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Biorisk management

Laboratory biosecurity guidance

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EPIDEMIC AND PANDEMIC
ALERT AND RESPONSE

World Health Organization

Abbreviations

BSL3 Containment laboratory – Biosafety Level 3

BSL4 Maximum containment laboratory – Biosafety Level 4

FAO Food and Agriculture Organization of the United Nations

GMO Genetically modified organism

LBM3 Laboratory biosafety manual, third edition, 2004

LBG Biorisk management: laboratory biosecurity guidance, first edition, 2006

OIE World Organisation for Animal Health

VBM Valuable biological materials

WHO World Health Organization

Definitions

The following terms are defined in the context in which they are used in this document.

Accountability
Accountability ensures that valuable biological materials (VBM, see definition below) are controlled and traced as intended, by formally associating the specified materials with the individuals who provide oversight and are held responsible for them.

Bioethics
The study of the ethical and moral implications of biological discoveries, biomedical advances, and their applications as in the fields of genetic engineering and drug research (adopted from *1*). In this document, bioethics is one of the three components that contribute to a successful biorisk management culture.

Biological laboratory
A facility within which microorganisms, their components or their derivatives are collected handled and/or stored. Biological laboratories include clinical laboratories, diagnostic facilities, regional and/national reference centres, public health laboratories, research centres (academic, pharmaceutical, environmental, etc.) and production facilities (manufacturers of vaccines, pharmaceuticals, large scale GMOs, etc) for human, veterinary and agricultural purposes.

Biorisk
The probability or chance that a particular adverse event (in the context of this document: accidental infection or unauthorized access, loss, theft, misuse, diversion or intentional release), possibly leading to harm, will occur.

Biorisk assessment
The process to identify acceptable and unacceptable risks (embracing biosafety risks (risks of accidental infection) and laboratory biosecurity risks (risks of unauthorized access, loss, theft, misuse, diversion or intentional release)) and their potential consequences.

Biorisk management
The analysis of ways and development of strategies to minimize the likelihood of the occurrence of biorisks. The management of biorisk places responsibility on the facility and its manager (director) to demonstrate that appropriate and valid biorisk reduction (minimization) procedures have been established and are implemented. A biorisk management committee should be established to assist the facility director in identifying, developing and reaching biorisk management goals.

Biosafety
Laboratory biosafety describes the containment principles, technologies and practices that are implemented to prevent the unintentional exposure to pathogens and toxins, or their accidental release (*2*).

Code of conduct, code of ethics, code of practice
Non-legislated guidelines which one or more organizations and individuals voluntarily agree to abide by, that set out the standard of conduct or behavior with respect to a particular activity (adopted from *1*).

Control
Control is the combination of engineered and procedural measures that ensure valuable biological material (VBM, see definition below) are used only as intended.

Dual-use
Initially used to refer to the aspects of certain materials, information and technologies that are useful in both military and civilian spheres. The expression is increasingly being used to refer not only to military and civilian purposes, but also to harmful misuse and peaceful activities (adopted from *1*).

Genetically modified organisms (GMO)
Organisms whose genetic material has been altered using techniques generally known as "recombinant DNA technology". Recombinant DNA technology is the ability to combine DNA molecules from different sources into one molecule in a test tube. GMOs are often not reproducible in nature, and the term generally does not cover organisms whose genetic composition has been altered by conventional cross-breeding or by "mutagenesis" breeding, as these methods predate the discovery (1973) of recombinant DNA techniques.

Hazard
A danger or source of danger; the potential to cause harm.

Laboratory biosecurity
Laboratory biosecurity describes the protection, control and accountability for valuable biological materials (VBM, see definition below) within laboratories, in order to prevent their unauthorized access, loss, theft, misuse, diversion or intentional release.

Misuse
The misuse of valuable biological materials (VBM, see definition below) describes their inappropriate or illegitimate use, despite existing and subscribed agreements, treaties and conventions (*3*).

Threat
The likelihood for an adverse event to occur, as an expression of intention to inflict evil, injury, disruption or damage.

