



**Responsible  
life sciences research  
for global health  
security**

**A GUIDANCE  
DOCUMENT**



**World Health  
Organization**

# Responsible life sciences research for global health security

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**World Health  
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# Acronyms

BSL	Biosafety level
BWC	Biological and Toxin Weapons Convention
BBSRC	Biotechnology and Biological Sciences Research Council (United Kingdom)
CDC	Centers for Disease Control and Prevention of the Department of Health and Human Services (United States of America)
CSE	Council of Science Editors
EC	European Commission of the European Union
GMO	Genetically modified organism
IAP	InterAcademy Panel
ICLS	International Council for the Life Sciences
ICSU	International Council for Science
IHR	International Health Regulations
IUBMB	International Union of Biochemistry and Molecular Biology
IUMS	International Union of Microbiological Societies
HRS	Health research systems
MRC	Medical Research Council (United Kingdom)
NGO	Nongovernmental organization
NIH	National Institutes of Health of the Department of Health and Human Services (United States of America)
NRC	National Research Council of the National Academies (United States of America)
NSABB	National Science Advisory Board for Biosecurity (United States of America)
PHEIC	Public Health Emergencies of International Concern
rDNA	Recombinant DNA
RS	Royal Society of the United Kingdom
VBM	Valuable biological materials
WAME	World Association of Medical Editors
WHA	World Health Assembly of the World Health Organization
WHO	World Health Organization

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# Definitions

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

**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 (1).<sup>1</sup>

**Biological laboratory** A facility within which biological agents, their components or their derivatives, and toxins 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 (the manufacturing of vaccines, pharmaceuticals, large-scale genetically modified organisms, etc.) for human, veterinary and agricultural purposes (1).

**Biorisk** The risk (risk is a function of likelihood and consequences) that a particular biological event (in the context of this document: naturally occurring diseases, accidents, unexpected discovery, or deliberate misuse of biological agents and toxins), which may affect adversely the health of human populations, may occur (1, 2). An assessment of these risks can be both quantitative and qualitative.

**Biorisk spectrum** A continuum of biorisks ranging from naturally occurring diseases (chronic and infectious diseases), to accidents, to the deliberate misuse of biological agents and toxins with the intention to cause harm (Figure 1) (2).

**Biorisk reduction** The reduction of the occurrence of risks associated with exposure to biological agents and toxins, whatever their origin or source, encompassing the full spectrum of biorisks (2).

**Laboratory biosafety** The containment principles, technologies and practices that are implemented to prevent unintentional exposure to biological agents and toxins, or their accidental release (3, 4).

**Laboratory biosecurity** The protection, control and accountability for valuable biological materials<sup>2</sup> within laboratories, in order to prevent their unauthorized access, loss, theft, misuse, diversion or intentional release (1).

**Dual-use life sciences research** Knowledge and technologies generated by legitimate life sciences research that may be appropriated for illegitimate intentions and applications (2, 5).

**Life sciences** All sciences that deal with organisms, including humans, animals and plants, and including but not limited to biology, biotechnology, genomics, proteomics, bioinformatics, pharmaceutical and biomedical research and techniques.

**Global health security** The activities required, both proactive and reactive, to minimize vulnerability to acute public health events that endanger the collective health of populations living across geographical regions and international boundaries (6).

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<sup>1</sup> International Futures Program of the Organisation for Economic Co-operation and Development (OECD), Biosecurity oversight and codes ([www.biosecuritycodes.org/gloss.htm](http://www.biosecuritycodes.org/gloss.htm), accessed October 2010).

<sup>2</sup> Valuable biological materials (VBM) are “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)

**Health research systems** The people, institutions, and activities whose primary purpose in relation to research is to generate high-quality knowledge that can be used to promote, restore and/or maintain the health status of populations; it should include the mechanisms adopted to encourage the utilization of research (7).

**Public health** The science and art of preventing disease, prolonging life, and promoting health through the organized efforts and informed choices of society, organizations, public and private, communities and individuals (8). Health is defined by the Constitution of the World Health Organization as a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity.

**Research excellence** Research that is of high quality, ethical, rigorous, original and innovative.

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# Executive summary

Advances in life sciences research are inextricably linked to improvements in human, plant and animal health. Promotion of excellent, high-quality life sciences research that is conducted responsibly, safely and securely can foster global health security and contribute to economic development, evidence-informed policy making, public trust and confidence in science. Yet opportunities may also be accompanied by risks that need to be acknowledged and addressed. The risks under consideration in this guidance are those associated with accidents, with research that may pose unexpected risks and with the potential deliberate misuse of life sciences research. The opportunities offered by the life sciences are too important for governments and the scientific community (including individual researchers, laboratory managers, research institutions, professional associations, etc.) to leave the attendant risks unaddressed.

The purpose of this guidance is to inform Member States about the risks posed by accidents or the potential deliberate misuse of life sciences research and to propose measures to minimize these risks within the context of promoting and harnessing the power of the life sciences to improve health for all people. Although the issues addressed in this document can potentially interest a quite large audience, the proposed measures and the self-assessment questionnaire are of a public health nature. Health researchers, laboratory managers and research institutions are therefore the primary audience of this guidance.

There is no single solution or system that will suit all countries, institutions or laboratories. Each country or institution that assesses the extent to which it has systems and practices in place to deal with the risks posed by accidents or the potential deliberate misuse of life sciences research will need to decide which measures are most appropriate and relevant according to their own national circumstances and contexts.

However, as recognized by the World Health Assembly in 2002 (Resolution WHA55.16), one of the most effective ways to prepare for deliberately caused disease is to strengthen public health measures for naturally occurring and accidentally occurring diseases. This guidance contributes to the implementation of WHA55.16 and promotes a culture of scientific integrity and excellence, distinguished by openness, honesty, accountability and responsibility. Such a culture is the best protection against the possibility of accidents and deliberate misuse, and the best guarantee of scientific progress and development.

Moreover, countries and institutions may consider drawing on the biorisk management framework for responsible life sciences research developed by this guidance. This integrated framework rests on three pillars supporting public health.

■ **Research excellence** – this concerns fostering quality in life sciences activities, which is the basis for developing new treatments and therapeutics, strengthening health research systems, and promoting public health surveillance and response activities. These elements are essential to protecting and improving the health and well-being of all people.

As such, countries and institutions are invited to:

- Support capacity development for research as this is essential for reducing health inequalities and for ensuring the proper use of life sciences;
- Use existing tools and frameworks, such as health research systems (HRS), the WHO strategy on research for health and the International Health Regulations (IHR) as these can provide useful tools for contributing to responsible life sciences research.

- **Ethics** – this involves the promotion of responsible and good research practices, the provision of tools and practices to scientists and institutions that allow them to discuss, analyse and resolve in an open atmosphere the potential dilemmas they may face in their research, including those related to the possibility of accidents or misuse of the life sciences.

As such, countries and institutions are invited to:

- Use existing ethical platforms, if appropriate;
- Promote ethics education and training for students and professionals;
- Encourage discussion and reflection on research practices;
- Hold institutions and researchers to account and ensure they are aware of their responsibilities;
- Ensure institutions and researchers are aware of existing and new legislation, regulations at the country but also at the regional and international levels.

- **Biosafety and laboratory biosecurity** – this concerns the implementation and strengthening of measures and procedures to: minimize the risk of worker exposure to pathogens and infections; protect the environment and the community; and protect, control and account for valuable biological materials (VBM) within laboratories, in order to prevent their unauthorized access, loss, theft, misuse, diversion or intentional release. Such measures reinforce good research practices and are aimed at ensuring a safe and secure laboratory environment, thereby reducing any potential risks of accidents or deliberate misuse.

As such, countries and institutions are invited to:

- Conduct biosafety and laboratory biosecurity risk assessments and, based on these, apply appropriate risk reduction measures;
- Implement a laboratory biorisk management system;
- Explore the use of existing biorisk management structures (e.g. laboratory biorisk management adviser and the biosafety committee) to address issues related to the risks posed by life sciences research;
- Set performance objectives and work on continuous improvement.

