Key Features of a Biosafety Program for the Biopharmaceutical Industry

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KEY FEATURES OF A BIOSAFETY PROGRAM FOR THE BIOPHARMACEUTICAL INDUSTRY

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Prevention of microbial contamination and assurance of microbial control in the development, manufacture and testing of parenteral biopharmaceutical therapeutics and vaccines are critical to personnel safety and the environment. Biological agents including pathogens may be utilized to produce or test parenteral medicines, presenting potential exposure considerations for operators and analysts. Many of the same principles of microbiological contamination control, and good manufacturing practices (GMPs) which enable product quality and safety, apply to biosafety, with the focus on containment and worker protection.

This chapter focuses on the prevention of release of biological agents including microorganisms and the protection of research, manufacturing and quality control personnel from exposure to these agents, which may be utilized to develop, manufacture and test medicines and provide life-changing and life-saving parenteral

drugs to patients. It also provides guidance on the occupational health and safety aspects of cleaning and disinfection operations.

This chapter is organized as follows:

- Relevance of biosafety to drug development, manufacturing and testing operations
- The importance of biosafety: impacts of exposure
- Key features of a biosafety program
  - Regulations
  - Biological risk assessment/risk factors
  - Applying Hierarchy of Controls (HoC) to prevent exposure
  - Medical surveillance
  - Incident investigation and emergency preparedness
  - Communication
- Future challenges of biopharmaceutical biosafety
- Conclusion
- References

RELEVANCE OF BIOSAFETY TO DRUG DEVELOPMENT, MANUFACTURING AND TESTING OPERATIONS

Historically, biological manufacturing has evolved from the production of vaccines and toxoids, to biopharmaceuticals including recombinants and monoclonal antibodies and the application of advanced therapy medicinal products (ATMPs) e.g., protein and gene therapies. This has resulted in a diverse range of biological agents being used to develop and produce medicines and to a greater focus on prevention of biological agent release to ensure the protection of personnel and the environment. The complexity related to risk assessment of some of these agents may be greater than those of more conventional large molecule, biotech manufacturing processes because they may have genetically novel

properties and limited published data on the impact of exposure to personnel or the environment. A resulting biosafety breach may be prevented with compliance with appropriate regulations and appropriate precautions based on accurate risk assessments conducted throughout the agent's lifecycle. A biosafety breach in the manufacturing process may also impact business continuity and reputation.

An overview of typical biological operations used for parenteral drug production and quality testing and biosafety program recommendations are summarized within Table 1 below.

Table 1 Worker biosafety risk assessment summary of selected parenteral drug production and quality testing operations)National Institutes of Health, 1988)

Operation or scenario	Typical worker biological risk level	Precautions and biosafety measures
Chinese Hamster Ovary (CHO) mammalian cell culture	NIH-GLSP or Risk Group (RG) 1 classification	Standard microbiological practices
GLSP GMO bacterial fermentation (e.g., K12-eColi, etc.)	NIH-GLSP or RG 1 classification	Standard microbiological practices
Bacterial (pathogenic) fermentation of vaccine intermediate materials	RG 2 and RG 3 pathogens	Comprehensive worker biological safety and infection control program required for processes with viable organisms
Live-virus (pathogenic) culture in chicken ovum or other cell line (insect, plant, mammal)	RG1–RG3	Comprehensive worker biological safety and infection control program required for processes with viable organisms in RG2 and RG3
Viral vector delivery (e.g., lentivirus, adenovirus, etc.)	RG1 and RG2	Comprehensive worker biological safety and infection control program required for processes with viable organisms in RG2 and RG3 vectors to be replication deficient
Post-deactivation intermediates	No viable microorganisms; risk is associated with biologically active molecular entities and cleaning agents	Occupational hygiene measures appropriate to the toxicology risk assessment of molecular entities

Operation or scenario	Typical worker biological risk level	Precautions and biosafety measures
Quality Control (QC) Microbiology sampling and testing	RG1–3	Comprehensive worker biological safety and infection control program required for processes with viable organisms in RG2 and RG3 categories
Human blood and other human tissue processing	RG 2	Occupational Safety and Health Administration (OSHA) (or equivalent) Blood Borne Pathogen Compliance Program
Unplanned facility or equipment contamination with pathogenic microorganisms (e.g., cooling towers with legionella, or bioreactor contamination with unknown agent, etc.)	To be determined	Seek advice from biosafety professional

Risk Group 1 (RG1) not associated with disease in healthy adults.
Risk Group 2 (RG2) associated with human disease, a preventative or therapeutic intervention may be available.
Risk Group 3 (RG3) associated with serious or lethal human disease, a preventative or therapeutic intervention may be available.

In developing a biosafety program the following checklist should be considered to assure the health and safety of workers in operations with viable microorganisms, and prevent release from the facility:

Checklist of considerations for worker biosafety (Avizinis, 2018)

	Yes/No
Are microorganisms utilized within the operations?	
Are these microorganisms potential human, animal or plant pathogens? • If yes, has the biological Risk Group rating been defined?	
Are there specific regulatory requirements with your local, state or federal authorities regarding work with the identified microorganisms?	
Have you established a formal biosafety program? • Does this address the specific regulatory requirements? • Is the program supported by a competent resource such as a qualified biosafety professional?	

	Yes/No
Is your facility designed, operated and maintained in a manner appropriate to the biological risk level?	
Have you established validated cleaning and disinfection procedures together with waste disposal requirements for the operations with microorganisms?	
Do you have procedures for responding to accidental releases or personnel exposures to microorganisms? • Does this include disinfection requirements? • Do they define post exposure requirements in the event workers are potentially exposed?	
Have you verified through appropriate medical clearance procedures that none of the workers potentially exposed to these microorganisms have work restrictions due to such personal medical conditions, e.g., immuno-compromised, or other considerations, e.g., pregnancy etc.?	
Do you have policies and practices that requires sick employees who could transmit infections (e.g., influenza, Hepatitis A (Hep A), Tuberculosis (TB), etc.) to report their conditions and restrict their work activities to reduce impacts on fellow workers or product quality?	
Does your Management of Change procedure include a requirement to review your biosafety controls to verify that they remain effective?	

If these questions raised concerns or identified gaps in site existing programs, helpful information is included in this chapter that may assist to improve their robustness.

THE IMPORTANCE OF BIOSAFETY: IMPACTS OF EXPOSURE

Peer-reviewed journal articles on the prevalence of work-related infections among workers specifically in the parenteral drug industry are not easy to find. However, as published in the *Morbidity, Mortality Weekly Report* (MMWR, 1988) from the Centers for Disease Control (CDC), the *Journal of Clinical Pathology*, the *Journal of Clinical Infectious Diseases* (CDC, 1988; Ford, 2009; Weinstein et al., 2009), it is thought that Laboratory Acquired Infections (LAIs) have been and are currently underreported. This could be due to the similarity of symptoms between infection caused by biological agents studied in the laboratory and common illnesses like colds and flus. Underreporting

could also be a result of asymptomatic infections, or even misdiagnosed infections when a physician does not consider the occupational hazards associated with a patient's work when making a diagnosis. There are a range of factors associated with infection progressing to illness (disease pathogenesis) including modes of transmission, health status (immunity) and microbial concentration; therefore, control at source is the most effective mechanism to prevent release.