Transfer of VBM
Legal and/or administrative policies and procedures relating to the oversight and approval process for the transfer of custody and/or ownership of valuable biological materials (VBM, see definition below) between countries, entities (organizations, institutions, facilities, etc.) or individuals.

Transport of VBM
Procedures and practices to correctly categorize, package, document and safely and securely transport valuable biological materials (VBM, see definition below) from one place to another, following applicable national and/or international regulations.

Valuable biological materials (VBM)
Biological materials that require (according to their owners, users, custodians, caretakers or regulators) administrative oversight, control, accountability, and specific protective and monitoring measures in laboratories to protect their economic and historical (archival) value, and/or the population from their potential to cause harm. VBM may include pathogens and toxins, as well as non-pathogenic organisms, vaccine strains, foods, genetically modified organisms (GMOs), cell components, genetic elements, and extraterrestrial samples.

1. Introduction

Background

Disease diagnosis, human or animal sample analysis, epidemiological studies, scientific research, and pharmaceutical developments: all of these activities are carried out in biological laboratories in the private or public sectors. Biological materials are handled worldwide in laboratories for numerous genuine, justifiable and legitimate purposes, where small and large volumes of live microorganisms are replicated, where cellular components are extracted and many other manipulations undertaken for purposes ranging from educational, scientific, medicinal and health-related to mass commercial and/or industrial production. Among them, an unknown number of the facilities, large and small, work with dangerous pathogens or their products every day.

The general public expects laboratory personnel to act responsibly and not to expose the community to biorisks, to follow safe working practices (biosafety) associated with practices that will help keep their work and materials safe and secure (biosecurity), and to follow an ethical code of conduct (bioethics). Often suspicious of work taking place in laboratories, the uninformed public may even feel threatened by the presence of a biological laboratory in their neighborhood. It is the technical and moral duty of laboratory managers and laboratory workers, with the support of national authorities, to reassure the general public, to persuade them that the activities being conducted are beneficial and necessary, and to prove that the biorisks inherent to laboratory work are controlled with appropriate safeguards to meet their expectations.

However, despite advances in technology, the availability of more and more sophisticated instruments for laboratory use, increasingly effective techniques and the availability of personal protective equipment, human error remains one of the most important factors at the origin of accidents. Poor concentration, denial of responsibilities, inappropriate accountability, incomplete record-keeping, suboptimal facility infrastructure, refusal to acknowledge ethical considerations, lack of (or lack of respect for) codes of conduct, etc. may be at the origin of laboratory-acquired infections, loss of material and inappropriate manipulations, or even possibly intentional misbehaviour.

Pathogens and toxins have been used, even in the recent past, to threaten and harm people, to disrupt society, economies and the political status quo (*5*). This has happened in spite of applicable international agreements banning the use of biological agents for malicious use. As those who carry out such acts show disregard for ethical values (*6*), do not respect the right of people to a safe and peaceful life, or do not recognize global treaties and conventions, several regulatory approaches to limit unauthorized access to biological agents and toxins available in biological laboratories are now being carefully considered and implemented worldwide.

Three examples illustrate the need to respond to the international community and articulate biosecurity in the laboratory:

1. Smallpox has been eradicated some 26 years ago. However, its causative agent, variola virus, remains stored in two WHO Collaborating Centres under maximum containment. The accidental or deliberate reintroduction of variola virus into the environment threatens not only public health, but also the economy and political stability of the whole world. For this reason, the known remaining variola virus stocks are subject to WHO scrutiny for the research they are subject to (*7*), and each site is regularly assessed by WHO for its biosafety and laboratory biosecurity (*8*). Despite these existing international arrangements, this guidance document offers an opportunity for further improvement of their working and storage conditions.

2. As the final stages of the poliomyelitis eradication campaign approach, steady progress is being made towards the safe-keeping of facilities containing poliovirus samples and stocks, which will then be advised to decide whether to keep these polioviruses and upgrade their biosafety containment and biosecurity levels and tighten their codes of conduct, transfer their poliovirus samples to a better-equipped reference laboratory, or destroy the remaining stocks. Experience gained and lessons learnt from the containment of variola viruses post eradication offer an invaluable opportunity to plan for the polio post eradication phase and for the development of most appropriate biorisk management plans and goals.