A culture of responsible life sciences practice is most likely to result when the leadership within the organization supports and fosters such a management framework.

In implementing the above biorisk management framework for responsible life sciences research, countries and institutions are encouraged to consider:

- Reinforcing public health capacities in terms of research for health, biosafety and laboratory biosecurity management and ethics;
- Investing in training personnel (laboratory staff and researchers) and students in ethics, the responsible conduct of research, and biosafety and laboratory biosecurity.
- Ensuring compliance with biosafety and laboratory biosecurity;
- Seeing multi-stakeholder issues, with different layers of responsibilities and encourage coordination among stakeholders;
- Using existing mechanisms, procedures and systems and reinforce local institutional bodies (if they exist).

Another major component of this guidance is a self-assessment questionnaire, which is intended to help health researchers, laboratory managers, and research institutions identify and build on strengths and address weaknesses in each of the three pillars of the biorisk management framework. Going through this process will provide an assessment of the extent to which systems are in place in the national public health system and individual laboratories to address the risks of accidents and the potential deliberate misuse of science and to identify priority areas where action is necessary to ensure high-quality, safe, secure and responsible research practices across the life sciences.

In general, oversight, safety and public security should be pursued in a manner that maximizes scientific progress and preserves scientific freedom. Any controls over life sciences research need to be proportionate and risk-based, should not unduly hamper the development of the life sciences and should not discourage scientists from working with important pathogens. This requires excellent facilities, and the management of them (including laboratories), leadership with integrity, a robust ethical framework, training and capacity development, institutional development and regular review.

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# 1. Introduction

## 1.1 Context, purpose, audience and scope of the guidance

### 1.1.1 Context

When the reconstruction of the 1918 influenza A (H1N1) pandemic virus, also known as the Spanish Flu virus, was published in 2005, many people considered it a remarkable achievement that could help combat future influenza pandemics. At the same time, it raised concerns that the resurrected virus might escape from laboratories (as happened with severe acute respiratory syndrome [SARS] coronavirus in 2003–2004) or that the knowledge gained from this research could be deliberately misused to cause harm. Research-related laboratory accidents have the potential to affect laboratory workers, the environment, and local and more distant communities. The 2001 anthrax letters in the United States of America, which killed five people and infected 22, had a worldwide impact and underscored the role of public health systems in responding to the deliberate misuse of a biological agent (9). Other kinds of research misuse that may be dangerous to public health and have a significant economic burden include deliberately neglecting or side-stepping good research practices and codes of conduct, which are meant to ensure standards of ethics, safety and quality (10, 11).

The reconstruction of the 1918 influenza A (H1N1) pandemic virus is one of a few experiments in recent years that have grabbed the media's attention and led to calls for better management of the potential risks associated with accidents or the deliberate misuse of life sciences research. There is a wide recognition that there is no "one size fits all" management measure and that such measures may be issued by different stakeholders. The need to have clear guidelines about what researchers, publishers, funding bodies, governments and other actors are expected to do with research raising possible risks as well as the need to have guidelines

to avoid measures that would go beyond what is appropriate, have been emphasized (12–14).

The role of WHO in this area has been underlined by several groups, including by the National Research Council of the US National Academies of Sciences in their 2004 seminal report on the subject "Biotechnology Research in an Age of Terrorism: Confronting the Dual-Use Dilemma, also called the "Fink report" (15). It has also been noted that WHO as an international organization with direct links to policy makers and having wide acceptance as an authority in preserving public health, is particularly equipped to promote responsible life sciences research. By emphasizing the public health perspective of dual-use issues, this guidance can achieve a broad acceptance of the need to raise awareness in this area and thus be better able to implement the objectives of promoting responsible life sciences research in general on a global level.

A scientific working group, which met in WHO in 2006 to discuss the risks and opportunities of life sciences research for global health security, also underlined the important role of WHO to lead, in coordination with other stakeholders and in line with its public health mandate, global efforts and help maintain effective policies that will maximize the benefits of public health research while minimizing the risks (2). Moreover, participants at a WHO workshop on responsible life sciences research also underscored the need to have a foundational document on this topic (see [Annex 3](#)). As this subject is being addressed by many stakeholders with different interests and agendas, this document provides a unique international public health perspective on this issue, which is important to complement with other policy measures. Such a perspective also provides a platform for discussion.

The importance of a public health perspective on this topic is important for several reasons. The life sciences have the potential to address a host of public health, agricultural and environmental

challenges, making them a key driver of economic growth and an important element of health innovation for developing, as well as for developed countries (16–19). It is widely perceived that advances in the life sciences will continue to be significant in this century and that the impact will be similar to that of the life and physical sciences in the 20th century (20).

Capacity development for research is necessary for ensuring the proper use of life sciences research and minimizing accidents and potential for deliberate misuse (21). Research on conditions affecting the health status of poor people along with access and delivery tools are crucially needed. Despite the substantial increase in funding for research and development (R&D) in developing countries (22) and the investment in life sciences R&D expertise by countries such as Brazil, China and India (22), only a small proportion of the quadrupling global investments in R&D since 1986 has been spent on diseases affecting poor people (23). Over the same time, health status has deteriorated in many developing countries,<sup>1</sup> which are increasingly suffering from the double burden of disease, combining the so-called diseases of poverty (infectious diseases and maternal, perinatal and nutrition conditions) with injuries and chronic noncommunicable diseases such as cancers, diabetes and cardiovascular diseases (22, 24).

It is well recognized that more needs to be done to reduce inequities in health conditions among populations, to bridge the technological gap between developed and developing countries (16, 25), and to translate new knowledge into health products. Access to biotechnologies therefore remains a major aspect for health development (18). The Millennium Development Goals have stressed the important role of the life sciences for human security. Biomedical research and emerging genomics techniques along with international collaboration and partnerships can help to achieve these and other development goals (26).

Yet opportunities are often accompanied by a number of risks. Advances in life sciences research and new biotechnologies such as genomics, synthetic biology, stem-cell research, and genetically modified organisms and foods have already raised a series of complex legal, social and ethical issues. In response, many countries have designed and implemented different regulatory frameworks that

reflect their own political cultures, national priorities, local contexts and perceptions of risks (27, 28). The same country-based approach may be taken for the equally complex and challenging issues around the potential risks of accidents or the deliberate misuse of life sciences research.

The field of public health is concerned with protecting and promoting the health of communities and therefore must give due consideration to both the benefits and the possible risks of life sciences research for public health. At the same time, managing these risks may potentially harm public health if controls on research are so stringent that they stall advances in the life sciences and make international collaboration difficult (2). Any controls on life sciences research need, therefore, to be proportionate and balance risks and benefits.

Finding the right balance is essential for several reasons. First, control over research should not unduly hamper the development of the life sciences and should not impede access to biological materials and resources necessary to address public health challenges, including new infectious diseases. A situation that discourages scientists from working with important pathogens should be avoided. At the same time, increasing capacity for the life sciences should be accompanied by the promotion of responsible life sciences management.

Second, strong public confidence in life sciences research needs to be established and continuously nurtured. Research is essential for public health. Communication, international collaboration and openness, which are central to a public health perspective, are indispensable for global health security, scientific discovery and evidence-based measures.

Finally, information on this issue is uneven among Member States. Providing information on this topic to the various ministers of health in WHO Member States will:

- help them to rationally explain the issues to their constituencies and populations;
- help them to inform, educate and advise colleagues in other ministries;
- help them to plan rational and feasible emergency response plans should an adverse event occur;
- better equip them to assess what capabilities (and bioresources, e.g. exotic pathogens) existing within their own countries for the types of potentially dangerous research;
- should Member States be considering national regulations, understanding this issue will help

<sup>1</sup> By 2003, the number of people living in developing countries represented more than 80% of the total world population (22).

them formulate workable and effective guidelines and safeguards;

- understanding it will enable them to contribute better to global debate on the topic and, at the same time, bringing with them their own unique perspectives.