While the modes of transmission for microbial agents are well understood to include inhalation, ingestion, mucous membrane exposure and parenteral inoculation, the understanding of the role of an exposed person's immune system has evolved due to advancements in the field of immunology. Because a person's immune status is unique to the individual and not static over time, exposure to biological agents can result in severe impacts in some but not others, and may depend on the person's current health status. Immune system differences can mean the "infectious dose" may differ between individuals as well. For example, a healthy person may not develop disease after exposure to a very low viral concentration of influenza virus 1×10^2 (vg or "viral genomes") while a person with an immune deficiency develops severe flu after exposure to the same viral concentration. Controlling the biohazardous agents at the source reduces the risk of a worker being infected, regardless of the variability in immune status among workers.

Byers and Harding designed a survey to try to quantify LAIs which required self-reporting by Principal Investigators (PIs) and laboratorians (Byers and Harding, 2013). They found that worldwide, in a 34-year span up to 2013, there were 2,033 LAIs and 37 deaths reported. It's likely that there are gaps in the data due to underreporting because some surveys went unanswered, people did not self-report, some infections may cause asymptomatic infection and some Laboratory Acquired Infections may have been misdiagnosed.

The impacts of exposure from novel technologies and ATMPs now being used in biotherapeutics such as viral vectors and gene therapy are not well understood in non-target populations, and no

published LAI reports were found for this chapter. These agents, while potentially life-improving and life-saving, may have an adverse impact on the non-target population such as during manufacturing or testing if they are accidentally infected. The impact may not be beneficial, reversible or preventable through prophylaxis such as a vaccine. Biosafety control measures should be reviewed by a multi-disciplinary team such as the laboratory supervisor, PI, Environmental Health and Safety (EHS) staff, biosafety officer (BSO) and industrial hygienist (IH). Training should be provided to all affected personnel including the laboratory analysts and production-line workers.

Microbiological agent release can impact those outside of laboratory or production line workers such as custodial staff, office and administrators through entry into the facility environment if the materials are not well-controlled at source. The root cause of such a release may be inadequate risk assessment, inadequate application of control strategies, poor management of waste materials, inadequate segregation of clean and dirty materials, poor personnel and/or equipment traffic flow, ineffective gowning, cleaning and/or disinfection.

Exposure risk is not limited to the human population or the indoor confines of laboratories and manufacturing facilities. Accidental release of biological agents from the facility can potentially lead to significant and economically challenging incidents. For example, a research strain of an agricultural pathogen was released into the outside environment resulting in the culling of livestock and banning of export and trade of livestock during an accidental release of foot and mouth disease from the Pirbright Institute in the UK in 2007 (UK Health and Safety Executive, 2007).

Application of biosafety controls via a well-established biosafety program is the best way to ensure that high-consequence releases to the environment or exposures to personnel do not occur. Biological risk assessment throughout the biological agent lifecycle is a key feature of a good biosafety program.

KEY FEATURES OF A BIOSAFETY PROGRAM

Application of biosafety controls via a well-established biosafety program is the best way to ensure that high-consequence releases to the environment or exposures to personnel do not occur. A formalized, documented program structure is the foundation of an effective biosafety program.

Containment of microbiological materials at the source, knowledge of the process and potential points of release are essential for an effective biosafety program, supported by contemporary biosafety resources including: reference documents, and a competent BSO, and/or biosafety committee.

Key features of a robust biosafety program include:

- Regulations. Evaluation of all applicable jurisdictional regulatory requirements through the process lifecycle from purchasing and receiving, research and development, manufacturing, testing to shipping and disposing.

- Biological risk assessment. Nature of the agent used, routes of transmission, the procedures employed, personnel involved, facility design and workspace.

- Hierarchy of Controls. Application, mitigation of risk, control measures.

- Medical surveillance, including pre and post exposure prophylaxis and treatments.

- Incident investigation and emergency preparedness.

- Communication.

These key features are described in detail below.

Biosafety program key feature: regulations

In many jurisdictions, there are regulatory requirements outlining expectations for evaluation and control of biological risks. For example, in the United States, there are regulations put forth by the Occupational Safety and Health Administration (OSHA) requiring certain programs and safeguards for employees such as 29 CFR 1910.1450 the Occupational Exposure to Hazardous Chemicals in Laboratories standard, 29 CFR 1910.1030, and the Bloodborne Pathogens standard, 29 CFR 1910.1030. Scenarios not governed by a specific OSHA standard are governed by the General Duty Clause of the Occupational Safety and Health Act, 29 USC 654, which requires employers to provide employment and a place of employment free from recognized hazards that are causing or are likely to cause death or serious physical harm to its employees. The Federal Select Agents and Toxins Program managed by the United States Department of Agriculture (USDA) through its Animal and Plant Health Inspection Service (APHIS) requires implementation of management systems for the oversight of bioterrorism, plant, and livestock pathogenic agents (US Federal Select Agent Program, 2017).

Resources to evaluate regulatory requirements and determine their applicability may include specific country government agencies, regulatory bodies, industry experts, scientists, professional organizations, BSOs, and if available, peer-reviewed literature. It is important to establish a listing or register of applicable requirements, together with key compliance requirements including reporting to agencies, and to establish and maintain a schedule to ensure these requirements are met. Engagement of a credentialed biosafety expert such as an American Biological Safety Association International (ABSA) Registered Biosafety Professional (RBP), or Certified Biological Safety Professional (CBSP) may be necessary for this process. Guidance is also available from organizations such as the World Health Organization (WHO), the CDC, National Institutes of Health (NIH), the Public Health Agency of Canada (PHAC), National Science Foundation (NSF), American National Standards Institute (ANSI).

The NIH, via its Office of Science Policy, regulates research related to the use of recombinant or synthetic nucleic acids. Some cities and states (e.g., Cambridge, MA and the state of New York in the US) have adopted this legislation that requires permits to operate when the hazards of the proposed microbiological agents trigger certain threshold limits. Internationally, there are various regulations/directives that cover these same aspects of biosafety including as examples: the Canadian Biosafety Standard (Public Health of Canada, 2015), EU Directive 2001/18/EC (European Union, 2010), Ireland's Safety, Health and Welfare at Work (Biological Agents) Regulations 2013 (SI No. 572 of 2013).

There are also expectations outlined by governmental agencies that define requirements to ensure appropriate management of recombinant DNA (rDNA) and genetically modified organisms (GMOs) through facility design, function and engineering controls; the NIH, the Federal Drug Administration (FDA), the European Union (EU) Community Commission and other regulatory or funding bodies publish industry standards and funding requirements. Examples of facility design requirements include closed processing of large scale manufacture of biotechnology products including High Efficiency Particulate Air (HEPA) filters on exhaust valves, consideration of single-pass air, and use of specific surface materials that are non-porous.

Biosafety program key feature: Biological risk assessment

An effective risk assessment covers the entire life cycle of the biological agent use including ordering, shipping, receiving, use of, inactivation and destruction. Proper containment, transport, handling and storage strategies should be evaluated and employed as a result of the assessment.