3. Laboratory biosecurity provisions may not have impeded the release of the anthrax letters in the USA in 2001 (*5*). In hindsight however, laboratory biosecurity provisions to write records on research and activity, access shared documentation, consult approved research projects and available results data, may have helped discharge alleged facilities and perpetrators from the list of possible suspects.

Historical awareness of the dual-use (*9*) of agents, equipment and technology, is also considered in the development of laboratory biosecurity guiding principles.

Current situation

Facilities containing biological agents may represent tempting procurement opportunities, thus advocacy for security-related scrutiny of biological facilities, their personnel and their visitors is increasing worldwide. In recent years, several countries have developed and implemented laboratory biosecurity legislation to regulate possession, use and access to biological materials to permit their appropriate use.

Despite the advances of some countries, in many other countries and for many laboratories, guidance or specific requirements for the appropriate handling and storage of valuable biological materials (VBM, described below) do not yet exist. This raises the following questions: How are these agents generally kept in such countries? Who has access to them? What kind of research is allowed and conducted with them? Who oversees this research? Who has the ultimate responsibility for these agents? Who should have access to information related to these agents, including research

results and storage details? Should research results be published? Is there a scrutiny for the publication of research data?

Many open questions still remain in the context of laboratory biosecurity, and much still needs to be done to reassure the public, scientists, laboratory managers, regulators, national authorities and the international community that the appropriate measures to prevent, manage, control and minimize the biorisks associated with possessing and handling infectious agents are in place. The biorisk management approach described in this document, encompassing biosafety and laboratory biosecurity, represents a step towards the clarification of these questions.

Globally, one common trend can be identified: rather than providing a prescriptive approach to addressing biosafety and related issues, and requesting compliance with a set of strict rules, the move to a goal-setting approach describing performance expectations for facilities, and placing the responsibility on single facilities to demonstrate that appropriate and valid biorisk minimization measures have been established, is proving very successful. Leaving the choice of procedures, control measures and verification systems to facility managers to ensure that set goals are reached requires the involvement of dedicated managers and of leaders who express appreciation for specific measures, and are instrumental in encouraging and supporting the development of a global biorisk management culture. Indeed it is such a biorisk management culture that the international bioresearch community should strive for.

International biorisk management

While an understanding of the need to safeguard VBM is becoming more widespread, universally agreed-upon laboratory biosecurity principles and practices are not. The resulting inconsistencies represent the complexity of the issue and a challenge for the international community to identify what should be addressed and how to respond to real needs. In the framework of public health, the challenge for the World Health Organization (WHO), the Food and Agriculture Organization of the United Nations (FAO) and the World Animal Health Organisation (OIE) is to provide Member States with balanced, appropriate and sustainable recommendations that address the biosecurity of biological materials in laboratory environments, expanding the strict mandates of these organizations in the fields of human and animal public health to the area of security, generally associated with entities that have law-enforcement mandates.

International organizations and agreements use the word biosecurity in a variety of contexts and for different purposes, in response to recommendations to protect different assets. FAO and OIE refer to biosecurity in the context of biological and environmental risks associated with food and agriculture, including forestry and fisheries, a sector that covers food safety, and the life and health of plants and animals. The risks include everything from the introduction and release of GMOs and their products, the introduction and spread of invasive alien species, alien genotypes and plant pests, animal pests and diseases and zoonoses, to the erosion of biodiversity, the spread of transboundary cattle diseases, or the preservation of food supplies after production.

The purpose of this document is to define the scope and applicability of "laboratory biosecurity" recommendations, narrowing them strictly to human, veterinary and agricultural laboratory environments. The operational premise for supporting national laboratory biosecurity plans and regulations generally focuses on dangerous pathogens and toxins. In this document, the scope of laboratory biosecurity is broadened by addressing the safekeeping of all *valuable biological materials* (VBM), including not only pathogens and toxins, but also scientifically, historically and economically important biological materials such as collections and reference strains, pathogens and toxins, vaccines and other pharmaceutical products, food products, GMOs, non-pathogenic microorganisms, extraterrestrial samples, cellular components and genetic elements. This is done in order to raise awareness of the need to secure collections of VBM for many reasons, including: for the sake of biology, to preserve biological diversity and endangered species, to perform microbiological studies and better understand the living world and the science behind it; to safeguard resources from which new drugs, vaccines and life-saving materials may be developed, for historical reasons, and to advance the state of knowledge.

