Biohazards: Selection, Installation, and Use of Biological Safety Cabinets.*

BMBL establishes biosafety levels and associated prudent biosafety practices. While these practices are intended for laboratory environments, the concepts can be scaled to include manufacturing environments where biologic agents dictate such practices. These practices will be explored in greater detail later in this chapter.

The *Primary Containment for Biohazards: Selection, Installation, and Use of Biological Safety Cabinets* also provides biologic containment guidance. While the document specifically provides Biological Safety Cabinet (BSC) design, performance, placement, testing, maintenance, decontamination, and disinfection criteria, it also provides additional criteria for High Efficiency Air Particulate (HEPA) filters, as well as facility and engineering requirements such as secondary barriers and building exhaust. Both publications can be found on the CDC website *www.cdc.gov*.

NIOSH

The National Institute for Occupational Safety and Health (NIOSH), also a government agency, provides specific guidance for preventing workplace illnesses and injuries. NIOSH publishes many guidance documents, including the *Pocket Guide to Chemical Hazards* (Figure 5-4), which provides chemical specific properties, routes of exposure, target organs, exposure symptoms, exposure limits, protection and respirator recommendations, and first aid guidance. NIOSH publications can be found at *www.cdc.gov/niosh/.*

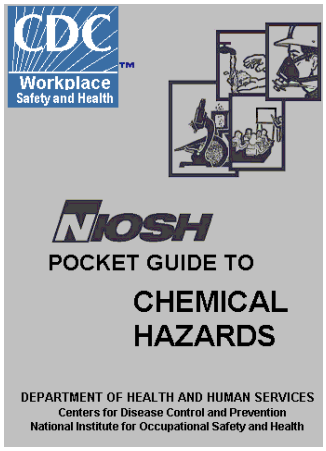

Figure 5-4. *Pocket Guide to Chemical Hazards*, published by NIOSH

Fire and building codes

Many municipalities around the world have established fire and building codes that set criteria intended to prevent, control, and mitigate fires. Enforcement of these codes is often administered by the local fire service. Two of the most important codes in the biomanufacturing industry are building codes and fire codes.

Building codes provide specific design and operational criteria associated with specific structure sizes and occupancy types (i.e., residences, assemblies, and industrial processes). Code requirements often include structural designs necessary to resist fire; the number and placement of fire detection and alarm systems; the number and size of egress routes in a structure, placement of mitigating measures such as fire extinguishers and sprinklers; and hazardous material storage limits. These codes also provide installation criteria for electrical systems and open flame sources such as gas-fired boilers with the intent of controlling ignition sources.

Fire codes provide specific design, testing, and maintenance criteria associated with fire safety features such as fire-rated doors and walls, detection and alarm systems, and suppression equipment. These codes also provide specific practices related to unique hazards (i.e., storage, handling and use of flammable, combustible, and pyrophoric materials) and outline additional precautionary measures such as permit processes for hot work activities and pyrotechnic exhibitions. Finally, fire codes often outline enforcement and inspection practices that can be employed by the authority having jurisdiction.

One of the best sources of fire codes is the National Fire Protection Association (NFPA). Established in 1896, NFPA is an international, nonprofit organization that has generated more than 300 consensus codes and standards. A few of the more widely recognized and applied codes include:

- NFPA 1, which provides requirements to establish a baseline level of fire safety and property protection

- NFPA 70, which summarizes electrical design and installation practices
- NFPA 101, which sets forth minimum design requirements needed to protect building occupants from fire, smoke, and toxic fumes

A complete list of NFPA standards can be found at *www.nfpa.org*.

Hazardous materials/dangerous goods transportation

Certain hazardous agents, including biological substances, have internationally enforced air, sea, and land transportation requirements that are intended to assure that the public and the personnel engaged in the transportation of such materials are protected. The protection requirements include rigorous packaging standards to address rough handling, and they guarantee that all liquid materials remain within the package without leaking if the container is damaged. There are also requirements addressing package labeling (using the internationally recognized biohazard symbol, Figure 5-5), manifests, and other documentation to track biological materials during transit, along with vital information necessary in case of an emergency.

In the United States, the Department of Transportation oversees various aspects of dangerous goods transportation. Organizations such as the World Health Organization (WHO), International Air Transportation Associate (IATA), and International Maritime Organization (IMO) provide guidance on such transportation issues.

Figure 5-5. Signs/labels indicating dangerous goods and their associated hazards

ISO

The International Organization for Standardization (ISO) is recognized as the world's largest developer and publisher of international standards. Comprised of a network of national standards institutes across more than 150 nations, ISO is a non-governmental organization that

builds relationships between the public and private sectors in an effort to compile best practices. These best practices are summarized in a series of consensus standards that address a variety of subjects and industries. ISO 14001 outlines specific requirements for compiling an Environmental Management System (EMS). While the standard does not provide specific environmental goals or criteria, it does provide guidance for building the key components needed in the EMS, such as identification of significant environmental aspects, policies and objectives, summation of legal requirements, and documentation of operational methodologies. (Another ISO standard, 9001, is described in ***Chapter 6 Operational Excellence***). Additional information on ISO standards can be found at *www.iso.org*.

International standards

British Standard OHSAS 18000 is an internationally recognized occupational health and safety management system specification. It is comprised of two parts, 18001 and 18002, and was developed in an effort to provide health and safety management system criteria similar to the environmental management system criteria put forth by ISO 14001. While BS OHSAS 18001 specifies elements needed to create an occupational health and safety management system, BS OHSAS 18002 provides general guidance for establishing, implementing, and continuously improving the occupational health and safety management system. More information on these standards can be found at *www.bsigroup.com*.

In the European Union a series of Normatives (standards) has been established and includes three distinct types of requirements—types A, B, and C. Type A standards provide basic concepts, design principles, and general aspects for devices and systems. Type B standards address safety aspects or safety-critical setups and can be applied to an entire series of machines, devices, and systems. Type B standards are further divided into two sub categories—types B1 and B2. Type B1 standards refer to specific safety considerations such as safety distances, surface temperatures, noise reduction, and strategies. Type B2 standards provide safety-critical set-up criteria such as design requirements associated with two-hand controls, safety interlocks, and presence-sensing devices. Finally, type C standards provide detailed safety requirements for a single kind or group of machines.

More information of the European Union Normatives can be found at *www.cen.eu/cenorm/homepage.htm*.

Non-regulated industry standards

The American National Standards Institute (ANSI) has helped compile more than 10,000 industry-wide voluntary standards in the United States, many of which address environmental, safety, and health practices in industrial workplaces. These standards reflect industry best practices, which are accredited by ANSI if they meet requirements for openness, balance, consensus, and due process. A complete list of available standards is located at *www.ansi.org*.