A systematic review should be conducted by a multi-disciplinary team which may include members of the scientific team (e.g., scientist, PI) and EHS to confirm the hazards associated

with the agent, the procedures, the personnel planned to be involved in the work, the facility and the adequacy of the controls to be used through the life cycle of the work. We will consider five biosafety risk factors in the risk assessment process:

- Hazard characterization of the agent
- Biosecurity assessment
- Procedures
- Personnel
- Facility design/workspace

Biosafety risk factor A: Hazard characterization of the agent

The starting point of a biological risk assessment is undertaking a hazard characterization of the proposed agent(s). Once the features of the biological agent are known, the potential release scenarios related to proposed activities can be evaluated and recommendations made about how to safely utilize the agent(s).

- Risk group classification
- Materials handled within the process e.g., tissue, cell line, in process sample
- Infectivity
- Route of transmission
- Consequences of genetic modification e.g., hazards of expressed protein, toxin effect
- Availability of prophylaxis or treatment

Evaluation of the features of hazard characterization of the agent, listed above, are discussed in detail below:

- *Risk Group classification* according to the CDC/NIH and WHO are based on the hazardous characteristics of the agent including:

  "its capability to infect and cause disease in a susceptible human or animal host, its virulence as measured by the severity of disease, and the availability of preventive measures and effective treatments for the disease." (WHO, 2007)

  There may be differences in the definitions of risk groups between government agencies and professional bodies, and therefore a good point of reference for risk group definitions is the WHO Laboratory Biosafety Manual (WHO, 2007). It defines microbiological risk groups as follows:

  Risk Group 1 (RG1) (no or low individual or community risk)
  A microorganism that is unlikely to cause human or animal disease.

  Risk Group 2 (RG2) (moderate individual risk, low community risk)
  A pathogen that can cause human or animal disease but is unlikely to be a serious hazard to laboratory workers, the community, livestock or the environment. Laboratory exposures may cause serious infection, but effective treatment and preventative measures are available and the risk or spread of infection is limited.

  Risk Group 3 (RG3) (high individual risk, low community risk)
  A pathogen that usually causes serious human or animal disease but does not ordinarily spread from one infected individual to another. Effective treatment and preventative measures are available.

  Risk Group 4 (RG4) (high individual and community risk)
  A pathogen that usually causes serious human or animal disease and that can be readily transmitted from one individual to another, directly or indirectly. Effective treatment and preventative measures are not usually available.

  Note: Certain countries (e.g., Russia and China) the Risk Group hierarchy is reversed whereby Risk Group 1 is the highest risk group and Risk Group 4 is the lowest.

Wild type agents' (those agents or strains that are not attenuated or modified) risk group information is typically published by government agencies or industry experts, e.g., PHAC's Pathogen Safety Data Sheets, US CDC's Biosafety in Microbiological and Biomedical Laboratories (BMBL) Agent Summaries, ABSA Risk Group Database, the UK Health and Safety Executive (HSE), CDC, ABSA, PubMed and National Center for Biotechnology Information (NCBI). Classifying the risk group of the wild type version of the proposed agent is an important starting point in risk assessment. Because even if the specific agent proposed has been genetically modified, some of the features of the wild type may still exist in the modified agent. The modifications should be reviewed and incorporated into a revised risk group if needed. For example, wild type strains of *E. coli* that can cause disease in humans may be Risk Group 2, but a modified strain *E. coli* (e.g., K-12) may be Risk Group 1 and therefore safe to handle for testing yet representative of the wild type strain.

Table 2 describes quality control laboratory typical microbiology agents and risk groups.

- *Materials handled within the process*
  An assessment of the process stream should be performed for the potential risk of release of the agent. Handling potentially virus-contaminated human tissue samples may have a different potential risk level than handling an aliquot of a high titer virus in process production sample. Similarly, if the material is frozen or preserved in formalin, the risk profile may be reduced because frozen material may be less likely to aerosolize and preserved material may be completely inactivated. For unknown materials, it is best to follow what is known in the US as the "universal precautions principle" which is to assume that they are contaminated with infectious agents and proceed accordingly. For such samples the CDC/NIH recommend utilizing Biosafety Level 2 (BSL2) containment and practices.

Table 2 Quality control typical microbiology laboratory agents, risk group and expected biosafety measures

Test Organism (Reference standards – not genetically modified)	Worker Biological Safety WHO Risk Group (WHO, 2007)	Precautions and biosafety measures when handling the agent in production and quality testing areas
Pseudomonas aeruginosa	RG2	Biosafety Level 2 Containment and Practices
Salmonella typhimurium	RG2	Biosafety Level 2 Containment and Practices
Candida albicans	RG2	Biosafety Level 2 Containment and Practices
Bacillus spizizenii	RG1	Biosafety Level 1 Containment and Practices
Aspergillus brasiliensis	RG2	Biosafety Level 2 Containment and Practices
Staphylococcus aureus	RG2	Biosafety Level 2 Containment and Practices
Candida sporogenes	RG1	Biosafety Level 1 Containment and Practices
Escherichia coli	RG1	Biosafety Level 1 Containment and Practices
Geobacillus stearothermophilus	RG1	Biosafety Level 1 Containment and Practices
Bacillus pumilus	RG1	Biosafety Level 1 Containment and Practices
Bacillus atrophaeus	RG1	Biosafety Level 1 Containment and Practices
Bordetella bronchiseptica	RG2	Biosafety Level 2 Containment and Practices

Source: Author, with information from PHAC Pathogen Safety Data Sheets (2017), ASBA Risk Group Database (2016), WHO (2018)

"*Infectivity* is a measure of the ability of a disease agent to establish itself in the host. This term can be used qualitatively, when an agent is referred to as being of low, medium or high infectivity, or quantitatively. Attempts to quantify infectivity normally involve the use of a statistic known as ID_{50}. This refers to the individual dose or numbers of the agent required to infect 50% of a specified population of susceptible animals under controlled environmental condition." (FAO, 2017)

Bacteria, for example, that require only a few microorganisms to infect a healthy human through inhalation are significantly more infectious than those that require a large number through ingestion. The inhalation-hazard bacteria should be handled in containment systems at all times, and bacteria infectious in large numbers via ingestion should be handled with precautions to prevent mucous membrane contact in the occupational setting. The infectivity detail is closely related to the route of transmission in a risk assessment.

- *Route of transmission*
  Route of transmission is the movement of organisms from a reservoir to a susceptible host (WHO, 2007). Once an organism has exited the reservoir, it needs a route of transmission to the host through a portal of entry. Transmission may be by direct contact, indirect such as a surface or dirty equipment (e.g., needles), oral, or through airborne transmission (e.g., aerosols). For example, if a known highly-infectious agent that has an airborne route of transmission is to be poured from a flask into another container, the risk assessment should conclude that this activity should be re-engineered to eliminate pouring which may create aerosols, or that this activity should be contained within a Biological Safety Cabinet (BSC), isolator, or a closed transfer system such as a tube welder/fusion system, to provide containment at the point of potential release.

The persistence of an agent in the environment must be considered when looking at infectivity and route of transmission as well. An

agent that can stay viable outside of the body for a long period of time and that can cause infection through mucous membrane exposure, if spilled on a surface and not properly decontaminated could lead to exposure and a Laboratory Acquired Infection or cross-contamination. A persistent agent trekked outside of the facility may remain infectious. A way to prevent this is for personnel to wear dedicated clothing in the facility and verifying decontamination methodology.