### 1.1.2 Purpose and audience

The purpose of this guidance is to inform Member States about the risks posed by accidents or the deliberate misuse of life sciences research and to propose measures to minimize them within the context of promoting and harnessing the power of the life sciences to improve health for all people. This guidance aims at strengthening the culture of scientific integrity and excellence characterized by openness, honesty, accountability and responsibility: such a culture is the best protection against accidents and deliberate misuse, and the best guarantee of scientific progress and development.

This guidance provides Member States with a conceptual framework for individual adaptation according to national circumstances, contexts, needs and capacities. Countries, research institutions, and laboratories are encouraged to review the proposed measures and to adapt them accordingly.

The issues addressed in this document can potentially interest a quite large audience: from policy-makers, relevant national regulatory authorities to scientific community (including researchers, laboratory scientists and managers, research institutions, professional associations, students, educators and journal editors).

However, the measures proposed under the biorisk management framework are of a public health nature and the self-assessment tool has been designed and field-tested within this framework and with the help of health researchers and laboratory managers. Health researchers, laboratory managers and research institutions are therefore the primary audience of this document, noting that the self-assessment questionnaire can be adapted to countries and institutions' needs.

Using this guidance will provide researchers and institutions with:

- a better understanding of the potential risks associated with accidents and the deliberate misuse of life sciences research;
- learn about practical measures that will enable them to manage some of the risks posed by life sciences research;

- assess their needs and capacities using a self-assessment tool to review existing structures and mechanisms and identify potential needs.

### 1.1.3 Scope of the guidance: WHA55.16 and the biorisk management framework for responsible life sciences research

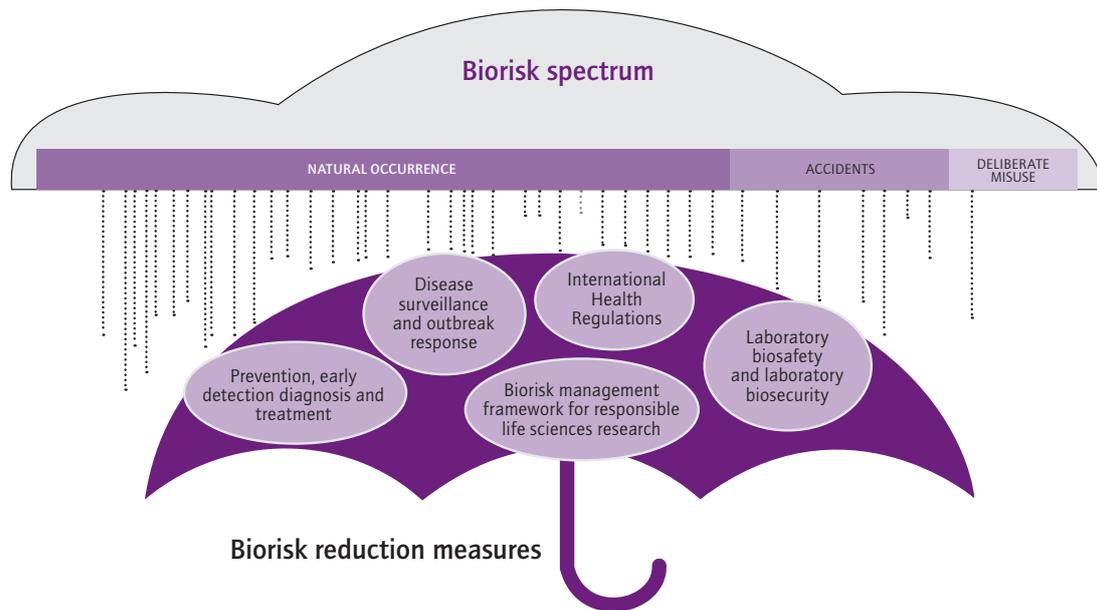
This document complements previous publications on the subject published by WHO (2, 5, 29) and links up with other areas of work of WHO, in particular, biosafety and laboratory biosecurity, ethics and some areas of work falling under research policy and cooperation. Compared to other documents and approaches published on this subject, the WHO approach is unique because it looks at this issue from a public health angle. As this is a multi-stakeholder issue, policy measures have been proposed by different sectors, including governments, security, academic and private sectors. This guidance, its biorisk framework and its self-assessment tool however only discuss measures based on and supporting public health. Moreover, this document looks at life sciences activities in general and does not focus on a particular field of life sciences. In addition, it takes a country-based approach, noting that over time, comparison and sharing of experiences and best practices of country and institutional approaches can be done at regional and global levels in order to support international cooperation and ensure that no incompatible measures are put forward.

The document and its approach are also to be understood within the context of the World Health Assembly in 2002 (Resolution WHA55.16). As recognized by resolution WHA55.16, one of the most effective ways to prepare for deliberately caused disease is to strengthen public health measures to address naturally occurring and accidentally occurring diseases. While recognizing the important role of other actors, such as the security<sup>1</sup> and academic communities, this guidance has a public health objective and the conceptual framework and measures proposed re-emphasize the WHA55.16 approach.

This guidance has also been developed within the wider context of the "biorisk spectrum" in that it advocates an all-encompassing risk management approach, in accordance with WHA55.16. The continuum of potential natural, accidental or deliberate exposure of humans, animals and/or plants to

<sup>1</sup> See the 1975 Biological Weapons Convention and the United Nations Security Council 1540.

Figure 1. The biorisk spectrum and biorisk reduction measures



pathogens or toxins likely to harm public health encompasses the full spectrum of biological risks to global health security (see **Figure 1**) (2). Such risks include, for instance, new infectious diseases such as the pandemic influenza A (H1N1) 2009 virus, avian influenza (H5N1) and severe acute respiratory syndrome (SARS), re-emerging diseases and modified strains of long-established diseases (e.g. multi- and extensively drug resistant tuberculosis), laboratory accidents, the unintended consequences of research, lack of awareness, negligence, and the deliberate misuse of life sciences research.

In this guidance, the term “biorisk reduction” is defined as the reduction of the occurrence of risks associated with exposure to biological agents and toxins, whatever their origin or source. Different levels of risk can be assigned across the biorisk spectrum, according to a country’s situation or institutional contexts (2). Measures put forward using this approach will both help to address the consequences of naturally occurring diseases and reduce the likelihood of accidents or the deliberate misuse of life sciences research.

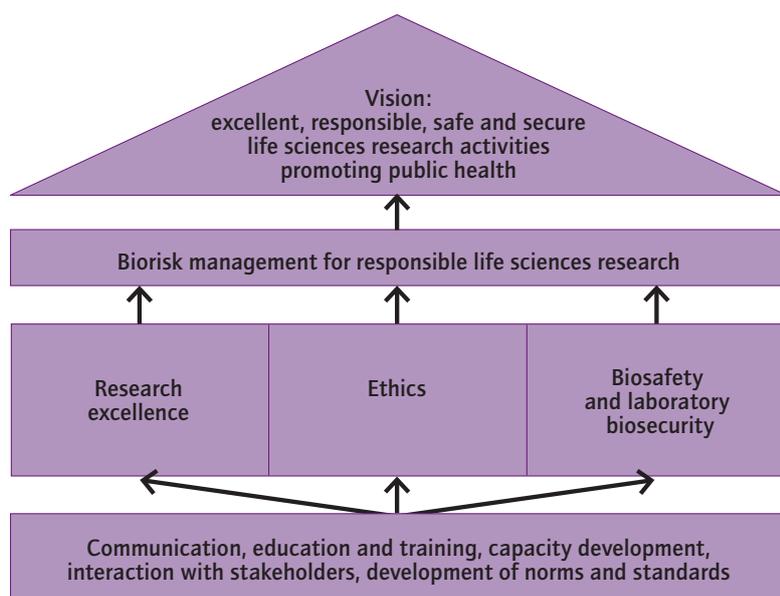
Responsible life sciences research that is conducted ethically by well-trained professionals in laboratories that have safety and security measures in place, constitutes one public health component of biorisk reduction. Other complementary public health measures that are an integral part of biorisk reduction, but which are not detailed in this guidance, include prevention, early detection,

diagnosis and treatment of naturally occurring diseases, disease surveillance, preparedness and outbreak response, compliance with the International Health Regulations (2005),<sup>1</sup> and laboratory biorisk management through biosafety and laboratory biosecurity.