Hazard Recognition, Identification, Analysis, and Risk Assessment

Biomanufacturing EHS strategies must include a system of hazard recognition, identification, analysis, and risk assessment. Recognition and identification are the first steps of any EHS efforts, as they allow an organization to both understand what constitutes a hazard and to identify potential hazards in the workplace.

Recognition and identification

Incidents such as injuries, spills, fires, and explosions can occur as a result of a potential hazard combining with either a straightforward situation or a complex series of variables. Understanding the relationship between hazards and variables and using proactive methods to analyze potential hazards and situations is critical. This can assist biomanufacturing organizations in identifying and preventing an incident or accident.

A hazard, by definition, is a potential source of harm, loss, or damage and poses a threat to life, health, property, or environment. There are many different ways to rationalize and categorize hazards. Traditional methods provide long lists that catalog a mix of hazards, hazardous situations, and conditions. As mentioned in the introduction, one type of hazard recognition uses four categories: chemical, biological, physical, and ergonomic. Another type of categorization uses five primary categories: agents, electromagnetic, mechanical, motive forces, and biophysical. Referring to these two methods of categorization, which overlap in some areas, the remainder of this section will examine each of the nine categories in the following order:

- chemical (also referred to as an agent)
- biological (also referred to as an agent)
- physical (includes electromagnetic, mechanical, and motive)
- ergonomic/biophysical

Chemical and biological hazards are also referred to as **agents**. Chemicals pose a wide range of hazards, and many systems exist both domestically and internationally for characterizing the degree of **chemical hazards**. The Globally Harmonized System of Classification and Labeling of Chemicals (GHS) is an attempt to standardize chemical classification by defining chemical hazard types and correlating these hazards to a category that illustrates the degree of severity (Figure 5-6).

Figure 5-6. Chemical hazard signs and labels

Health issues related to chemical exposure include acute injuries related to corrosion, irritation, and sensitization and chronic illnesses such as germ cell mutagenicity, carcinogenicity, reproductive toxicity, target organ systemic toxicity, and aspiration toxicity. Exposure can occur through skin contact, inhalation, ingestion, or injection. Factors that affect exposure include the chemical's lipid solubility, water affinity and solubility, and particle size. The degree of harm relates to the chemical's toxicity, level of exposure, frequency, and exposure duration.

In addition to adverse health effects, chemicals can also pose a variety of **physical hazards**. Chemicals with distinct physical hazards include:

- explosives
- flammable gases and aerosols
- oxidizing gases
- gases under pressure
- flammable liquids and solids
- combustible solids and dusts
- self-reactive substances
- pyrophoric liquids and solids
- self-heating substances

- substances that emit flammable gases upon contact with water
- oxidizing liquids and solids
- organic peroxides
- substances corrosive to metal

Biological hazards are organisms and products of organisms that can cause harm. Biological hazards in the biomanufacturing industry include bacteria, viruses, and toxins. The **CDC** characterizes biological hazards as Level 1 (have minimal risk of harm or non-infectious), Level 2 (cause mild disease or difficult to contract), Level 3 (cause severe to fatal disease but have readily available vaccines and treatments), and Level 4 (cause severe to fatal disease and do not have effective vaccines or treatments).

Physical hazards can include Electromagnetic Radiation (EMR), mechanical forces, and motive forces. Temperatures and pressures are also categorized as physical hazards, as both high and low levels of each can affect the human body and potentially cause incidents in the workplace. Noise is categorized as well, as is trips and falls. The former can cause hearing damage and stress, affect equilibrium, and cause communication problems, while the latter can occur due to workplace conditions such as wet floors, uneven surfaces, elevated work areas, etc.

Electromagnetic radiation carries energy that may be imparted to the matter that it contacts. Highly energetic short wave EMR (gamma rays, x-rays, and ultraviolet light) can cause harm to DNA, thus resulting in chronic injuries and illnesses over time. Gamma rays have a number of industrial applications, including use as fluid level gauges in biomanufacturing reactors, thickness measuring devices, and laboratory instruments. X-ray uses include radiography, microscopy, and spectroscopy. Ultraviolet light (UV) is often used in sterilization devices, as well as in lasers, spectrophotometry, and other analytical methods. Longer waves tend to impart energy by heating materials, causing more acute injuries. Infrared Radiation (IR) can be used for heating, along with a number of non-heating applications, including imaging, communication, and spectroscopy. IR is not visible to the human eye but can cause significant damage depending on the type of exposure. Microwaves are used in communication, remote sensing, navigation, spectroscopy, and heating devices; they cause dielectric heating within the body and can cause substantial damage, particularly to tissue that does not have the ability to carry heat such as the cornea. Radio and sound waves can be produced by numerous sources. Sound waves above 80dB (referred to as noise) are considered potentially harmful. Harm is dependent upon the amount noise and the exposure duration.

Mechanical hazards are present in machinery and equipment and create various hazards through their motions (e.g., rotation, reciprocation, transverse) and action (e.g., cutting, punching, shearing, and bending). Mechanical hazards can generally be classified as follows:

- point of operation: the location on a machine or equipment where work is performed (e.g., cutting, shaping, or forming of various materials)
- power transmission: components of a mechanical system that transmit energy to the part of the machine performing work (e.g., flywheels, pulleys, belts, connecting rods, couplings, cams, spindles, chains, cranks, and gears)

- other moving parts: parts of the machine that move while the machine is performing work (e.g., reciprocation, rotation, and transverse motions resulting from functions such as feed mechanisms, rollers, and robotic arms)

Motive forces cause a body or mass to accelerate. The hazards result either directly from the force or as the result of its unintended and sudden release. There are various types of motive forces.

Pneumatics, pressurized gases such as air or nitrogen, that are used in cylinders to drive motors, brakes, and hand tools are categorized as motive forces as well. Hydraulics is similar to pneumatics but utilizes pressurized liquids rather than pressurized gases. Steam is used in many facilities as a source of energy to drive turbines and other motors (Figure 5-7). High pressure steam can cause extremely severe burns and can also cut through materials if released through a pin-hole leak.

Figure 5-7. Steam generation system in a biomanufacturing facility

Potential energy is a frequently overlooked latent motive physical hazard. Raised and suspended loads, materials stored on elevated surfaces, and equipment or materials placed above ground level all represent sources of potential energy that have the ability to become kinetic energy if they fall.

Ergonomic/biophysical hazards are the result of physical tasks performed in the workplace (typically in a repetitive way) and are generally caused by a combination of force, posture,

repetition, duration, and frequency. Injuries and illnesses can be acute or chronic repetitive trauma disorders.

None of the aforementioned hazards alone can cause harm. It is only when certain variables come together to create hazardous conditions that the possibility exists. Examples would be: a person knocking over a vial containing a chemical; flammable vapors reaching an open flame; a valve sticking and a process fluid building up in a tank; etc. Hazardous situations often arise as the result of a number of variables that fall into two general categories: hazardous acts and hazardous conditions.