Scope of this document

This document introduces a new concept and approach to minimize or prevent the occurrence and consequences of human error within the laboratory environment: the biorisk management approach, composed of biosafety, laboratory biosecurity and ethical responsibility.

Biosafety and its internationally acknowledged advantages have already been extensively described in LBM3. Laboratory biosecurity and its as yet poorly appreciated advantages and responsibility in coordinating personnel and scientific activities (research), and code of ethics are discussed here.

Within a comprehensive biorisk management approach, this document aims to define and guide the reader in the field of laboratory biosecurity. It is addressed to laboratories wishing to handle and store VBM, and discusses the legal framework within countries holding and supporting such laboratories. Setting the goal of managing biorisks should drive national authorities, laboratory managers and ultimately laboratory workers to take responsibility in developing the necessary safeguards. This in turn should demonstrate that biorisks in all their potential forms are appropriately addressed, managed and minimized.

Rationale

While Member States are expected to address laboratory biosecurity issues in the context of their regional, national and local situations and needs, this document provides guidance to help frame the concepts. A comparative description of biosafety and laboratory biosecurity is provided below for clarification.

Member States are encouraged to introduce these concepts within their local contexts and to develop national frameworks for the security of biological materials they consider valuable, in recognition of the ever-increasing importance of global regulatory harmonization (*10*). In the absence of national regulatory guidance, laboratory managers are encouraged to consider adopting a biorisk management approach adapted to their particular situation and developing guiding principles to be implemented in response to the specific needs of their facilities.

2. Laboratory biosecurity as a complement to laboratory biosafety

Laboratory biosafety and biosecurity mitigate different risks, but they share a common goal: keeping VBM safely and securely inside the areas where they are used and stored.

Laboratory biosafety (*2*) is the expression used to describe the containment principles, technologies and practices that are implemented to prevent unintentional exposure to pathogens and toxins, or their accidental release.

A comprehensive biosafety culture translates into the understanding and routine application of a set of safe practices, procedures, actions and habits that protect the people working with biological materials.

Laboratory biosecurity may be addressed through the coordination of administrative, regulatory and physical security procedures and practices implemented in a working environment that utilizes good biosafety practices, and where responsibilities and accountabilities are clearly defined. Biosafety and laboratory biosecurity are complementary. In fact, the implementation of specific biosafety activities already covers some biosecurity aspects. The systematic use of appropriate biosafety principles and practices reduces the risk of accidental exposure and paves the way for reducing the risks of VBM loss, theft or misuse caused by poor management or poor accountability and protection. Laboratory biosecurity should be built upon a firm foundation of good laboratory biosafety.

Through microbiological risk assessments performed as an integral part of an institution's biosafety programme, information is gathered regarding the type of organisms available at a given facility, their physical location, the personnel who require access to them, and the identification of those responsible for them. A laboratory biosecurity risk assessment should further help establish whether this biological material is valuable and warrants security provisions for its protection that may be insufficiently covered through recommended biosafety practices. This approach underlines the need to recognize and address the ongoing responsibility of countries and institutions to ensure the expectation for a safe and secure laboratory environment.

A specific laboratory biosecurity programme, managing the identified biorisks, should be prepared and designed for each facility according to its specific requirements, to the type of laboratory work conducted, and to local and geographical conditions. Laboratory biosecurity activities should be representative of the institution’s various needs and should include input from scientific directors, principal investigators, biosafety officers, laboratory scientific staff, maintenance staff, administrators, information technology staff, law-enforcement agencies and security staff, if appropriate. A sound code of practice should be included for personnel practice.