This guidance document focuses on one measure of biorisk reduction, namely the biorisk management framework for responsible life sciences research (see **Figure 2**). The framework focuses on a vision of promoting excellent, high-quality, responsible, safe and secure research, where the results of the research foster advancements in health, economic development, global health security, evidence-informed policy-making, and public trust in science. Underpinning this vision is the importance of managing risks posed by accidents and the deliberate misuse of life sciences research activities through an integrated approach that recommends investing in capacities in three pillars supporting public health: research excellence, ethics, and biosafety and laboratory biosecurity (each pillar is discussed in detail in **Section 3**). At the foundation are several cross-cutting elements: communication, education and training, capacity development, interaction with stakeholders (scientists, publishers and editors, ethicists, national academies of sciences, security communities, gov-

<sup>1</sup> For additional information on the International Health Regulations (<http://www.who.int/ihr/en/>, accessed October 2010). See also (9).

**Figure 2. Biorisk management framework for responsible life sciences research**



ernments and international organizations), and the development of norms and standards. A self-assessment questionnaire has also been developed and is presented in [Section 4](#) to help countries and institutions assess their strengths and weaknesses and to support implementation of the biorisk management framework. The self-assessment questionnaire is not a tool to evaluate the adequacy of the measures developed by other sectors (security, academia, publishers and editors, etc.) but it recognizes the importance of collaboration between different sectors.

## 1.2 Methodology

A review of the available evidence of the risks and of the policies put forward to manage those risks (see [Section 2](#)) has been made by doing a literature review of a variety of different documents. These included peer reviewed journals, background documents, meeting reports, codes of conducts, laws, information shared at international meetings and provided by countries. Most of this information has been collected over the past four years and builds up on previous WHO publications.

[Section 3](#) builds upon the evidence collected in [Section 2](#) and develops a conceptual framework, which has been presented and discussed at several international meetings. This framework recognizes that “one size does not fit all”, and neither should it; that the uniqueness of countries and their specific needs should be identified and met, and that each country would have its own vision

on where it wishes to go and how to get there. At the same time, it has to be understood, that in the national and global interest, certain essential standards of the pursuit of science and of scientific research need to be in place: these are the three pillars (research excellence, ethics and biosafety and laboratory biosecurity) and to help evaluating those essential standards, a self-assessment questionnaire has been developed in [Section 4](#) of this guidance.

A first draft document was commented in April/May 2009 by the Guidelines review group. The Guidelines review group workshop on responsible life sciences research was held in Geneva, 22–24 June 2009 to review the

content of the document and its implementation ([Annexes 2 and 3](#)). The workshop re-emphasizes the importance of the document and its approach. Sections of this guidance have also been reviewed internally with colleagues working on research policy, ethics and on biosafety and laboratory biosecurity ([Annex 1](#)).

After the tenure of the Guidelines review group workshop, comments were accommodated and the document was edited. This second draft was sent for peer review in December 2009/January 2010 ([Annex 1](#)).

A pilot test of the self-assessment questionnaire presented in [Section 4](#) was conducted in October 2009 with a small group of scientists at the National Institute of Communicable Diseases (NICD), South Africa. It helped to strengthen and refine some of the questions and assess the type of information and results that could be expected from such a questionnaire. Additional pilot tests of the questionnaire will be performed, as appropriate.

As the issues raised in this document are evolving, modifications to this guidance will be made as additional evidence becomes available. This guidance will be reviewed two years after its publication.

### 1.2.1 Terminology

Although the use of the word “biosecurity” is increasing, no universally agreed definition has emerged. As is the case with biosafety, different sectors are using the same word with different

meanings, which in turn may lead to some confusion (30–32). Biosecurity was initially used in reference to animal and plant health;<sup>1</sup> more recently, it has been used by public health, academic (33), policy and security communities.<sup>2</sup> This guidance uses the WHO concept of “laboratory biosecurity”, which is an extension and a complementary dimension of laboratory biosafety (1)<sup>3</sup> (see **Section 3.3**). In other words, by implementing good laboratory biosafety practices, laboratories are already implementing some of the requirements of laboratory biosecurity.

There is a similar lack of agreement around the concept of “dual-use research”. Several definitions have been put forward, but there is no commonly agreed understanding as to what constitutes dual-use research.<sup>4</sup> Some also argue that the dual-use label is misleading and may cause confusion in regard to certain types of research that nevertheless need to be undertaken for public health. For the purpose of this guidance, dual-use research is understood as knowledge and technologies generated by legitimate life sciences research that may be appropriated for illegitimate intentions and applications. This working definition has to be understood within WHA55.16, whose language has the advantage of focusing more on the action and less on the definition.

This document will refer to the “potential risks posed by accidents or the deliberate misuse of life sciences research”. In this guidance, the words “accidents” (or research accidents) reflects the fact that research activities may unexpectedly pose some risks via “accidental” discoveries (such as the mousepox experiment, see **Box 1**). Under this approach, dual-use research can both be associated with “accidents” and risks caused by “deliberate” misuse. This guidance is not specifically concerned with “laboratory accidents”, as this important area of work is already being covered by the WHO laboratory biosafety manual (3).

### 1.3 Structure of the guidance

This document is organized into four sections. This section provides an overview of the guidance, describing the context, purpose, audience, scope and methodology.

**Section 2** reviews cases of life sciences research that have raised concerns over the past few years and examines the policy options that have been put forward by different stakeholders to address these concerns.

Building on this, **Section 3** describes the three

pillars of the guidance’s biorisk management framework for responsible life sciences research: research excellence, ethics, and biosafety and laboratory biosecurity. It also shows how the pillars respond to several key issues raised in **Section 2** and how investing in these areas is complementary and self-reinforcing for public health.

**Section 4** presents the main steps for carrying out a self-assessment of national and institutional biorisk management capacity. It includes a questionnaire, which assesses elements of the three pillars, and can be used to inform a tailored approach to implementing the biorisk management framework, adapted to each country’s circumstances and needs.

<sup>1</sup> For animal health, biosecurity refers to good hygiene practices that help prevent the emergence and spread of animal diseases. For plant health, biosecurity refers to controls to protect plants against different types of pests but also against animals or practices that could have adverse effects on plants. The Food and Agriculture Organization (FAO) considers biosecurity to be a “strategic and integrated approach that encompasses the policy and regulatory frameworks (including instruments and activities) that analyse and manage risks in the sectors of food safety, animal life and health, and plant life and health, including associated environmental risk.” Biosecurity for agriculture and food production (<http://www.fao.org/biosecurity/>, accessed October 2010), ([http://www.fao.org/ag/agn/agns/meetings\\_consultations\\_2003\\_en.asp](http://www.fao.org/ag/agn/agns/meetings_consultations_2003_en.asp), accessed October 2010) and (34).

<sup>2</sup> States Parties to the Biological Weapons Convention have also noted their common understanding on “biosafety” and “biosecurity” within the context of the Convention (35).

<sup>3</sup> The Organisation for Economic Co-operation and Development (OECD) has also developed best practices guidelines for their Biological Resources Centres (BRCs). OECD refers to biosecurity as the “institutional and personal security measures and procedures designed to prevent the loss, theft, misuse, diversion or intentional release of pathogens, or parts of them, and toxin-producing organisms, as well as such toxins that are held, transferred and/or supplied by BRCs”. While the OECD and WHO definitions are relatively similar, they differ in their approach because the OECD does not link laboratory biosafety to laboratory biosecurity measures (36).