Hazardous acts involve the undesired response of human behavior to a series of external influences. The following are examples:

- operators/technicians may lack sufficient skill and knowledge, causing unintended exposure.
- an experienced individual's overconfidence may lead to an unintentional incident.
- an operator/technician may not recognize the hazards or the way in which a hazard manifests itself.
- operator/technician's attention can wander.
- mundane tasks or lengthy service can lead to the "blinder" effect (tunnel vision) when conducting tasks.
- multi-tasking responsibilities can result in safe practices being ignored or overlooked.
- operators/technicians may intentionally circumvent protective features that inhibit performance.
- production demands such as cost, quality, and cycle-time can lead to poor choices.

Hazardous conditions can be attributed directly to buildings, processes, equipment, and the environment. The following are examples:

- high, low, or unintended flows, pressures, temperatures, and/or volumes can occur due to an equipment failure or malfunction.
- a deteriorating infrastructure or poor maintenance can cause process upsets.
- the design and/or operation of the facility or building, such as confined spaces, elevated work surfaces, and poor housekeeping can create hazardous conditions.
- the external environment, such as adverse weather, can create hazardous conditions.

EHS recognition and identification is an ongoing process, as workplace conditions are in a constant state of change or transformation. It is impossible to compile a comprehensive list of potentially hazardous acts and conditions. The types and number of hazard variables, the way in which these variables can interact, and the potential situation of multiple variables arising at once is limitless. Oftentimes post-incident investigations reveal that the cause of an incident results from either multiple concurring variables or a cascading effect of variables (one leading

to the next). Using multiple approaches and methods can ensure that all hazards are recognized and identified.

To facilitate hazard recognition and identification, a better understanding is required of the potential hazardous acts and conditions that could lead to an incident. To determine which preventive and mitigating measures would be most appropriate, a hazard analysis and risk assessment should be performed.

Hazard analysis and risk assessment

Once hazard recognition and identification efforts are performed in the workplace, the hazards are analyzed and a risk assessment is performed. Hazard analyses can be qualitative, semi-quantitative, and entirely quantitative, with the approach largely dictated by the complexity of the system being analyzed and the type of data available.

The hazard analysis begins with a team of representatives from management, engineering, operations, maintenance, EHS, and other groups as necessary. Personnel with direct experience and knowledge specific to the process being evaluated are a necessity. It is important for the team to recognize that processes, workplaces, conditions, and practices frequently change; as a result, it is necessary to review hazard recognition/identification and analysis results in response to these changes. The review can involve simply validating existing analyses and results but could also require conducting an entirely new analysis. A simple yet effective method involves inspections and Internal Compliance Audit techniques to identify hazardous conditions and EHS program gaps. Inspection tools typically catalog conditions of concern related either to the workplace environment, the process, or employee behaviors. Compliance audits often use protocols that describe elements of a management system and guide the auditor to explore evidence of implementation in the operational setting.

As mentioned earlier, the method and approach used by the team during analysis is dependent upon the complexity of the system and type of data available. There are many options available to the team where the method choice is concerned.

Job Hazard Analysis (JHA), also referred to as Job Safety Analysis (JSA), is a relatively simple and effective technique used to analyze the tasks associated with a job and identify the associated hazards. A JHA begins by listing all of the steps necessary to perform a particular task: the hazards associated with each task step are identified, along with the potential consequences, causes, contributing factors, and probability of occurrence. Existing or potential methods to control the hazard are then evaluated.

Root Cause Analysis (RCA) is often used following an incident to understand how the event occurred. The general process involves:

- determining a problem statement (what is the event?)
- gathering evidence
- determining why the event occurred
- ascertaining causal relationships
- identifying which causes, if removed or changed, will prevent recurrence

- implementing preventive measures
- assessing if preventive measures were successful

There are many techniques available in determining the root cause of an incident, but a very common approach is to ask the “5 Whys” in order to determine the root cause. The technique is to ask a "why" question concerning an issue with the incident. After the question is answered, a follow-up "why" question concerning that answer is then asked. This continues until the root cause is revealed. This technique applies to any troubleshooting situation, including process operations, quality, etc. Table 5-1 is an example of the “5 Whys” process.

Table 5-1. Example of “5 Whys” Process

Why did an alarm go off for the tank?
Because there was too much liquid flowing into it and the level rose.
Why was there too much liquid flowing?
A valve was stuck in the open position.
Why did the valve get stuck open?
The valve positioner failed.
Why did the valve positioner fail?
It was not properly maintained.
Why was the valve positioner not properly maintained?
A preventative maintenance schedule was not used to keep the valve in good working condition.

Failure Mode Analysis (FMEA) is a study of component failures and the resulting event. An FMEA generally involves reviewing process drawings or diagrams that include all components that could fail, such as valves, pumps, controllers, etc. Failure modes are considered for each of these components related to the way in which the component functions (e.g., a valve can be positioned in an open, closed, or mid position). The worst credible consequence of the failure mode is evaluated, and a risk value is assigned based on the probability and severity potential. The information derived during the analysis is then used to implement risk minimization strategies.

A Fault-Tree Analysis considers all potential undesirable outcomes that could result from a specific initiating event (Figure 5-8). Boolean logic (*If, Then, Else*, etc.) and graphical symbols are used to create a tree. This method can help predict the possible independent paths that could cause the primary failure or event. Probabilities can be applied, either qualitatively or semi-

quantitatively, using failure rate data to predict probability of occurrence of the undesired event.