- *Consequences of genetic modifications*
  While the wild type may have a specific hazard profile, a genetically modified version may be attenuated, serially passaged or genetically modified and potentially be less infectious or less pathogenic. For example, the most common form of vaccinia virus used in biopharmaceutical research and development (R&D) is the Modified Vaccinia Ankara (MVA) virus strain which has been attenuated and thus is less pathogenic. Because it is attenuated, personnel may not be required to be vaccinated in order to work with the MVA strain. However, it may be more infectious or pathogenic in different ways than the wild type. An HIV-based lentivirus used in research may be modified so that it has a different viral protein coat that enables it to be infectious through aerosol rather than exclusively by parenteral exposure. Attenuated and modified viruses may "recover" their wild type form if contaminated by other microbiological agents with complementary nucleic acid sequences or other wild type agents. Monitoring of the purity of the agents and of ancillary areas may be used to demonstrate controls are in place.

- *Evaluation of the available prophylaxis or treatment*
  This should be reviewed from the perspective of preventative prophylaxis and post-exposure prophylaxis. This aspect of the agent assessment should be conducted in conjunction with occupational health specialists or health care providers with expertise in this area. Also refer to the Occupational Health Relationship section of this chapter.

Biosafety risk factor B: Biosecurity assessment

The need for a biosecurity assessment and associated facility controls will have been identified during the review of the regulatory framework and the hazard profile of the agent. Biosecurity is the combination of access controls, material lifecycle tracking and biosafety practices to prevent the intentional release, diversion or distribution of harmful biological material. If the outcome of the assessment indicates that a biosecurity program is warranted, this should result in a discussion with the local security personnel. As part of an effective program, a joint biosafety/biosecurity review is recommended on an annual or semi-annual basis with site/building security to ensure transparency and collaboration between biosafety officers, laboratory supervisors and site security as necessary to prevent activity that could result in an incident. The assessment should determine what level of security is needed for each applicable agent, e.g., additional locks, key cards or codes, personnel screening, and entry and exit policies/procedures. Another example would include limiting freezer access to approved people only whenever live agents, such as rabies are stored in a laboratory/manufacturing freezer. The biosecurity review should have also considered management of transport in the event materials have to be moved internally or externally to the organization. Shipping instructions including applicable permits and labeling should have been identified if the agent needs to be transported off facility grounds over roads or airways.

Biosafety risk factor C: Procedures

The practices for handling microbiological agents and processing materials across the lifecycle of use should be evaluated to determine potential exposure and release points, which is the third key feature of a biosafety program. The most effective control is to prevent release at source. It is important to identify pathogens that have no available preventative or post-exposure prophylaxis, and

to specifically eliminate potential transmission routes associated with operations involving those agents. Procedures for handling and processing may include, with detail below:

- Sharps use
- What could go wrong:
  - Line breaking
  - Aerosol generation
- Scale up and tissue culture
- Transport of materials
- Decontamination and disinfection
- Waste disposal

Further detail is below:

- *Sharps use*
  Provide clearly visible and easily accessible areas for disposal of sharps (e.g., needles and scalpels). As a best practice it is safest to avoid sharps when possible or use safety engineered disposable sharps devices if sharps must be used.

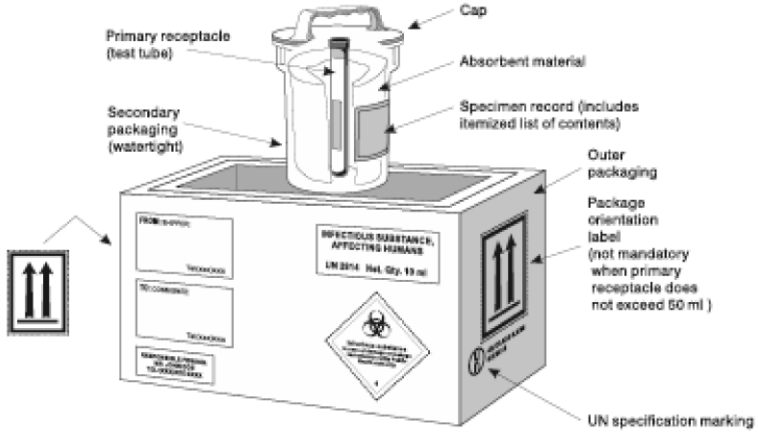
- *What could go wrong*
  There should be provisions for containment and Personal Protective Equipment (PPE) and post-exposure plans in place in the event a line breaks and aerosolizes live agent(s). Many tasks in laboratory and production spaces are capable of producing aerosols although not all are obvious (e.g., pouring, stirring, aspirating, vortexing, microtoming, cryostatting, cell sorting, pipetting and centrifuging). These should be contained to prevent exposures.

- *Scale up and tissue culture*
  The moving from small research quantities to commercial manufacturing is referred to as scale up. An incidental amount of infectious organism in an environmental monitoring sample

carries likely much less risk than the amount generated through tissue culture from a concentrated aliquot. Increasing the number of infectious agents through tissue culture passage increases the potential for a deleterious exposure to those agents. An RG2 agent may be considered moderately hazardous in standard environmental conditions however, when highly concentrated in very large volumes, the consequences of exposure are likely to be more significant, which has implications for exposure control and spill response recommendations. Facility design, applied controls and procedures should reflect these specific circumstances.

- *Transport of materials*
  Infectious materials must be in transported in containers that will assure the organisms will not be accidentally exposed in areas outside of their use. Double walled, unbreakable containers are often used, (WHO, 2007) and must be appropriately labelled as to contents and risk level. See Figure 1 below.

Figure 1 Example of the three layer system for shipping (WHO, 2007)



- The primary receptacle containing the specimen must be watertight, leakproof and appropriately labelled as to content. The primary receptacle is wrapped in enough absorbent material to absorb all fluid in case of breakage or leakage.

- A second watertight, leakproof packaging is used to enclose and protect the primary receptacle(s). Several wrapped primary receptacles may be placed in a single secondary packaging. Volume and/or weight limits for packaged infectious substances are included in certain regulatory texts.

- The third layer protects the secondary packaging from physical damage while in transit. Specimen data forms, letters and other types of information that identify or describe the specimen and identify the shipper and receiver, and any other documentation required, must also be provided according to latest regulations. (WHO, 2007)

- *Decontamination and disinfection*
  The concentration, amount and nature of the biological agent must be evaluated to ensure the effectiveness of the selected methodology per agent. The effectiveness of the decontaminants may vary among agents which must be factored into the biological risk assessment, e.g., enveloped viruses tend to be easier to inactivate than non-enveloped viruses, just as non-spore-forming bacteria are easier to inactivate than spore formers. The greater the amount of organic material present, the greater the challenge to the inactivation methodology because it may prevent direct contact of the disinfection agent/mechanism. The consequences of ineffective decontamination could result in cross-contamination in multiuse facilities, exposure to personnel leading to an LAI, and/or an environmental release.

There are several ways in which a surface, object, piece of equipment that has been in contact with biological agents can be decontaminated. An absorbent wipe soaked in a chemical agent may be used to decontaminate surfaces after work has been concluded provided the instructed contact time can be achieved. There are many different chemical agents available commercially. They must be qualified for their effectiveness vs. the agents in use. The size of the area to be decontaminated, together with the compatibility between the surface and decontaminant are considerations in the selection process, e.g., sodium hypochlorite (bleach) can be corrosive to certain metals, including stainless steel, so a residual removal may be needed using alcohol or water. Key considerations to be reviewed during the disinfectant selection process include:

- Disinfection efficacy studies. What evidence is available to confirm that the selected disinfectant is capable of inactivating the microbe for an acceptable log reduction? How frequently and when should it be revalidated? See USP<1072>, EN 14476 for recommended log reductions.