<sup>4</sup> For definitions of dual use, see for instance (5, 15, 37).

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## 2. Review of experiments and policy options

### 2.1 Examples of experiments of concern

The issue of preventing the misuse of legitimate research is not new – it was recognized by Francis Bacon in the 17th century (38) and is embodied in the 1972 Biological Weapons Convention<sup>1</sup> – but several recent experiments (39–43) have given salience to the topic within policy and scientific circles. Although these research activities were carried out for legitimate purposes, they also raised questions about biosafety, national security, ethics and the potential for the research data to be misused. A few examples from the literature<sup>2</sup> illustrate the potential benefits, opportunities and risks.

#### 2.1.1 Accidentally increasing the virulence of mousepox as part of an experiment to control mice as pests in Australia

In an attempt to create a contraceptive vaccine for mice as a means of pest control, Australian scientists unexpectedly increased the virulence of mousepox (see **Box 1**). After discussion it was decided to pursue publication of the findings in part to stimulate public debate on how to handle such a situation in the future (44).

When the paper was published in the *Journal of Virology* in January 2001 (39) widespread media coverage drew attention to the fact that unexpected research results could have potentially dangerous

#### BOX 1

##### Accidentally increasing the virulence of mousepox as part of an experiment to control mice as pests

■ Australian researchers were attempting to produce a contraceptive vaccine that could be used to control the mouse population in Australia. By inserting interleukin-4 (IL-4), a gene that enhances antibody production into mousepox, they accidentally increased the virulence of mousepox.

■ The new virus proved to be highly lethal in infected mice, including those that had been vaccinated against it.

Source: Jackson RJ et al. Expression of mouse interleukin-4 by a recombinant ectromelia virus suppresses cytolytic lymphocyte responses and overcomes genetic resistance to mousepox. *Journal of Virology*, 2001, 75:1205–1210.

consequences for public health. Questions were raised about genetic manipulation in general and there were concerns that similar experiments on orthopoxviruses, such as smallpox, could potentially increase its virulence. Some warned that the paper provided information that could be used to render the smallpox vaccine ineffective (15).

#### 2.1.2 Variola virus immune evasion design

Another controversial experiment investigated the differences in a virulence gene from variola major virus, which causes smallpox, and vaccinia virus to understand the mechanism of the virulence of variola (see **Box 2**) (41). The researchers concluded that the difference between the viruses' inhibitor of immune response enzymes could explain the difference in virulence.

Critics maintained that the paper provided information that could be used to increase the virulence of the vaccinia virus, which is, unlike variola virus, widely available. Proponents argued that it was

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<sup>1</sup> Robinson J. The General Purpose Criterion and the importance of its implementation. *Paper presented at the 19th Workshop of the Pugwash Study Group on Implementation of the CBW Conventions, The First CWC Review Conference and Beyond*. Oegstgeest, The Netherlands, 26–27 April 2003. Review conferences to the BWC are also examining every five years all relevant scientific and technological developments in relation with the Convention and, since 2008, annual background papers on possible relevant developments are published by the Implementation Support Unit of the BWC ([www.unog.ch/bwc](http://www.unog.ch/bwc), accessed October 2010).

<sup>2</sup> For additional experiments, see also Davidson EM et al. Science and security: practical experiences in dual-use review. *Science*, 2007, 316:1432–1433. See also the supporting online material.

**BOX 2****Variola virus immune evasion design**

■ Researchers compared the variola complement regulatory protein (SPICE, smallpox inhibitor of complement enzymes) with the corresponding protein in vaccinia virus (vaccinia virus complement control protein or VCP).

■ Researchers demonstrated that SPICE is a more potent inhibitor of human complement than the corresponding protein in vaccinia virus. Disabling it could represent one method for the treatment of smallpox.

■ In order to generate SPICE, the researchers mutated the amino acid sequence of the VCP into that of the variola protein.

■ This experiment also showed that the recombinant vaccinia protein was much more efficient than its natural counterpart in overcoming human complement activation, suggesting that the pathogenicity of vaccinia virus could be enhanced by manipulating the inhibitor.

Source: Rosengard A et al. From the cover: Variola virus immune evasion design: expression of a highly efficient inhibitor of human complement. *Proceedings of the National Academy of Sciences of the United States of America*, 2002, 99:8808-8813.

**BOX 3****Chemical synthesis of poliovirus cDNA**

■ Researchers synthesized a poliovirus genome using chemically synthesized oligonucleotides and the map of the polio genome that has been published on the Internet.

■ The result was a “live” poliovirus that paralyzed mice.

■ The published paper included a description of methods and materials.

Source: Cello J, Paul A, Wimmer E. Chemical synthesis of poliovirus cDNA: generation of infectious virus in the absence of natural template. *Science*, 2002, 297:1016-1018.

unlikely that such an experiment would allow vaccinia to reach the level of pathogenicity of variola and that the publication would allow scientists to work on these inhibitors to improve current treatments and vaccines against smallpox (15).

**2.1.3 Chemical synthesis of poliovirus cDNA**

In 2002, news of the chemical synthesis of poliovirus set off another debate (see **Box 3**). Researchers demonstrated that it was possible to assemble a synthetic virus by piecing together chemically synthesized oligonucleotides ordered through the Internet from commercial DNA synthesizing companies. On the benefit side, this experiment is reported to have stimulated research into viral genome synthesis for medical applications, such as new strategies in vaccine development (45). Chief among the concerns was that this research could yield a recipe for reconstructing the poliovirus (without obtaining a natural virus) or could enable the artificial synthesis of smallpox (the genome of which has also been published). Yet it was also pointed out that, due to the much greater complexity of the smallpox virus, experts doubted that this same approach would be successful in producing a working virus. Some were also sceptical about the scientific value of the research and the need for its publication (46), arguing the techniques used in the experiment were not new and the research did not lead to new knowledge or insights (13, 45–47).

**2.1.4 Reconstruction of the 1918 flu virus**

In 2005, researchers successfully reconstructed the influenza A (H1N1) virus responsible for the 1918 Spanish flu pandemic by using reverse genetics to generate the relevant 1918 viral coding sequences and outfitting a relatively avirulent influenza virus with all eight viral gene segments of the 1918 strain, which conferred the unique high-virulence 1918 strain phenotype on the engineered virus. Two articles on the 1918 flu virus were published in October 2005 (see **Box 4**) (42, 43). The article in *Nature* published the sequences of the final three gene segments of the flu virus genome while the *Science* article published the recreation of the flu virus based on the *Nature* article.

One funding body supporting this research explained that the aim of the research was to better understand the virulence of the 1918 Spanish flu (48). The knowledge gained from the reconstruction of the virus could be used to devise and evaluate current and future public health interventions should a similar pandemic virus emerge, including

strategies to diagnose, treat and prevent the disease. Further research on macaques infected in laboratories demonstrated the higher fatality rate of the resurrected 1918 influenza virus compared with a contemporary virus (49, 50).

But while some considered this research to represent a landmark breakthrough, others raised concerns about the risks posed by resurrecting the virus (51, 52), questioned the safety procedures for handling the virus (53) and even questioned the scientific value of the experiment, arguing that the research had limited utility (52, 54, 55). Others questioned whether the research findings should have been published (54, 56).

The article in *Science* was published with an accompanying editorial on responsible science (57) and with a note at the end of the paper stating it had been examined by the National Science Advisory Board for Biosecurity (NSABB). The Board concluded that the scientific benefits of the research far outweighed the biosecurity risks (56). The note further states:

This research was done by staff taking antiviral prophylaxis and using stringent biosafety precautions to protect the researchers, the environment, and the public. The fundamental purpose of this work was to provide information critical to protect public health and to develop measures effective against future influenza pandemics.