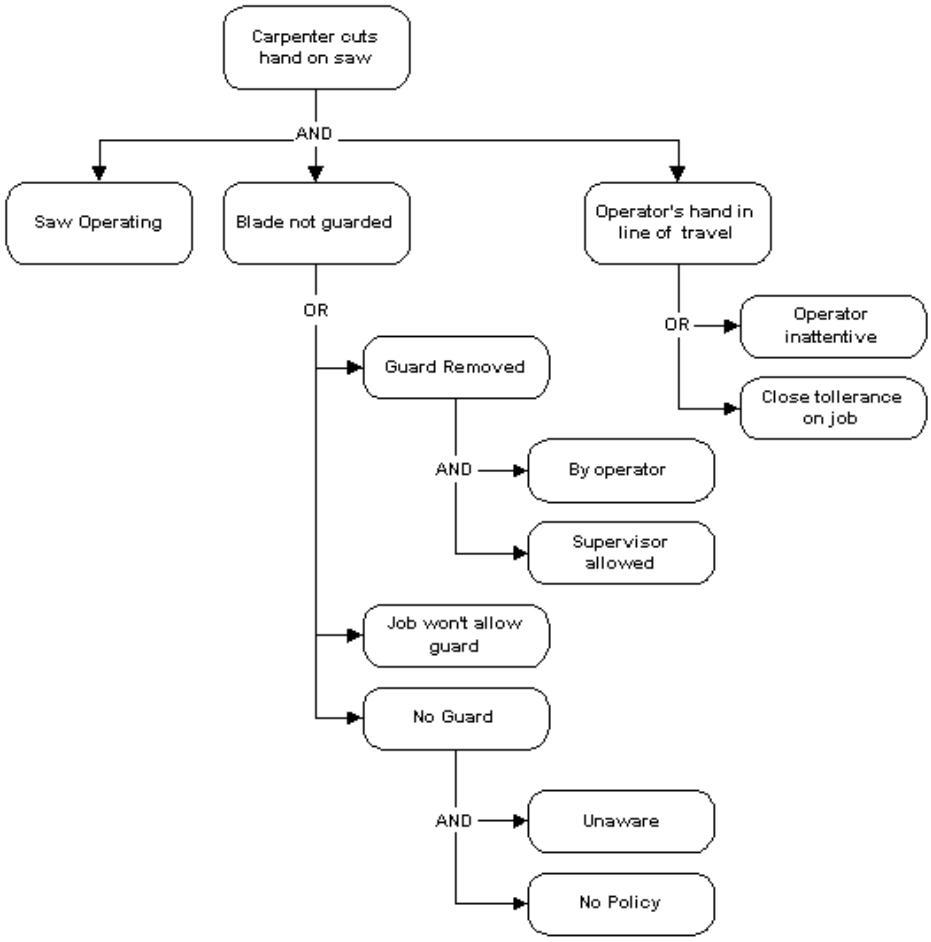

Figure 5-8. Example of a Fault-Tree Analysis

Hazard and Operability (HAZOP) studies are systematic examinations of a process or operation designed to consider and evaluate potential problems. The HAZOP technique relies on guide-words and process variables to help an analysis team step through various operational scenarios that could emerge. This method can be applied in a number of different formats.

Once an analysis has been conducted and hazards and their manifestations have been identified, risk assessment can be performed to estimate the severity potential and probability of an incident occurring associated with the hazard. Risk assessment begins by estimating the worst credible consequence associated with a hazard. Severity of harm addresses the degree of injury or illness that could occur. The severity potential is often characterized qualitatively based on the collective judgment of the team using terms similar to the following:

- catastrophic: death or permanently disabling injury or illness (unable to return to work)
- serious: severe debilitating injury or illness (able to return to work following a recovery period)
- moderate: significant injury or illness requiring more than first aid (able to return to work relatively quickly)
- minor: no injury or slight injury requiring no more than first aid (little or no lost work time)

Once the risk assessment team has considered the severity potential, the probability of occurrence can now be estimated. Probability of occurrence is estimated by taking into account a number of variables, including:

- the frequency, duration, and extent of use or exposure
- the effectiveness of existing and proposed controls
- the skill, training, experience, and awareness of the personnel involved
- incident and near-miss history (Note that neither the absence of an accident history nor a small number of accidents over a long operating history should be taken as an automatic presumption of a low probability.)
- the workplace environment, including elements such as workplace layout, lighting, noise, ventilation, temperature, and humidity
- equipment and system reliability rates

As with severity estimation, the collective judgment of the team is often used to apply a qualitative estimate to the probability. Probability can be described using terms such as:

- very likely (certain, high)
- likely (medium)
- unlikely (low)
- remote (negligible/so unlikely as to be near zero)

Using the severity and probability estimates, the analysis team can assign a level of risk and create a risk matrix. An example risk matrix is shown in Figure 5-9.

		Severity Potential			
		Catastrophic	Serious	Moderate	Minor
Probability	Very likely	High	High	High	Medium
	Likely	High	High	Medium	Low
	Unlikely	Medium	Medium	Low	Negligible
	Remote	Low	Low	Negligible	Negligible

Figure 5-9. Example of a risk assessment matrix

The risk assessment process yields a level of risk (probability of occurrence of harm and the severity of that harm). The team must then determine whether the resultant risk is tolerable. If each risk is not initially tolerable, protective measures need to be applied which will decrease either the severity of harm or the probability of the occurrence of that harm. The selection of one or more of these measures is to proceed until the associated risk is tolerable.

Some of the tools described in ***Chapter 6 Operational Excellence*** can also be used for performing various hazard analysis and risk assessment tasks, such as the fishbone diagram, process capabilities diagram, and Pareto chart.

Hazard Protection and Control Strategies

Risks can be reduced by either addressing the potential severity of harm presented by the hazard; decreasing the possibility of encountering the hazard; or reducing the potential exposure to the hazard. These fundamental approaches are the key to a hazard control strategy known as the hierarchy of controls, which involves listing the protective measures from most protective to least protective. The hierarchy controls should be applied in the following order when possible:

- elimination of the hazard by design or substitution
- **engineering controls** (equipment and facility design)
- **administrative controls** (protective practices and techniques)
- Personal Protective Equipment (PPE)

Elimination involves removing the hazard entirely and can be achieved in the following ways: by modifying the physical features of a piece of equipment so that the hazard is no longer present; by stopping the task that requires interfacing with the hazard; or by moving the location of operator interface with the hazard so that the exposure is eliminated. Substitution involves limiting the potential severity that a hazard can impart. This can be achieved through the use of less toxic materials and substances and reducing inherent process properties such as energy, force, mass, or volume.

Engineering controls involve introducing features that either eliminate the need for human interaction or physically impede human exposure to the hazard. Engineering controls include barrier guards and shielding; devices such as light curtains and safety curtains; process controls such as interlocks (special controls that prevent a particular event from occurring without some type of human interaction), and automatic intervention for upset conditions.

Administrative controls are intended to modify human behavior so that exposure to hazards are either minimized or managed. Administrative controls can include signs designed to highlight the presence of a hazard; procedures that describe hazards and the instructions necessary to avoid harm; and training on hazards/avoidance.

Personal Protective Equipment (PPE) refers to clothing, respirators, headgear, eyewear, boots, and other garments that provide protection from hazards. It is the last measure of defense for hazards that have not been eliminated. Indeed, employing PPE accepts that exposure and frequent interaction with the hazard is expected. Additionally, PPE requires a conscious choice by the user to correctly wear/use the equipment, inspect it, and maintain it. PPE can have limits to the duration of protection afforded and can be easily compromised.