- Application: is the decontamination limited to a discrete area (e.g., a BSC surface) or is it an entire laboratory suite?

- Does the disinfectant present additional hazards that require exposure control?

- Will the disinfectant cause damage to the equipment, e.g., rust?

- Is it more cost effective to use disposable tools and processing equipment (e.g., bioprocessing bags) rather than risk a manual disinfection/decontamination procedure?

The most effective method from a repeatability and sterility assurance level is steam sterilization. Equipment that can withstand this type of sterilization should be sterilized using this method. Decontamination of solid or liquid materials can also be achieved by thermal kill. The material being treated must be able to withstand the cycle without creating additional hazards.

To fully evaluate the effectiveness of decontaminants, published literature, product specification sheets, expertise and in-house validation studies and their applications will be critical to consider ensuring that the decontamination process selected is effective for the agent(s) involved.

Disinfection and decontamination methods used in Good Manufacturing Practice (GMP) settings may use toxic and otherwise dangerous chemicals that are effective because they kill or inactivate microbial agents. As summarized in Table 3 below, "Medium and High" risk decontaminants should be utilized following a risk assessment involving a qualified industrial or occupational

Table 3 Worker health and safety risk assessment of cleaning, disinfection, and sporicidal materials and operations (Geissert, 2017)

Decontaminant	Risk level (High-Medium-Low)	Precautions	Can an IDLH* be created with effective gas/vapor concentrations created for this operation?
Phenolic solutions	Low for inhalation; medium for eye and skin contact	Prevent eye and skin contact	No
Bleach	Low for inhalation; medium for eye and skin contact	Prevent eye and skin contact	No ... do *not* acidify bleach, which will produce chlorine and chlorine dioxide gas which is toxic
Clean in Place (CIP); Clean out of Place (COP)	Medium	Caustic and acid COP and CIP solutions are corrosive. Prevent eye and skin exposure	No
Formaldehyde and/or glutaraldehyde	High	Substitute with agents that are not carcinogenic. Occupational hygiene plan to be developed and implemented	Yes
Vaporous hydrogen peroxide	High	Occupational hygiene plan to be developed and implemented	Yes
Hydrogen peroxide and peracetic acid solutions	Medium	Prevent eye and skin contact. Consult with occupational hygienist on preventing excessive breathing zone exposures	No
Isopropyl alcohol and ethyl alcohol	Medium	Prevent ignition of vapor from liquid; reproductive toxin	No
Ethylene oxide	High	Only enclosed systems engineered to prevent explosions and exposures to carcinogen. Occupational hygiene plan to be developed and implemented	Yes
Chlorine dioxide	High	Occupational hygiene plan to be developed and implemented	Yes
Ultraviolet light	High	Significant risk of burns to eye and exposed skin at levels that are germicidal	Not applicable
Ozone	High	Closed systems and otherwise prevent inhalation exposure	Yes

IDLH*-Immediately dangerous to life or health (IDLH) is defined by the US National Institute for Occupational Safety and Health (NIOSH) as exposure to airborne contaminants that is "likely to cause death or immediate or delayed permanent adverse health effects or prevent escape from such an environment."

hygienist and use of a Safety Data Sheet (SDS) to ensure worker safety. Most operations include a worker safety and health and environmental review provision in their Management of Change procedure as in Table 3.

- *Waste disposal*
  The features of the agent, how it is regulated, and how it is used, may require specific disposal considerations like records of incineration, records of time, temperature and pressure of thermal kill system and so on. In the event that neither chemical nor thermal inactivation is conducted because the material is sent for vendor-supplied inactivation, the risk assessment should review how the material is being collected for disposal, e.g., aerosolizable agents should be placed in a sealed bag before being tossed into the waste receptacle to ensure handling of the waste container does not release infectious aerosols and access to active biological agent waste materials should be limited to authorized personnel. Incineration is a method enabling complete destruction of the waste materials. Typically, this will involve transfer of the waste from the primary use location to a disposal site; therefore the potential for release associated with material transport should be considered.

While vendor disposal service is effective in supporting operations, it is important to consider contingency plans for delays in pick-up or unforeseen large accumulations of waste that may need to be disposed (such as from an emergency spill), or in the instance that the waste vendor cannot remove waste as planned.

For new facilities, there may be a desire to consider on-site waste treatment capabilities are included within the design. A design review process is critical to ensure the methods are effective; and the installation meets jurisdictional regulatory requirement. If plans to dispose of certain waste streams by sink disposal are being

considered, local waste-water permitting may be required and should be evaluated.

Biosafety risk factor D: Personnel

Employees, contractors, ancillary staff, and service technicians must have appropriate:

- Training – examples of this include situational awareness, biosafety, general safety, how to complete the task, job aids, and knowledge checks. Case studies and potential breaches and near misses in the manufacturing process, extraneous contamination events and information about new agents/changes at the facility.

- Personal protective equipment (PPE) appropriate for the agent based on the risk assessment and that is maintained in working order. Changing clothes and/or showering may also be required.

- Understanding of the symptoms of the illness associated with the infective agents in the area.

- Skill – skills-based training that includes observation of operator/analyst technique after demonstration by trainer or supervisor using media instead of live agents for example for a non-consequential setting. When working in the laboratory, the personnel need to know how to assess risks and what they should do and not do if something goes wrong.

- Experience – examples include background skills. If the task is to genetically modify viruses using reagents, have they performed this task before, have they used these types of reagents and are they able to answer questions important to biosafety from this experience?

- Health status – there may be some restrictions due to immune compromised status, age (e.g., family planning/advanced age),

pregnancy, treatment with steroids or antibiotics. This information must be included in the risk assessment and is an important aspect of the biosafety program.

- Available oversight and supervision including biosafety expertise, e.g., someone in the facility who can help ensure the tasks are performed properly and safely.

There must be a person appointed the position of Biosafety Officer as the point of contact for the biosafety program. This person may be appointed through senior management (ATMP, 2017). This person will have the appropriate certification and education and experience to handle the biosafety program requirements, and to address control of hazards and understand the impacts of any breaches that may occur. This person would help conduct risk assessments, review documents for the program, and the training that the site receives, assist in incident investigations and work together with occupational health resources to develop pre- and post-exposure plans. Personnel working directly with the active biological agents are at the greatest risk of occupational exposure and depending on the hazards of the agent, recommendations must be made by the BSO as to how certain conditions or health status can impact exposure to the agent, this will include the shedding of the wild type counterpart of the viral vector virus. Extraneous virus testing and product safety testing may be reviewed by the BSO and area management to monitor for these types of events.

Biosafety risk factor E: Facility design/workspace

There should be a plan for an appropriate facility design and workspace, examples of points to consider include:

- Containment levels (facilities, practices and equipment specific to controlling the risks related to the hazard level of the agents in use).
- Laboratory or manufacturing facility design.