### 2.1.5 Creating and synthesizing *de novo* organisms

The emerging discipline of synthetic biology, which is “concerned with producing biological based entities (e.g. parts, devices, systems, organisms) which perform a new function” (58) (see **Box 5**) can through these new processes and techniques enable the synthesis of *de novo* organisms and the creation of specific, tailor-made new organisms (59, 60).<sup>1</sup> In May 2010, researchers at the J. Craig Venter Institute in Rockville, Maryland, United States of America, synthesized a bacterial genome and inserted it into a bacteria cell, which was then able to self-replicate (61). Synthetic biology, which has also been defined as “the design and construction of new biological parts, devices, and systems, and re-design of existing, natural biological systems for useful purposes”<sup>2</sup> is building on the advances in disciplines such as computing,

<sup>1</sup> The BioBricks Foundation (<http://bbf.openwetware.org/>, accessed October 2010).

<sup>2</sup> Synthetic Biology (<http://syntheticbiology.org/>, accessed October 2010).

#### BOX 4

##### Reconstruction of the 1918 flu virus

■ The research team re-created the extinct influenza virus using the gene sequences from archived materials and from lung tissues of an influenza victim who had been buried in permafrost in 1918.

■ Using reverse genetics, the researchers were able to generate the 1918 virus with the aim of increasing understanding of the biological properties responsible for the high virulence of the pandemic virus.

■ The experiment also indicated that the 1918 virus gene sequences were more closely related to avian (H1N1) viruses than any other mammalian influenza H1N1 strains.

Source: Tumpey TM et al. Characterization of the reconstructed 1918 Spanish influenza pandemic virus. *Science*, 2005, 310:77-80 and Taubenberger JK et al. Characterization of the 1918 influenza virus polymerase genes. *Nature*, 2005, 437:889-893.

#### BOX 5

##### Creating and synthesizing a minimal organism

■ Research has been done on the creation of a bacterium with the minimum number of genes necessary for the organism to survive.

■ *Mycoplasma genitalium* was selected by a team led by J. Craig Venter. After reducing the bacterium to the minimum 381 genes necessary for keeping it alive, the aim was to use the microbe as a “chassis” for building new synthetic biological devices able to perform specific tasks (e.g. biofuels).

■ Researchers reported in *Science* the construction of the same bacterial genome by chemically synthesizing small blocks of DNA.

Source: Gibson et al. Complete chemical synthesis, assembly and cloning of a *Mycoplasma genitalium* genome. *Science*, 2008, 319:1215-1220.

**BOX 6****Main policy options**

- Research oversight mechanisms
- Policies of funding agencies, publishers and editors
- Selected laws and regulations
- Codes of conduct and ethics
- Awareness-raising and educational initiatives.

genetic and mechanical engineering, physics and nanotechnologies.

Synthetic biology has many potential applications in the fields of environment and energy production (e.g. hydrogen production), health care (e.g. malaria drugs (62) and gene therapy), and the aeronautical and petrochemical industries (e.g. biofuels) (63). Along with its potential benefits come a number of issues associated with biosafety and laboratory biosecurity, the potential misuse of synthetic biology and a host of ethical, social and legal concerns about the impact synthetic biology may have on society, public health and the environment (64). These are in addition to questions of ownership, innovation, regulation and oversight (58, 65).

## 2.2 Review of policy options

This section summarizes the various policy options put forward by different stakeholders to manage the risks of accidents and the potential misuse of life sciences research. In considering the implementation of approaches for the management of these potential risks, a range of complementary options have been developed: 1) research oversight mechanisms; 2) policies for funding agencies, publishers and editors; 3) laws and regulations; 4) codes of conduct and ethics; and 5) awareness-raising and educational initiatives for scientific communities, policy-makers and the public. Some of these approaches – such as awareness raising and codes of conduct – are bottom-up approaches, others are top-down (e.g. laws and regulation), and still others mixed (e.g. research oversight mechanisms) (see **Box 6**). These options are not mutually exclusive.

### 2.2.1 Research oversight mechanisms

In 2004, the National Research Council of the US National Academies of Sciences published the semi-

nal report *Biotechnology Research in an Age of Terrorism: Confronting the Dual-Use Dilemma*, also called the “Fink report” (15). It thoroughly reviewed the issues associated with dual-use research and proposed several risk management measures.

The report identified seven classes of experiments of concern that warrant review prior to being carried out and before publication (see **Box 7**). As illustrated in **Section 2.1**, some of these experiments have already been conducted and published.

The Fink report proposed that research that meets any one of these criteria be reviewed utilizing “the already established system for review of experiments involving recombinant DNA,” that is, by the National Institutes of Health-based Recombinant DNA Committee. It also emphasized the need to educate the scientific community about this issue; to rely on the self-governance of scientists and journals to review research results and decide whether or not to publish; to rely on current legislation and regulation regarding the protection of biological materials; and to harmonize measures at the international level.

In response to this Report, in 2004 the United States Government established the National Science Advisory Board for Biosecurity (NSABB) to ensure continuing dialogue between the scientific and security communities and to provide specific advice on dual-use research and on the dissemination of life sciences research information.<sup>1</sup>

In June 2007, the NSABB issued its *Proposed Framework for the Oversight of Dual Use Life Sciences Research: Strategies for Minimizing the Potential Misuse of Research Information*, which provides recommendations to the United States Government for the oversight of dual-use research and is intended to serve as a springboard for the development of an oversight policy (66). The framework covers federally conducted or funded research and addresses steps throughout the scientific research process from the project concept and design to publication where research can be reviewed for its dual-use potential. The NSABB developed a criterion for identifying “dual use research of concern” and described seven categories of information, products or technologies that, if produced from life sciences research, might meet its proposed criterion. As such, research falling into one of these categories should be considered especially carefully for its dual-use potential (see **Annex 4**) (66).

<sup>1</sup> National Science Advisory Board for Biosecurity ([http://oba.od.nih.gov/biosecurity/about\\_nsabb.html](http://oba.od.nih.gov/biosecurity/about_nsabb.html), accessed October 2010).

In 2006, the Australian Government commissioned a report on the ethical and philosophical considerations of the dual-use dilemma in the biological sciences. The report also identified several salient experiments of concern, which are an expanded version of the NRC list in **Box 7**, and provided a set of five options for the regulation of dual-use experiments and information (see **Annex 5**) (67). These range from the “least intrusive/restrictive” where individual scientists are autonomous to the “most intrusive/restrictive” where the whole system ultimately relies upon the Government.

The report favours in-between options: establishing either a regulatory system composed of research institutions and the government with mandatory education and training, mandatory personnel security and licensing of dual-use technologies, or an independent authority comprising scientific and security experts.

In another attempt to define a system for research oversight, the United States Center for International and Security Studies (CISSM) at the University of Maryland proposes a system of tiered oversight for certain categories of research, in which the level of potential risk determines the nature and extent of oversight requirements. Under the CISSM model, most research would be subject to local, institutional oversight, if at all, with only a small subset of research considered at a higher level. Its key elements are licensing of researchers and facilities engaged in relevant research and independent peer review of experiments in advance. These requirements would apply to all relevant research institutions (government, academia and industry), would be mandatory rather than rely on self-governance, and would be harmonized internationally through the development of uniform procedures and rules (see **Annex 6**) (68).

Since 2003, States Parties to the Biological Weapons Convention, which bans the development, production, stockpiling and transfer of biological and toxin weapons, have been holding annual meetings with experts from the scientific community, academia, professional associations and international organizations. The mandate of these meetings is to discuss and promote common understanding and effective action on a number of topics, including:

- “strengthening and broadening national and international institutional efforts and existing mechanisms for the surveillance, detection, diagnosis and combating of infectious diseases affecting humans, animals and plants;
- “regional and international measures to improve

### BOX 7

#### Fink report's seven classes of experiments

Experiments that:

1. would demonstrate how to render a vaccine ineffective;
2. would confer resistance to therapeutically useful antibiotics or antiviral agents;
3. would enhance the virulence of a pathogen or render a nonpathogen virulent;
4. would increase transmissibility of a pathogen;
5. would alter the host range of a pathogen;
6. would enable evasion of diagnostic/detection modalities;
7. would enable the weaponization of a biological agent or toxin.