Though the following is not a comprehensive list, PPE, depending on the type employed, can protect against hazards such as:

- impact by blunt and sharp objects
- electrical energy
- electromagnetic radiation
- loud environments
- oxygen rich/oxygen deficient atmospheres
- heat
- chemical splashes/spills
- infectious agents

PPE can include (see Figure 5-10):

- head/eye/face protection (e.g., hard hats, safety goggles, face shields,)
- hearing protection (e.g. ear plugs, ear muffs)
- body/arm/hand protection (e.g., lab coats, gowns, full body suits, coveralls/FRC-Flame Retardant Clothing, aprons/smocks, sleeve protectors, gloves)
- respiratory protection (e.g., masks for air purifying, air line or Self Contained Breathing Apparatus ,SCBA, for air supply)
- foot protection (e.g., non-skid footwear, safety boots)

Figure 5-10. Examples of PPE

PPE selection can depend on a variety of factors, such as routes of entry (the manner in which a hazard such as a chemical or biological agent can enter the body):

- inhalation: breathing in fumes or vapors
- injection: being cut by a sharp, chemically contaminated surface
- ingestion: taking in a chemical substance by mouth (usually by eating or smoking around an area with contaminated surfaces)
- absorption: skin contacting a chemically-penetrating substance

Respirators are a critical form of personal protective equipment. Air-purifying respirators draw contaminated air through a filter to cleanse the air. Air-supplied respirators provide an alternate supply of fresh air. Respirators can have a face piece that covers the entire face and affords some splash protection. A half-face respirator is worn in environments where splashing is not possible and agents are not toxic to the eyes or facial area.

Air-purifying respirators (Figure 5-11) typically rely on two types of cartridges to purify the air; selection depends on the contaminants that need to be removed from the air.

HEPA cartridges can remove as much as 99.97 percent of all airborne particulates 0.3 micrometers in diameter or greater. HEPA filters have a finite life that depends largely on the particulate size and concentration of particles in the filtered air.

Chemical cartridge respirators remove gases, volatile organic compounds, and other vapors from breathing air through adsorption, absorption, or chemisorptions onto a media such as activated charcoal or certain resins. Chemical cartridges also have a finite service life that depends on a number of factors, including the concentration of vapor in the atmosphere, the relative humidity, and the breathing rate of the respirator wearer. When the chemical cartridges become saturated they must be changed.

Figure 5-11. Air-purifying respirator

Other PPE selection factors, along with use, training, fit testing, and related issues are often specific to an organization/facility.

The type and number of required protective measures is determined by the nature of the task and the associated hazard(s). Multiple protective strategies can be used, such as putting an engineering control in place, along with administrative procedures and required PPE. The degree of protection afforded by any single protective measure or combination of protective measures depends on the features associated with the each protective measure selected and the probability that the protective feature functions when needed.

In determining whether a tolerable risk has been achieved, it is beneficial to consider a residual risk level that is "As Low as Reasonably Achievable" or ALARA. The objective of this principle is to minimize the severity potential, or the extent of exposure to the hazard, as much as possible. There must be simultaneous recognition, however, that some exposure may be acceptable when considering business factors such as the degree of risk-reduction benefit achieved through application of additional measures; the technological feasibility of applying additional measures; the economic viability associated with these additional features; and the potential impact on productivity.

The ALARA principle does not place business factors ahead of the welfare of a person; rather, ALARA embraces the concept that any exposure, regardless of size or extent, can result in a negative effect. It does, however, consider the probability of the occurrence of negative effects as a result of the exposure, as well as the impact associated cumulative exposures. Note that it is critical to implement protective strategies that meet regulatory obligations. Risks that represent regulatory non-conformity or present clear threats to people, property, or the environment should never be tolerated.

Biomanufacturing-specific protective measures

Biomanufacturing-specific protection strategies depend first and foremost on attaining primary and secondary containment of hazardous materials. Primary containment is the protection of personnel and the immediate environment from exposure to infectious agents. Secondary containment is the protection of the environment external to the facility. Containment features generally fall in to one of these categories: facility design, equipment, and protective practices and techniques.

The CDC characterizes biological threats into one of four levels. As a corollary to these levels, CDC has assembled criteria that describe the minimum protective features necessary and relative to the degree of the hazard. These biosafety levels are administered in ascending order by the degree of protection afforded to personnel, the environment, and the community. The levels consist of combinations of protective features specifically designed for the operations performed, the routes of transmission of the infectious agents, and the facility function. The specific protective features prescribed by CDC for each biosafety level can be found at *www.cdc.gov*. Biosafety levels are described in ***Chapter 2 Facilities***.

Facility design

EHS-specific containment features related to facility design are described in ***Chapter 2 Facilities***.

Equipment

Biological Safety Cabinets

Biological Safety Cabinets (BSCs) are an important type of biomanufacturing safety equipment and are used to provide protection from splashes and aerosols that can be generated during microbiological procedures. Cabinets are typically used during small-scale work that is often conducted in laboratory settings that includes the handling of biological materials. Larger walk-in cabinets can be designed for pilot and scale-up laboratories but are generally not employed for more hazardous biological materials.

There are three types of Biological Safety Cabinets; the specific design features depend upon the degree of containment desired or needed:

Class I Biological Safety Cabinets are designed to provide personnel and environmental protection only—they do not protect the product. These are negative-pressure, ventilated cabinets and usually operate with an open front and a minimum face velocity at the work opening of at least 75 linear feet per minute. The air is drawn from the front of the cabinet and through a HEPA filter to cleanse the air. The air can be exhausted either back into the room (for extremely low hazards) or into pollution control devices for destruction before exhausting to the environment. Personnel are protected from the biological materials because air is drawn from the room into the cabinet and away from the user. Class I cabinets are suitable for work involving low to moderate risk agents where there is a need for containment but not for product protection.

Class II Biological Safety Cabinets operate on a similar principle to Class I BSCs (e.g., front access openings, inward air flow, HEPA filtering system), but the main difference between Class II and Class I BSCs are that Class II cabinets must also protect the product. As such, Class II cabinets have many sub-classifications according to the method by which air volumes are recirculated or exhausted. Class II cabinets are sub-classified into two types (A and B) based on construction, airflow velocities and patterns, and exhaust systems.

Class III Biological safety cabinets are totally enclosed, airtight, and designed for use with high-risk biological agents (Figure 5-12). Class III cabinets provide the highest level of personnel, product, and environmental protection. These cabinets are operated under negative pressure. The air is drawn in beneath the work surface and back up to the top of the cabinet where it passes through two HEPA filters configured in series (or through a HEPA filter which then enters an incineration chamber before being exhausted outside). Work is performed through attached arm-length rubber gloves or half-suits.

Figure 5-12. Class III Biological Safety Cabinet

BSCs must be maintained in proper working order to ensure functionality. Proper ventilation flow rate is required to create a negative pressure environment that draws the biological contaminant away from the breathing space. As such the flow rate must be routinely measured, and preventive maintenance schedules must be established to inspect and repair ventilation fans. Class III BSCs depend upon uncompromised containment to fully contain the atmosphere and provide the highest level of protection. Inspection of the gaskets and seals should be added to the ventilation system preventive maintenance schedule to verify the containment system integrity.