Laboratory biosecurity measures should be based on a comprehensive programme of accountability for VBM that includes:

1. regularly updated inventories with storage locations,
2. identification and selection of personnel with access,
3. plans of use of VBM,
4. clearance and approval processes,
5. documentation of internal and external transfers within and between facilities, and of any
6. inactivation and/or disposal of the material.

Likewise, institutional laboratory biosecurity protocols should include how to handle breaches or near-breaches in laboratory biosecurity including:

1. incident notification,
2. reporting protocols,
3. investigation reports,
4. recommendations and remedies, and
5. oversight and guidance through the Biosafety Committee.

The protocols should also include how to handle discrepancies in inventory results, and describe the specific training to be offered, and the training that personnel should be required to follow. The involvement, roles and responsibilities of public health and security authorities in the event of a security breach should also be clearly defined. Documenting procedures to manage behaviour and the interaction of workers with the facility and its equipment should also be considered.

These issues should be addressed according to a goal-setting approach to make sure the objective of minimizing biorisks is reached, rather than following a prescriptive approach to demonstrate compliance to a given set of rules. A goal-setting approach furthermore enables facilities to be creative, imaginative and innovative, allowing for responding to unexpected events, and for new findings and considerations to be easily incorporated into existing management systems. Goal-setting principles-based approaches enable staff to deal with the unpredicted and unfamiliar in the most prudent and safe manner until more expert opinion can be obtained.

2.1 Commonalities and conflicts: laboratory biosafety vs laboratory biosecurity

Commonalities

Good laboratory biosafety practices reinforce and strengthen laboratory biosecurity systems. Appropriate levels of biosafety may be achieved through carefully designed and implemented work practices, even in modestly-equipped facilities. The biosafety recommendations outlined in LBM3 provide clear levels of protection for VBM. For example self-closing doors, restricted access, physical separation from traffic areas, break-resistant windows and an emergency response plan may all be common to both biosafety and laboratory biosecurity.

LBM3 also advocates a "reliable and adequate electricity supply and emergency lighting" as well as a "stand-by generator". While this helps to ensure the function of critical biosafety equipment (ventilation systems, biological safety cabinets, autoclaves, etc.), it also supports components of physical security systems that may depend on electrical supply.

According to LBM3, the review of research protocols falls under the responsibilities of the biosafety officer and the biosafety committee, by delegation of the director of the facility. This includes risk assessments in consultation with local authorities, national regulatory bodies and the community for contentious or sensitive protocols under discussion. Adding the review of laboratory biosecurity to the existing biosafety mandate for biosafety committees represents a major change and an additional responsibility (*11*). The best advice to these committees is that they should follow transparent processes involving open discussions, and examine moral and ethical considerations before reaching risk management conclusions (*12*). The approval of research protocols should include guidance on how to keep or destroy the developed materials, and the criteria that should be applied before taking a final decision. Scientists for their part should play an active role in decision-making in order to protect intellectual rights and participate in determining the benefits and risks of the research to be undertaken, including protection and access to VBM. Only a well-structured dialogue involving researchers, the biosafety committee and facility managers may ultimately allow a facility to be adequately prepared to best mitigate the consequences of biosecurity breaches that may also result in external criticism.

However, even though biosafety and laboratory biosecurity are in most respects compatible, a number of potential conflicts exist that need to be resolved.

Figure 1. **Biohazard warning sign for laboratory doors**

Conflicts

In the absence of careful implementation, various aspects of biosafety may conflict with laboratory biosecurity. For example, controls that reduce unauthorized access might also hinder an emergency response by fire or rescue personnel. Mechanisms need to be established that allow entry by emergency responders but ensure uninterrupted and constant laboratory biosecurity, control, accountability and traceability of VBM. Likewise, staff members must be able to quickly and safely exit a laboratory during an emergency without at the same time allowing unrestricted access to sensitive VBM.

Signage may also represent a potential conflict between biosafety and laboratory biosecurity. In the past, biohazard signs placed on laboratory doors identified the biological agents present in the laboratory. However, as a laboratory biosecurity measure to better protect sensitive VBM, LBM3 now recommends limiting the information on biohazard signs to the laboratory biosafety level, the name and telephone number of the responsible investigator, and emergency contact information (*Fig. 1*).