It is important to note that the Risk Group of an organism does not always correlate with a *containment level* – the more significant the potential for harm due to exposure, the more stringent the controls. If working with a commercial manufacturing amount of material requiring open manufacturing steps, the containment must be more stringent than for a sample amount in the laboratory using the biosafety cabinet and closed systems. Containment level is synonymous with Biosafety Level or BSL:

> "BSLs ... consist of combinations of laboratory practices and techniques, safety equipment, and laboratory facilities. Each combination is specifically appropriate for the operations performed, the documented or suspected routes of transmission of the infectious agents, and the laboratory function or activity." (CDC/NIH, 2009)

Open transfer of test organisms, and potential generation of aerosols (vortexing, opening a centrifuge safety cup, pipetting etc.), whether the organism is RG2 or RG1 (WHO, 2007), is to be performed in a BSC or other containment system to protect both the laboratory workers and to prevent cross contamination in the microbiology laboratory.

Depending on the task or the characteristics of the agent, a determination may be made to work at a higher level than the assigned Risk Group. For example, an RG2 bacterial fermentation operation may only warrant a BSL2 level of containment to protect workers, but a BSL2 with enhancements or as somple people describe BSL2+ or BSL3 level of containment and practices may be implemented due to GMP cross-contamination concerns with adjacent operations in a multiuse facility or due to unknown impacts to health and safety.

Depending on the features of the proposed biological agents, an existing *laboratory or manufacturing space* may not be equipped to adequately contain the agent and meet BSL requirements. For example, if a planned space for biological work is not designed or built with appropriate differential pressure cascades, containment including BSCs, smooth cleanable surfaces, personnel controls including gowning and waste disposal areas, and the risk

assessment specifies a requirement for BSL2 containment, the proposed work should not be initiated until the space is renovated to ensure the appropriate exposure control systems are established and functional. Review CDC/NIH (2016), PHAC (Canadian Biosafety Standard) and WHO (2007) documents and best-practice guidance, for laboratory design, configuration and maintenance for use of microbiological agents.

Table 4 Example of an agent-based, biological hazard risk assessment: Modified Vaccinia Ankara Virus/HEK 293 cells (human cell line)

Biohazard assessment category	What is being assessed	Determination of hazard
Regulatory review	MVA and HEK 293 cells Applicable Regulations	MVA: not regulated in the US, however post-exposure prophylaxis will require communication with the CDC to get access to immunoglobulin HEK 293: (US) Institution determines the applicability to the OSHA Bloodborne Pathogen Standard and proceeds accordingly
Biosecurity assessment	MVA and HEK 293 cells	MVA: Should have restricted access to building, facility where it will be used and storage area to prevent exposure to compromised individuals, and theft
Agent	Wild type Risk Group classification	MVA: RG2 According to BMBL, PHAC, ABSA HEK293: RG2 according to institutional policy on human-source material
	Type of material	Aliquots, culture plates
	Infectivity	MVA: Unknown but vaccine titer is 10e8 HEK293: Human sourced material : Universal precautions assume it's infectious
	Route of transmission	MVA: Mucous membrane, parenteral, some evidence of aerosol transmission in non-human primates HEK293: Parenteral and mucous membrane
	Consequences of genetic modification	MVA: This strain is attenuated and has a green fluorescent protein transgene HEK293: No modifications proposed
	Availability of prophylaxis/treatment	MVA: There is a vaccine but it is the MVA strain and there is an immunoglobulin but it is only available from CDC HEK293: Cell line tested for BBPs. Post exposure may include assay panel

Biohazard assessment category	What is being assessed	Determination of hazard
Procedures	Sharps use	None
	Animal use	None
	Aerosol generation	Pipetting, aspirating
	Tissue culture	Yes HEK 293 cell line cultured for infection by MVA
	Volume/scale	MVA: Largest volume is 100 mL of virus HEK293: laboratory scale volumes of 20–100 mL
	Transfection/genetic modification	Chemical transfection agent used to apply GFP transgene to MVA
	Decontamination strategy	Both agents inactivated by bleach per review with PHAC, CDC, and other publications
	Waste disposal	Liquid waste inactivated with bleach, solid waste bagged, tied off and placed in biohazard box to be incinerated
	Transportation	Sealed, leak-proof primary and secondary containment, no shipping will be used
Personnel (employees, contractors, ancillary staff, service technicians and their:	Training	Project team trained in biosafety, laboratory safety, BBP and specific MVA training, tissue culture training and transfection training. PPE, symptoms, reporting of breaches or near misses. Ancillary staff trained in biosafety awareness, technicians trained in facility safety policies
	PPE	Disposable laboratory coats or jumpsuits with a high neck covering and tight fitting cuffs, gloves, goggles, shoe covers
	Skill	Project personnel have all had experience working with infectious agents and cell culture, except newest project person needs hands-on training
	Experience	Project personnel have all worked in this laboratory for six months or more except for newest person
	Health status	Project personnel have all been to occupational health services (OHS) to get information on MVA exposure and consultation based on their health status, no restrictions have been recommended by OHS

Biohazard assessment category	What is being assessed	Determination of hazard
Workplace	Containment level	BSL2
	Laboratory design	Suitable: facility designed as a BSL2 facility with directional airflow, hand-washing sinks, cleanable surfaces, Class II A2 biosafety cabinet
	Manufacturing plant design	N/A

Based on the initial hazard assessment BSL2 containment and practices should be employed along with a robust biosecurity program and medical surveillance program including pre and post exposure planning and consultation. The hazards and entry requirements to applicable facilities should be communicated to potential entrants to the facility and posted at the entrance to the laboratory.

Source: Avizinis (2018)

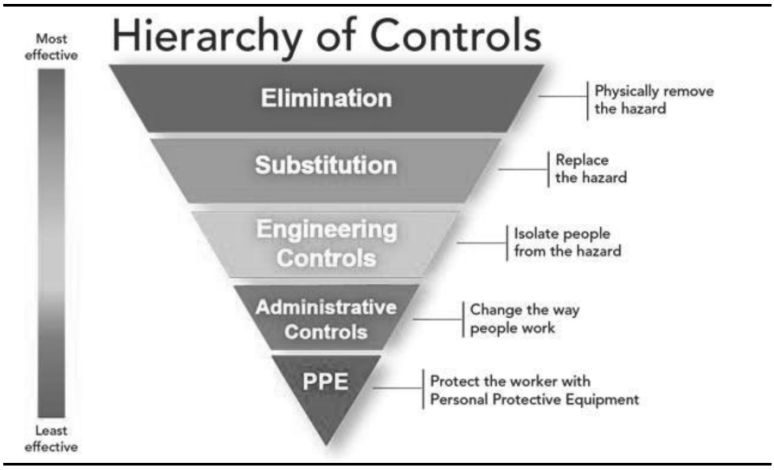
While it seems that there are many details to review for each proposed use of biological agents, establishment of a systematic risk assessment process is essential to ensuring the effectiveness of controls prior to the work being initiated. The risk assessment is a key tool to preventing exposures, releases, and business interruption as a result of regulatory issues. The risk assessment should be periodically reviewed to ensure it remains accurate as the scientific procedures evolve, and if any new agents are brought into the facility, or the quantities of use change the level of risk.

Biosafety key feature: Applying the Hierarchy of Controls to prevent exposure

There are many ways to contain biological agents to prevent cross-contamination, exposure and release to the environment. The specific means to contain biological agents initially depends on a review of the features of the agent, tasks performed, personnel and workplace. Ensuring containment and preventing exposure or release should be approached through the assignment of BSLs which include containment and practice recommendations based on the application of the Hierarchy of Controls. The HoC is a safety system broadly promoted by governmental and industry safety

organizations under which controls are applied in a particular layered order to ensure the most reliable and robust measures of protection are applied first and the least robust measures are applied last. These layers of protection are applied in an overlapping manner so that if a single layer has a breach, the next overlapping layer will provide protection. The HoC is often displayed visually as an inverted pyramid (Figure 2).