Process safety equipment

Large-scale biomanufacturing processes often utilize batch mixer vessels, reactors (Figure 5-13) and storage tanks connected in-series by piping. While these systems are designed to efficiently yield large quantities of bio-based products in a cost effective model, the system can contain significant volumes of hazardous materials that must be controlled. The operation of the processes can present a wide range of mechanical and motive force hazards related to pumps, piping, electrical systems, and other necessary equipment. Hazards that are part of industrial processes and systems can be managed by creating an inherently safe operating environment using passive design features, installing active control systems, and instituting procedural methods.

Figure 5-13. Bioreactor

Achieving a state of inherent safety entails removing hazards entirely or reducing the severity potential associated with the hazards and operating conditions. The Center for Chemical Process Safety (CCPS) has established four principles requisite for creating an inherently safe manufacturing environment:

- substitute
- minimize
- moderate
- simplify

Substitution involves using less hazardous materials, chemistries, and processes. The most obvious approach to substitution in biomanufacturing would be to use biological materials that are not known to cause disease in humans or not easily transmitted to humans—as described by biohazard levels 1 and 2.

Where chemicals are part of the biomanufacturing process, substitution includes using less toxic materials; switching to aqueous-based materials to eliminate combustibility and flammability; using pellets (rather than fine powders) that have less surface area and exhibit lower explosivity potential or less potential to hold static charges; and employing compatible chemistries to avoid hazardous reactions.

Relative to the mechanical features of the biomanufacturing processes, substitution involves using equipment that lowers the force, mass, velocity, or energy, such as pumps that require smaller motors.

Minimization seeks to reduce the magnitude associated with an upset condition. This can be achieved primarily through reducing the quantity of hazardous materials used in a manufacturing process. A closed, continuous loop system can contain hazardous materials so that exposure outside the process equipment is eliminated or reduced. Tubular reactors and small scale batch reactors can effectively produce product while requiring less volume. Reduced inventory can permit the use of smaller storage tanks, while smaller piping systems can reduce the volume of process substances in the system.

The techniques of moderation reduce the severity potential that could result from a hazardous event. Moderation can be achieved by operating at less hazardous conditions, employing control techniques to prevent hazardous conditions, and installing features to mitigate kinetic energy during a process upset condition. Diluting the concentration of hazardous materials can not only reduce the severity but also minimize the probability of a hazardous event. Changing process conditions, such as operating at lower temperatures and pressures; employing high-efficiency methods of heat exchange (using a type of equipment called a heat exchanger that draws heat away that can be generated during exothermic reactions); and refrigerating materials that are highly reactive can help ensure that a hazardous event or condition does not manifest.

Simplification efforts enhance the inherent safety of a process by minimizing the potential for a hazardous condition that results from human error or programmable logic complications. Using closed-pipe designs that require no manual connection to transfer reactants to a vessel or using unique hose fittings and couplings that permit connection only to the intended materials can help to prevent the transfer of incompatible materials. Removing obsolescent piping can prevent cross-connection errors. Reducing the complexity of visual control panels; displaying only process critical information; and simplifying procedural instructions can help to promote proper monitoring of operational conditions and avoid inappropriate responses.

Process safety design features can be passive or active. Passive features are intended to function without mechanical or electrical actions, such as using a reactor designed with wall thicknesses, gaskets and seals, chamber fasteners and other structural elements that can withstand and contain the maximum possible pressure resulting from a runaway (out-of-control)reaction. Pressure relief systems can be installed to prevent vacuum and over-pressurization conditions in a vessel. Employing intrinsically safe equipment such as a hermetically sealed motor can keep potential ignition sources separated from flammable vapors to prevent a fire or explosion. Active features, on the other hand, rely on mechanical or electrical actions that are intended to prevent an incident or reduce the severity potential; this is achieved through monitoring processes, detecting deviations and upset conditions, and invoking a response to counter the threat. Controllers referred to as Programmable Logic Controllers (PLCs) can monitor operating conditions such as level, pressure, and temperature. They can be interlocked, or tied, to process equipment such as valves, pumps, and emergency response equipment to automatically trigger corrective actions to process deviations. Smoke and heat sensors can be used to activate a fire extinguishment system (e.g., sprinklers).

Passive and active features are intended to function in the presence of the hazard. System integrity can diminish over time due to improper installation/construction, corrosion, poor

maintenance, damage, or mechanical failure. As a result, it is imperative that passive and active systems are routinely inspected and properly maintained.

Procedural methods related to process safety equipment attempt to improve human reliability and response; examples include Standard Operating Procedures, EHS policies and practices, and emergency action plans. Initial and recurrent training is necessary to ensure that operators/technicians fully understand the procedural methods and execute them properly. Additionally, these methods must be reviewed and updated routinely to account for changes to the process. As previously discussed, human behavior can be unpredictable, so this approach to hazard management should only serve to supplement the more robust hazard prevention and control strategies.

Environmental equipment

Pollution-control devices can be used in biomanufacturing operations to destroy contaminants or remove them from an exhaust stream before they are discharged into the environment. Systems can be designed to destroy, collect, or break down potential contaminants such as particulates, gases, vapors, and biological materials. There are a variety of methods used for the control of pollution in a biomanufacturing environment, including mechanical collectors, scrubbers, thermal oxidizers, and catalytic oxidizers. Some examples of the devices and methods used in the process are as follows:

- biological and particulate matter can be removed from exhaust streams using mechanical collection methods.
- HEPA filters can be installed in exhausting systems to remove particulates using diffusion, impaction, or interception.
- bag houses continuously pull particulate matter from the exhaust (using dust filters with blowers, filter cleaning mechanisms, and dust collection receptacles).
- electrostatic precipitators use an induced electrostatic charge to effectively remove dust and smoke from exhaust streams without substantially impeding exhaust flow rates.
- wet particulate scrubbers use a liquid to remove particulates from the exhaust stream; the exhaust can be sprayed with cleansing liquid or forced through a liquid reservoir.
- gases and vapors can be removed from exhaust streams through thermal oxidizers that use high temperatures to decompose the material. Regenerative Thermal Oxidizers (RTOs) are widely used since they have high destruction effectiveness and can be operated for long continuous processes. A Regenerative Catalytic Oxidizer (RCO) uses a catalyst to allow oxidation at reduced temperatures and lower operating costs.