Source: . U.S. National Academies, National Research Council, Committee on Research Standards and Practices to Prevent the Destructive Application of Biotechnology. *Biotechnology research in an age of terrorism*. Washington, DC, The National Academies Press, 2004.

biosafety and biosecurity, including laboratory safety and security of pathogens and toxins;

- “oversight, education, awareness raising and adoption and/or development of codes of conduct with the aim of preventing misuse in the context of advances in bio-science and bio-technology research”<sup>1</sup>

As a result of these exchanges of information States Parties have agreed on the value of implementing a series of measures (35, 69).

#### Implementation of oversight frameworks

To date, implementation of research oversight mechanisms for dual-use research has primarily been done on a voluntary basis at the institutional level (see **Annex 7**). Experience suggests that incorporating this issue into existing training and education programmes is the most practical approach. With oversight mechanisms, a common challenge is developing criteria for identifying research with the potential for misuse. Current oversight systems have mostly been implemented using the criteria identified in the Fink report and by the NSABB.

<sup>1</sup> The United Nations Office at Geneva, the Biological Weapons Convention (<http://www.unog.ch/bwc>, accessed October 2010).

**BOX 8****Joint agreement by BBSRC, MRC and Wellcome Trust to modify their respective policies and procedures in four areas**

- Introduction of a question on application forms asking applicants to consider risks of misuse associated with their proposal.
- Explicit mention of risks of misuse in guidance to referees as an issue to consider.
- Development of clear guidance for funding committees on this issue and the process for assessing cases where concerns have been raised.
- Modification of organizational guidelines on good practice in research to include specific reference to risks of misuse.

Source: *Managing risks of misuse associated with grant funding activities. A joint Biotechnology and Biological Sciences Research Council (BBSRC), Medical Research Council (MRC) and Wellcome Trust policy statement. September 2005.*

A point of discussion in policy development is the scope of dual-use research that is really of concern and should therefore be subject to formal oversight (37).

Other critical issues associated with oversight mechanisms include:

- the appropriate level of reporting (i.e. concerns should be reported to whom?);
- the composition of review boards (i.e. discussion over whether these should include scientific experts, ethicists, security experts and/or civil society);
- the evaluation of research experiments (i.e. subjectivity and replicability of these evaluations);
- the assessment of risks and benefits (i.e. at the individual level or among peers).

### 2.2.2 Policies of funding agencies, publishers and editors

In the United Kingdom, three research funding agencies – the Biotechnology and Biological Sciences Research Council (BBSRC), the Medical Research Council (MRC) and the Wellcome Trust – have issued a joint policy statement on managing risks of misuse associated with grant funding activities (70). The position statement of the three agencies also addresses the issues of “balancing benefit and risk; funding decisions; dissemina-

tion of research; international collaboration and training; and promoting research best practice and ensuring public trust” (71, 72). The three agencies propose that a system based upon self-governance by the scientific community will be the most effective means of managing the risks of misuse. It is also suggested that “the community should take active steps to further develop mechanisms of self-governance, and that through doing so the community can ensure that responsibly conducted research is not unnecessarily obstructed.”

In addition, the three bodies have modified their policy statements, guidance and procedures in four areas (see **Box 8**) (70). The Wellcome Trust has also inserted a paragraph on the risks of research misuse in their guidelines on good research practice (73).

The European Commission (EC) has a system in place regarding the submission of research grant applications (37, 74). An ethical review panel and a security scrutiny committee can be convened if a research project has ethical or security implications. The EC has also published a green paper on bio-preparedness, including measures against the potential misuse of research, for the consideration of European Member States (75). A public-private chemical, biological, radiological and nuclear (CBRN) task force has been established by the EC to examine actions in the area of awareness raising, training, codes of conduct, and the role of publishers and funding organizations (37).

Following the concerns posed by the publication of several experiments, 32 editors and authors representing some of the most prestigious peer-reviewed journals, including *Nature*, *New England Journal of Medicine* and *Science*, agreed in 2003 on a joint statement on scientific publication and security (76). The statement underlines several significant points:

- “We must protect the integrity of the scientific process by publishing manuscripts of high quality, in sufficient detail to permit reproducibility. (...)
- “We are committed to dealing responsibly and effectively with safety and security issues that may be raised by papers submitted for publication, and to increasing our capacity to identify such issues as they arise. (...)
- “Scientists and their journals should consider the appropriate level and design of processes to accomplish effective review of papers that raise such security issues.(...)
- “We recognize that on occasion an editor may conclude that the potential harm of publication

outweighs the potential societal benefits. Under such circumstances, the paper should be modified, or not be published. Scientific information is also communicated by other means: seminars, meetings, electronic posting, etc. (...)”

Several journal editors have put in place mechanisms for papers that may need additional peer-review because of the potential risks for misuse (37). The Council of Science Editors (CSE), which aims to promote excellence in the communication of scientific information, has published a white paper that includes a section on the responsibilities of editors to the public. This white paper encourages editors to “educate journal boards, reviewers, and authors; establish screening methods to recognize [dual-use research of concern]; obtain reviews of these manuscripts from individuals with technical and security expertise; create an ongoing network to share experience and further refine ways for managing [dual-use research of concern];” and “develop guidelines and procedures to allow the scientific evaluation as well as evaluation of the possible risk of communicating information with dual use potential” (77). In its recommendations to the United States Government, the NSABB has included communication tools that contain points to assist researchers and journal editors when communicating research that may raise some concern (78).

#### **Implementing the policies of funding agencies, publishers and editors**

Research funding bodies have noted since 2005 that applicants are increasingly thinking about issues of misuse and address those topics in their applications. At the same time, very few research proposals have raised concerns (37). The Wellcome Trust identified only three studies between 2005 and 2008 and among the 10 000 applications received by the BBSRC over these three years, fewer than a dozen were found to be of potential concern.

Several journals have adopted policies and review processes to monitor this issue in submitted papers. Some of the issues that have been raised during implementation include: What should a journal do with a rejected paper? What authority can legitimately ask a journal to pause the publication of a paper (37)? Given that researchers may always seek to publish elsewhere, including in non-journal publishing (i.e. scientific web site, conference, etc), journals should not be seen as the only safety net. Efforts should also be developed upstream of submission to journals, at the institute

level where the research is carried out and by those funding the research (37).

Available evidence has so far shown that very few papers have raised concerns. Among the 74 000 biology papers received by the various *Nature* journals from 2004–2008, only 28 papers raised concerns and were forwarded to *Nature’s* dual-use review committee. No paper was rejected due to a potential risk for misuse (37). During this time other journals (*Science*, the *Proceedings of the National Academy of Sciences of the United States of America* and the journals of the American Society for Microbiology) encountered only one or two of this type of paper each year and no papers have been rejected for dual-use reasons since 2003. From 2002–2008, the journal *Biosecurity and Bioterrorism*, which has developed specific questions for authors and reviewers on dual-use, received only three papers that raised concerns. One was published with modification and the remaining two were rejected by the journal (37).

#### **2.2.3 Selected national laws and regulations on research oversight and biosafety and laboratory biosecurity**

Very few countries have enacted specific laws establishing the oversight of research with dual-use potential. However, a number of countries have laws on dangerous pathogens, including lists of pathogens and microorganisms that are subjected to several controls. And many more have enacted national laws to implement their obligations under the 1972 BWC.