Figure 2 Hierarchy of Controls



Source: NIOSH (2016)

The first measure of control to be applied via the HoC is "elimination". The intent is to eliminate the hazard from the process if possible, e.g., if a project task involves using a scalpel to slice a tissue sample, purchasing tissue samples pre-cut would be an elimination of the contamination hazard (accidental cut and infection from the contaminated scalpel). The elimination measure should be done at every opportunity of the project thereby removing as many hazards as possible.

The next measure of control that should be applied is "substitution". This measure requires the project team to consider substituting a hazard for something non-hazardous or less

hazardous, e.g., rather than using a pathogenic and highly infectious strain of Tickborne Encephalitis virus, a project team could use a highly attenuated strain or a different, inherently less harmful arbovirus for their experiment, thereby reducing the RG of the agent used.

Engineering controls are devices or equipment that are designed to reduce or eliminate the hazard through an engineering solution. BSCs are an example of an engineering control because they provide control at source to prevent infectious aerosols from coming in contact with the worker. They are designed to pull air away from the breathing zone of the worker and capture any infectious aerosol within HEPA filters which prevent recirculation of the agent into the general laboratory space or out into the environment. Another example of an engineering control is a safety-engineered sharps device like a syringe with a self-retracting needle that gets pulled into the barrel after use. It removes the sharps hazard and the risk of injuring or infecting anyone through parenteral exposure.

Administrative controls are work practices that can be employed to make the work safer, e.g., a policy that an agent may only be transported in a leak-proof, sealed container to prevent release as the material is moved from one location to the next. A policy in which work is not to be done until the agent-specific training has been completed also prevents infection by ensuring personnel are aware of the precautions they must take at each step of the project process.

The last layer of protection that is applied through the HoC is application of PPE. It is worn in many different procedures and work environments and can be very effective, if worn correctly. However, as it only protects the wearer, it is the last line of defense against hazardous materials. For example, when manipulating adenovirus – even a strain that has been engineered to be replication – incompetent (or "safer" in terms of an attenuated, non-replicating infection) but nonetheless still capable of causing

conjunctival damage, wearing splash-proof goggles ensures that in the event that the material makes it beyond the sash of the BSC, the eyes are protected against potential harmful exposure. A laboratory coat will protect personal clothing from contamination by a biohazardous agent in the event that an engineering control like a centrifuge safety cup fails and biohazardous material splashes. Some agents require a shower out of the area, and that only scrubs are worn under laboratory coats so no personal street clothing is worn outside the positive area.

It is important to remember that the HoC exist as layers of protection that should be employed and work together to effectively control exposure. While engineering controls are designed to buffer or remove the exposure to the hazard from direct contact with personnel, they may not be fail-safe due to manufacturing defects, operator error, or operational failure. Applying administrative controls like training to ensure personnel are appropriately trained on how to use the engineering controls and PPE to ensure that should both engineering and administrative controls fail a person is still protected gives the greatest likelihood that an injury or LAI will be prevented.

Biosafety key feature: Medical surveillance, pre and post exposure prophylaxis and treatments

As part of the biological risk assessment, a pre- and a post-exposure plan is developed in conjunction with healthcare providers to address identified risks. If available vaccines or prophylactic treatments exist that will prevent infection or minimize the impact of an infection, these should be identified during the biological risk assessment and be made available prior to the commencement of work.

If there are recommended treatments or screenings to be applied post-exposure to a biological agent, those must be identified prior to commencement of work as well so that in an emergency personnel have been trained and know exactly what to

do to ensure the best outcome following such an incident. Similarly, some post-exposure treatments are strictly controlled and ensuring their availability requires planning ahead.

While literature about these treatments may be available through sources such as BMBL or the CDC, the Center for Infectious Disease Research and Policy (CIDRAP), PHAC, it is appropriate to work collaboratively with occupational health professionals or the intended health care providers to develop pre- and post-exposure plans. Biological Safety Officers (BSOs), laboratory supervisors, managers, and other safety professionals can start by learning what treatment options may be currently recommended by reputable organizations. This plan should consider required resources that should be acquired to support the response plan and follow-up measures, e.g., provision of a data sheet agent describing the hazard characterization of the agent; enabling any further assays specific to the agent if needed to confirm effectiveness of treatment.

One fatal case of occupational exposure to a biohazardous agent could have been prevented by collaborative planning in addition to better application of the HoC. A worker in California was exposed to and died from *Neisseria meningitidis* resulting from an unknown exposure incident which likely occurred when he worked with the agent on the open benchtop (CDC, 2014). The researcher also did not have nor execute a post-exposure plan when he began to show symptoms of a flu-like illness. Vaccines, use of a BSC, showering out, disinfection practices, dedicated clothing and PPEs, and a specific post-exposure plan defining response following the initial exposure may have reduced the impact of exposure.

Policies on health impaired workers and where it's safe for them to work without impacting product quality should be considered with the collaboration of occupational health practitioners and appropriate legal counsel. Employers and supervisors should comply with applicable regulatory and privacy requirements regarding the use of an employee's health status to influence assignment to a laboratory with biosafety risks. An

institution should employ a medical surveillance program to enable personnel to be appropriately counselled in making decisions regarding their personal health status and work projects. These details related to potential health impacts should be covered in sharing the risk assessment but also through training.

Emergency response planning should also involve collaboration and planning between the supervisor, the BSO, occupational health services and site/building facility. Additional resources besides what's available "in house" may be needed for responding to emergency exposures or releases depending on the specific features of the agent. An aerosolized agent infectious via aerosol may require settling time before emergency responders can safely enter wearing appropriate PPE like Self-Contained Breathing Apparatus (SCBA) respirators to clean up the spill. Depending on the quantity, a large-scale decontamination process like vaporous hydrogen peroxide or gaseous chlorine dioxide may be required for the entire laboratory, room, suite, etc. Plans for a variety of emergency scenarios should be established, documented and trained upon before work with the agent begins to ensure no hesitation to contain the materials, treat the exposed and decontaminate the facility in the event something goes wrong.

Biosafety key feature: Biosafety incident investigation

Despite careful planning, incidents may still happen but if the pre- and post-exposure plans have been implemented and training completed, response to an incident should be straightforward. It may not be enough to conceptually discuss post-exposure response with personnel but rather perform drills periodically to ensure everyone feels comfortable about what to do. Experienced workers have responded in unexpected ways to emergencies due to lack of knowledge and practice.

Once an incident occurs first aid must be initiated, and arrangements for follow-up medical consultation if necessary. All

colleagues should be trained in the arrangements including how to access and use emergency equipment such as eye wash stations and showers. Next, it will be important to follow the appropriate reporting procedures. Most organizations/institutions have formalized reporting requirements related to incidents, which typically establish expected timelines for reporting. Additionally, regulatory agencies or other oversight bodies may have reporting requirements that must be fulfilled within a certain timeframe of the incident. For example, in the US, the NIH requires applicable institutions to report overt exposures to recombinant/synthetic biological agents in BSL2 laboratories within 30 days. Also, some regulatory authorities require the recording of injuries that meet certain criteria, e.g., US OSHA (2012) requires the recording of:

- Any work-related injury or illness that results in loss of consciousness, days away from work, restricted work, or transfer to another job.