Protective practices and techniques

Depending upon the biosafety level, protective practices and techniques may include, but are not limited to, the following:

- restricting access to the work area. Special restrictions may be needed for immunocompromised or immunosuppressed persons due to their increased risk of acquiring infections
- employing sound hygienic practices by washing hands after handling hazardous materials, after removing gloves, and before leaving the facility
- prohibiting the storage or use of, tobacco, contact lenses, and cosmetics or the consumption of food and beverages in the work area
- using only mechanical pipetting devices (Figure 5-14) and prohibiting mouth pipetting
- instituting policies to manage the handling, storage, and disposal of objects such as needles, syringes, and other sharp instruments in order to minimize exposure to bloodborne pathogen hazards
- substituting glassware with plastic when possible and implementing practices to address broken glassware through the use of mechanical methods such as brushes, dustpans, tongs, and forceps
- designing operating practices to minimize splashes and aerosols
- implementing decontamination procedures to disinfect equipment, personnel, and facilities both routinely and immediately following a spill of viable material
- posting biohazard signs at the entrance to the laboratory where infectious agents are present
- conducting immunization or testing programs that address the agents handled or potentially present in the laboratory
- compiling, reviewing, and practicing emergency action plans that address spills, injuries, fires, and containment failure

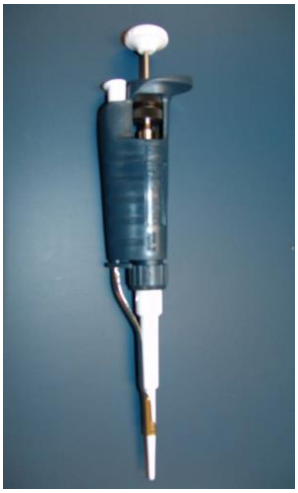

Figure 5-14. Mechanical pipette

Work performed with materials that are more hazardous can also require the following practices:

- ensuring personnel enter and exit through a clothing change area equipped with decontamination shower rooms
- removing and storing personal clothing in outer change rooms
- providing operational clothing for personnel entering the work area and removing soiled clothing in an inner change area so that it can be autoclaved before laundering
- supplying materials needed in the area through a double-door autoclave, fumigation chamber, or airlock that is appropriately decontaminated between each use
- ensuring materials being removed are transferred to a non-breakable and sealed primary container that is then enclosed in a non-breakable and sealed secondary container

Protective practices and techniques alone are not sufficient to address the risk in biomanufacturing environments. These practices supplement the protection from facility design, engineering features, safety equipment, and PPE.

Components of a Biomanufacturing EHS Program

Formalized and well-implemented EHS programs are the foundational element for establishing a proactive, performance-based EHS culture with clear roles and responsibilities. Comprehensive EHS programs can help to communicate hazards, identify practices necessary to minimize exposure and prevent injuries, outline emergency responses, serve as the basis for employee training, and demonstrate the basis for regulatory compliance initiatives. Written EHS program must be designed to meet the needs of the operation, employees, management, facility, and operations, and must clearly define all performance expectations. The remainder of this chapter will examine the major components of a written biomanufacturing environmental, health, and safety program; these components will vary among individual facilities and the operational requirements of each.

Accident reporting and investigation

As employers have a legal responsibility to report and document workplace incidents, all employees must understand their obligation to the same. If an incident occurs, government agencies (e.g., OSHA, EPA, CDC, etc.) may conduct inspections depending on the severity of the incident. As a result, an inspection team will request documents that are related to the incident, including employee-training records, and employees may be interviewed. Additionally, it is necessary for employers to conduct accident investigations so that prevention strategies can be identified and implemented.

Biological and chemical inventory

Controlling biological and chemical materials begins with the understanding of an accurate inventory. A careful system to acquire, store, and distribute hazardous materials can help to

create an inherently safe environment and prevent materials from being removed from the facility inappropriately.

Bloodborne pathogens

OSHA requires employers to construct a bloodborne pathogen (e.g., Hepatitis B and C, HIV) exposure control plan, which must be kept current to reflect changes in technology that eliminates or reduces exposure to such pathogens. Employers must also maintain a "Sharps Injury Log" for recording percutaneous injuries from contaminated sharps.

Communication

A system must be implemented that promotes open dialog between employees and members of leadership in order to promote early intervention strategies and continuous improvement. An employer should be willing to field and address complaints of unsafe practices or improvement suggestions in a way that prohibits or eliminates employee fear of retribution.

Confined space entry

Employers must create a confined space entry program that includes a written permit process. Permit-required confined spaces and their potential hazards must be identified, and before anyone enters such as space a permit must be issued. The permit must address hazard identification relative to the space, hazard control methods, entry procedures, surveillance of personnel entering the space, and procedures for a possible rescue.

Emergency Action Plans (EAP)

EAPs must be compiled, addressing responses to spills, injuries, illnesses, fires, and other events. Evacuation routes must be identified to facilitate exit from an area or facility in an emergency (Figure 5-15). EAPs should be practiced routinely to ensure all applicable personnel are prepared in case of an emergency.

Figure 5-15. Clearly marked exit routes

Employee responsibilities

There must be a clearly defined set of responsibilities for all employees. Employees should be informed and understand that EHS is the primary objective in every operational activity and that failure to comply with EHS expectations can result in progressive enforcement actions such as verbal reprimands, write-ups, suspension, and dismissal.

Ergonomics and human factors

Specific operating practices should be defined so that employees can properly and safely deal with ergonomic-related hazards. For example, lifting a light weight might simply require proper lifting using the legs, while lifting a moderate weight might require a two-person lift. Lifting heavy weights might require a lift-assist device. A workforce that is well informed on ergonomic issues will aid the organization in reducing or eliminating the possibility of these types of hazards or incidents.

Fire prevention/protection

These plans differ from Emergency Action Plans, as fire prevention and protection plans should include inspection, testing, and maintenance of fire protection systems such as alarms, sprinklers, fire barriers, and exit routes. These plans should also address storage and management of flammable and combustible materials.

Fleet safety

Transportation (trucks, forklifts, etc., Figure 5-16) presents a variety of hazards, and each year transportation-related accidents are a leading cause of workplace fatalities. Workplace plans should address safe transportation practices. Haulers of hazardous materials have additional requirements, including manifest requirements and incident response instructions that should be outlined in the fleet safety plans.

Figure 5-16. Forklifts are used to move materials from off-loading points to warehouses.

Hazard Communication (HazCom)

The purpose of a Hazard Communication program is to ensure that information concerning hazardous agents is made available to all employees. An effective hazard communication program will include hazard labeling on containers, warning signs for the workplace, and Safety Data Sheets (SDSs)—documents that provide important information about chemicals. An effective hazard communication program also includes hazard orientation and training for all employees.

Hearing protection

A manufacturing environment can be noisy due mainly to operating equipment (pumps, compressors, etc.) and material flow through systems. Noise, any unwanted sound, can cause temporary or permanent hearing loss/reduction, distraction, communication problems, and psychological effects. OSHA regulates noise exposure and duration through monitoring, medical monitoring (e.g. hearing tests), hearing conservation, noise controls, training, and PPE (e.g., ear muffs, plugs). It is imperative that an organization develops a plan to address these areas.

Industrial hygiene

Industrial (or occupational) hygiene is the science of anticipating, recognizing, evaluating, and controlling workplace conditions that can, according to OSHA standards, cause illness or injury to workers. Industrial hygienists use environmental monitoring and analytical methods to detect the extent of worker exposure then work to eliminate/reduce these hazards through EHS efforts. Much of the information derived during industrial hygiene activities is used to protect employees; the results of these efforts are used to implement hazard control strategies and train employees. As with all similar activities, the strategy and methods used to characterize workplace hazards should be documented.

Lockout-Tagout (LOTO)

Lockout-Tagout involves the control of hazardous energy by isolating an energy source (such as electricity or hydraulics) from a piece of equipment (Figure 5-17). LOTO protects workers from the accidental release of energy (such as that associated with equipment start-up) while performing tasks such as maintenance. Job-specific procedures must be compiled for each task performed at the workplace that address the scope, purpose, authorization, rules, and techniques to be used for the control of hazardous energy. Additionally, specific procedural steps must be documented for shutting down, isolating, blocking, and securing equipment to control hazardous energy. The placement, removal, transfer, and responsibility of locks or tags must be defined. Most importantly, a method must be identified to verify that the hazardous energy has been isolated.

Figure 5-17. Example of a lock and tag on an energy source

Machinery safeguarding

Machinery safeguarding involves protecting workers from the point of operation for a machine or piece of equipment. The point of operation involves actions such as rotating, moving, cutting, etc. A machine guard or barrier prevents the worker from accidentally making contact with the point of operation. Procedures should define how to operate equipment with machinery safeguarding in place.

Management of Change (MOC)

A sound EHS policy should include a methodology to update specific procedures and practices when changes occur to operating conditions, materials used, equipment, etc. EHS programs should be reviewed periodically to ensure they remain current.

Materials handling and management

The method to acquire, store, and transport materials inside the operational areas, as well as the personnel responsible for such activities, should be defined in the EHS program. This can help to prevent the incorrect use of material management equipment and supplies.

Measures to track performance

There are a number of measures that can be used to track a facility's EHS performance, including: OSHA recordable incidents and lost time rates, spill and release data, workplace inspection and audit observations, and behavior-based observation results. The specific measures and performance objectives should be included in the EHS program.

Natural disaster response and recovery

Every EHS program must address potential risks to the region in which the facility is located. These include risks from such events as floods, tornadoes, snowstorms, hurricanes, wild fires, and earthquakes. In certain situations, “sheltering in place” plans must be implemented. Preparing the facility for emergency mode, as well as getting the facility back up after the emergency, is an important part of planning.

Personal Protective Equipment (PPE)

Procedures should be in place to summarize when PPE is required. Additionally, the procedures should identify PPE selection (such as gloves, Figure 5-18), inspection, use, testing, wearing (donning and doffing practices), storage, maintenance, and disposal methods.

Figure 5-18. Glove selection is based on the materials being handled

Process safety

OSHA's 29 CFR 1910.119 Process Safety Management (PSM) regulation requires written information to be compiled to enable both the employer and the employees involved in operating the process to identify and understand the hazards posed by the process. Process safety information must include the hazards of highly hazardous chemicals used or produced by the process, the technology of the process, and the equipment used in the process. Additionally, the PSM regulation requires operating procedures to be compiled that indicate the safe operating steps, the consequences of process deviation, and the steps necessary to prevent or mitigate process upsets that could lead to catastrophic events.

Recordkeeping

The FDA requires several types of documents related to the production of biopharmaceuticals. For EHS-related issues, other government agencies (OSHA, EPA, the Department of Transportation, etc.) require documentation as well. This documentation involves topics such as accident reporting, training, and inspections. Additionally, there is often an accompanying requirement regarding retention of records; strategic-level policies should be established that define recordkeeping practices.

Respiratory protection

OSHA regulations address a variety of issues related to respiratory protection, including ventilation, hazardous materials, PPE, confined space entry, and HAZCOM. A facility's respiratory protection plan should address employee training, medical certification, fit testing, and other related topics.

Security

Measures should be documented that define how a facility's perimeter, process, assets, and personnel are to be protected (***Chapter 2 Facilities***). Additionally, expectations are set regarding the use and possession of hazardous devices, prohibited items, and elicit materials, as well as those regarding personal behavior.

Training

EHS programs should identify requisite training efforts necessary to perform specific tasks, as well as how the training will be provided. Training should generally be administered to new employees; when changes occur in the operation; as the result of performance deficiencies; and when new hazards are identified. The organization should determine the frequency for each individual topic; however, some government regulations specify training requirements and frequency. Furthermore, training records for every employee should be maintained and should provide evidence of attendance.

Waste management

All manufacturing processes generate waste. Understanding how to manage the waste is a critical regulatory compliance element. The procedures for accumulating, storing, and shipping solid hazardous waste must be specific and clear so that employees can execute the program properly. Situations in which effluent discharge or airborne emissions are acceptable must be defined by plant permits, which should also be attached to the EHS program.

Check Your Knowledge

1. The safety triangle proposes that for every 300 unsafe acts, 29 minor injuries occur and how many major injuries?

   a. 1
   b. 2
   c. 4
   d. 5

2. What types of hazards are also referred to as agents?

   a. chemical
   b. biological
   c. chemical and biological
   d. chemical, biological, and physical

3. Short wave EMR can cause harm to what type of genetic material?

4. Which of the following is NOT a motive force?

   a. electricity
   b. pneumatic
   c. hydraulic
   d. ergonomic

5. Hazardous _____ involve the undesired response of human behavior to a series of external influences.

6. Which of the following is often used following an incident to understand how it occurred?

   a. Job Hazard Analysis
   b. Fault-Tree Analysis
   c. Risk Assessment
   d. Root Cause Analysis

7. What is the most preferred way to control a hazard?

   a. PPE
   b. engineering
   c. elimination
   d. substitution

8. Air-_____ respirators draw contaminated air through a filter to cleanse the air.

9. What does the "R" stand for in ALARA?

   a. rational
   b. reasonably
   c. reduction
   d. recognition

10. Class _____ Biological Safety Cabinets provide the highest level of personnel, product, and environmental protection.
11. What is a vital document that provides important information about a chemical?
    a. HAZCOM
    b. EAP
    c. MSDS
    d. MOC
12. What term describes the control of hazardous energy by isolating an energy source (such as electricity or hydraulics) from a piece of equipment?)

Activities

1. Select an everyday activity and identify all the potential hazards associated with it. Make a list then describe ways those hazards can be reduced or eliminated.
2. Choose a recent industrial incident and research what happened. Were there any injuries or fatalities? What property damage was done? Was the environment impacted, and what were the suspected cause(s)? Write a two-page report.
3. Locate an MSDS for a chemical used in your school or workplace. Read through the MSDS and discuss your findings with you classmates, such as the substance identification, hazards, first aid, accidental release measures, exposure, PPE, etc.

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