- Any work-related injury or illness requiring medical treatment beyond first aid.

- Any work-related diagnosed case of cancer, chronic irreversible diseases, fractured or cracked bones or teeth, and punctured eardrums.

There are also special recording criteria for work-related cases involving:

- Needlesticks and sharps injuries
- Medical removal
- Hearing loss
- Infections, including reportable diseases such as tuberculosis

For US companies with over 250 employees these logs must be submitted annually per OSHA regulations, otherwise the recording is to be kept on an OSHA 300 Log, available when requested by a

government representative, provided within four business hours of the request. If a hospitalization has occurred as the result of an incident, it must be reported to OSHA within 24 hours.

After incident reporting requirements have been met, the focus should be turned to incident investigation including documentation and photographs. Investigating an incident should be a careful and deliberate process that identifies the immediate, contributory and root causes of the incident.

By reaching the root cause of an incident, appropriate measures (Corrective and Preventative Actions or CAPAs) can be applied to reduce the likelihood of the same or similar incident happening again. An example methodology to support root cause analysis is the "5 Why" methodology, which is a common Six Sigma tool for root cause analysis. Through this method the question "why?" is asked in series to dig-down to the failures of the layer or layers of protection that enabled an incident to occur.

The first "why?" identifies a condition or act that directly caused the incident. The second "why?" identifies contributing causes to an incident, the third "why?" identifies a gap or a failure of a direct management system that lead to the incident, "Why 4" identifies a failure of supporting or enabling management systems such as training, communication, risk assessment or planning as well as cultural aspects. "Why 5" may be needed in the case of several contributing causes in which one would want to find commonalities between them and consider what other incidents could occur.

Once the root cause and contributory causes have been identified, it is appropriate to identify CAPAs as a preventative action to ensure this or a similar incident does not repeat, and others do not occur going forward. Driving identified actions to completion is imperative.

Table 6 Outlining an example of an incident and a series of questions (5 Why's) to reach the root cause (Avizinis, 2018)

(1) *Why did a person receive an ocular exposure to a biological agent?*	Because the biological agent was in a liquid form and when a container of the liquid dropped, it splashed into the person's eye.
(2) *Why the liquid was able to enter the person's eye?*	The person was not wearing eye protection (PPE) and the container was being carried around outside of secondary containment (insufficient protection during transport) so that when the liquid splashed it went straight up into the person's eye.
(3) *Why was the person not wearing appropriate PPE to protect from splashes? And why the container was being carried outside of secondary containment?*	This task was not covered by the Standard Operating Procedure (SOP.) The hazard was not communicated to the person.
(4) *Why wasn't the task covered by the SOP?*	There were no biosafety risk assessment precautions in the SOP because there was no biosafety program.
(5) *Why wasn't the biosafety program in place?*	The company did not have that a biosafety program which must be in place for protection of the worker before startup of biopharmaceutical manufacturing.

Biosafety key feature: Communication

Once the regulatory review, risk assessment, pre- and post-exposure planning has been completed, the outcomes or recommendations for medical surveillance, containment, administrative controls, PPE, and emergency response procedures should be communicated to all applicable personnel. There are several ways to communicate these outcomes including training, signage, risk assessment review and the drafting of SOPs. Ensuring that all personnel and entrants fully understand the risk assessment outcomes and proper expectations for safe work with biological agents is key to preventing release or exposure. Communications should also include any breaches and

near misses, extraneous contamination events and information about new agents/changes at the facility.

Despite the application of these measures and communicated recommendations, the risk of release or exposure may not be fully eliminated. Residual risk associated with workspaces or procedures should be incorporated into training and hazard communication and should also be considered as an opportunity in the strategy for continuous improvement whereby the hazard mitigation is planned, the work is conducted, the procedures are reviewed and if modifications are required for increased safety, they are applied. This is often referred to as "Plan, Do, Check, Act" which is a simple means of remaining vigilant of improvement opportunities which enable a safer workplace. This process can be formalized through the working group and/or biosafety or safety committee which meets periodically to discuss a procedure or project and opportunities for improvement. It could also be a less formal process during a daily or weekly check-in. The benefit to formalizing this process through these mechanisms is that it enables periodic review, documentation and memorialization of the continuous improvements.

FUTURE BIOPHARMACEUTICAL BIOSAFETY – SPECIAL CHALLENGES

Advances in biological science in the past few decades have been significant and rapid. As such, biological safety considerations have become an increasingly important component of EHS programs. The ability to genetically modify any microbial agent is a challenge in that there are limited reference sources to verify potential impacts to an exposed person (without the specific disease condition) or environmental release. Modifications can make hazard characterization and assigning an RG or BSL difficult as the definitions may not directly correlate. Nanoparticles have become a desirable vehicle for delivery of transgenes and nucleic acids, and their synthesis and use carry a unique set of exposure control and environmental release considerations.

Collection of human source materials from global sources, while valuable to research or manufacturing, may pose the risk of exposure to uncommon or even unknown agents. The use of human donor lymphocytes to create autologous or allogenic cancer treatment involves human sourced material, genetic modification and purification as part of the biomanufacturing process. There is an evolution to accommodate these new processes and technologies but it is seemingly continuous.

Regardless, the more that is learned about biotechnology, molecular biology, immunology, emerging infectious diseases, the more varied the techniques, assays, tasks, and treatments. Facility design, containment, HoCs and contamination control are areas for which biosafety professionals must have current knowledge of these new processes and technologies to continue to play a vital role in pre-work planning and throughout the agent's lifecycle.

CONCLUSION

Biological agents involved in drug supply chain operations – development, manufacture and testing, must be well understood in terms of biosafety. Impact exposure for employee protection and environmental containment must be managed at the same level of priority and rigor as GMP requirements to assure product quality and safety. Key features in a biosafety program include review of regulations, risk assessment of key factors, controls to prevent exposure, incident investigation programs, emergency preparedness and effective communication.

New drug delivery systems and biotechnology are advancing at such a rapid pace, that the strategies and challenges for biosafety programs to protect human health and the environment from a large and diverse group of biological agents must be proactive, comprehensive, continuously improved and evaluated for risk. The industry and regulatory guidance in the area of biosafety is growing and requires collaboration with all stakeholders including site leadership, quality and laboratory personnel including

contamination control microbiologists, manufacturing and biosafety professionals.

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Currently Jessica supports several projects at Pfizer Inc. in Research and Development (R&D) as well as clinical/commercial manufacturing in biotechnology including gene therapy. She supports the EHS external supply team to assess biosafety capabilities at contract researcher, manufacturing, supplier and vendor facilities. She leads Pfizer's Biosafety Network driving improvements in strategy and biosafety practices across the enterprise.

Jessica also serves as the secretary for the Pharmaceutical Benchmarking Group (PBG), a group of biosafety professionals in the biopharmaceutical industry who meet annually to identify industry best practices, as well as a community member of a US government research facility IBC. She holds a B.S. in Wildlife Conservation Biology and an M.S. in Medical Laboratory Science and she is a Registered Biosafety Professional under the American Biological Safety Association (ABSA) International.

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