In Israel, a steering committee on Issues in Biotechnological Research in an Age of Terrorism (COBART) was established in 2006 to address biosecurity in the areas of biomedical and life sciences research. It recommended the establishment, at the national level and within the Ministry of Public Health, of a National Biosecurity Council to oversee biomedical research at universities, medical centres and biotechnology companies and, at the local level, a scientist-based oversight model. These became the basis of a 2008 law (37). Raising awareness and education were considered top priority areas as this issue is not a well-known topic in the life sciences or medical communities.

In 2007, Australia enacted the National Health Security Act, which established a National Authority within the Department of Health and Aging

<sup>1</sup> For additional information, see the United Nations Office at Geneva, the Biological Weapons Convention (<http://www.unog.ch/bwc>, accessed October 2010).

to regulate and monitor facilities working with security-sensitive biological agents (79). The Act includes a list of security-sensitive biological agents; a national register of facilities; security provisions for handling security-sensitive biological agents; regulations for storage, transport and handling of those agents; inspection, monitoring and sanctions; and training and awareness-raising campaigns (37).

In Brazil, the Biosafety Law N°11.105 of 24 March 2005 provides for safety norms and inspection mechanisms for activities related to genetically modified organisms (GMOs) and their derivatives (80, 81). In addition the law establishes a National Biosafety Council, a National Biosafety Technical Commission, biosafety internal committees and a biosafety information system. Brazil has also established the National Program for the Promotion of Dialogue Between the Private Sector and the Government in Matters Related to Sensitive Assets (Pronabens) in order to define procedures for the control of sensitive goods. This is done through technical visits, raising awareness, support in the handling of sensitive goods (importing and exporting) as well as in the maintenance of a list of sensitive goods.

In China, administrative authorities supervise and manage biosafety and biosecurity issues from different aspects, including Ministries of Science and Technology, Education, Agriculture, Forestry, Health and Environmental Protection, and National Development and Reform Commission. A series of regulations, frameworks, rules and standards have been issued to address biosafety and biosecurity in life sciences research as well as the handling of GMO and pathogenic biological materials.<sup>1</sup>

Singapore enacted the Biological Agents and Toxins Act (Chapter 24A) and the Biological Agents and Toxins (Transportation) Regulations in 2006 to regulate the possession, use, import, transshipment, transfer and transportation of biological agents and toxins. The Act and the Regulations are administered by the Ministry of Health. Under the Act, facilities handling high-risk biological agents and toxins are required to be certified as containment facilities and/or gazetted as protected places. Such facilities are inspected and certified annually. Exports of strategic goods (including a list of biological agents and toxins) are regulated under the Strategic Goods (Control) Act (Chapter 300), administered by Singapore Customs.

Common European Union (EU) legislation on biosafety has been developed and focuses on the

prevention of risks associated with the handling of dangerous biological materials by workers as well as during transport (82). EU Member States have developed national legislation, regulations and other measures covering for instance the possession, transport, export and import of biological materials, and biosafety and biosecurity.<sup>2</sup>

In the United Kingdom, the 2001 Anti-Terrorism Crime and Security Act establishes security measures for the possession and transfer of pathogens and toxins (83). Based on a list of pathogens and toxins, approximately 450 laboratories are registered under this legislation. Laboratories are required to put in place security procedures in accordance with the nature of the organisms they are keeping at their premises, and they are regularly visited and assessed. The legislation also establishes policy for personnel security.<sup>3</sup> In addition, a single regulatory framework governing human and animal pathogens has recently been developed that merges several existing frameworks (84).

In Germany, the Biological Agents Ordinance of 27 January 1999 contains provisions on the protection of workers from risks related to exposures to biological agents (85–87). This includes notification of the types of activities involving certain risk group biological agents to the competent authorities. Germany also has laws and regulations for the

<sup>1</sup> These include: the Safety Administration Regulation on Genetic Engineering (1993); the Safety Administration Implementation Regulation on Agricultural Biological Genetic Engineering (1996); the “National biosafety framework” (2000); Regulations on Safety of Agricultural Genetically Modified Organisms (2001); Administration Regulation on Labeling of Agricultural Genetically Modified Organisms (2001); General biosafety standard for microbiological and biomedical laboratories (2002); Regulation on Inspection and Quarantine of Import and Export of GM Products (2004); Administration Regulation on Biosafety of Pathogenic Microbiology Laboratories (2004); Laboratories – General Requirements for Biosafety (2004); Laboratory Biosafety Qualification Standards (CNAS-CL05:2006); Implementation Regulations on Labeling of Agricultural Genetically Modified Organisms (2007); Laboratories – General Requirements for Biosafety (New version) (2008); Laboratory Biosafety Qualification Standards (NAS-CL05:2009).

<sup>2</sup> For a review of European Union countries laws, regulations and other measures, see (87).

<sup>3</sup> A pilot project reviewing the implementation of the UK legislation found that the new controls were successfully conducted and that there was no substantial disruption, keeping a satisfactory balance between scientific freedom and security. The study identified three factors that contributed to this successful implementation: “pre-existing biosafety measures which ensured a degree of biosecurity; a responsive approach to regulation by the implementing body; and a flexible and socially responsible reaction to the new controls by the UK scientific community.”(88).

safe and secure transport of biological agents, the licensing and registration of facilities and persons handling biological materials, and the provisions for the security vetting of personnel handling dangerous biological materials.

The United States has developed a body of laws to control the possession, use and transfer of biological agents<sup>1</sup> based on lists of select pathogens and toxins that are regulated by the Centers for Disease Control (CDC) of the Department of Health and Human Services and the Animal and Plant Health Inspection Service (APHIS) of the Department of Agriculture.<sup>2</sup> The APHIS/CDC Select Agent Program oversees activities and registers all laboratories and other entities in the country that possess, use or transfer a select agent or toxin.

In South Africa, legislation to establish measures to account for and secure the safe production, use and storage of biological materials includes the Agricultural Pests Act (Act no. 36/1983), the Organisms Act (Act no. 15/1997), the Animal Health Act (Act no. 7002), the Non-Proliferation of Weapons of Mass Destruction Act (Act No. 871/1993) and the Health Act (Act no. 31/2003) (89).

#### 2.2.4 Codes of conduct and ethics programmes and initiatives

Codes of conduct and ethics programmes and initiatives are two other policy options that have attracted much attention (90, 91). A number of codes either directly make reference to the potential misuse of life sciences research or give more general statements. The purposes and functions of these codes vary in accordance with the extent to which they are voluntary, or subject to some form of institutional or legal enforcement. Medical associations (e.g. the World Medical Association, the British Medical Association and the American Medical Association's Council on Ethical and Judicial Affairs) have reinforced their existing codes to include issues related to the possibility of accidents or the deliberate misuse of research (see **Annex 8**).

In 1974 UNESCO issued the "Recommendation on the Status of Scientific Researchers" (92). More recently, the International Centre for Genetic Engineering and Biotechnology (IGCEB) has been undertaking a review of codes of conduct. Scientific and academic organizations (such as the American Society for Microbiology, the Chinese Academy of Sciences and the Royal Society in the United Kingdom) have also emphasized the importance of codes of conduct. The InterAcademy Panel (IAP) and the Royal Netherlands Academy of Arts and

Sciences have dedicated documents on this issue (see **Annex 8**).

Other codes include the NSABB's recommendations on the development of a code of conduct for scientists and laboratory workers and a code of ethics for the life sciences proposed by individual scientists Margaret Somerville and Ronald Atlas (93). Moreover, the International Committee of the Red Cross (ICRC) has been working with scientists in the life sciences to adopt "professional and industrial codes of conduct aimed at preventing the abuse of biological agents" (see **Annex 8**).

#### Implementation of codes

Critics of codes of conduct and codes of ethics often stress that self-governance will not stop accidents or the deliberate misapplication of science. They also point out that conflicts of interests may arise in the process of self-governance and that some scientists may not have the knowledge and skills needed to assess the future implications of their work (67). Moreover, while codes may have aspirational value, if voluntary, they are not like laws that can be enforced. Though voluntary codes may have limitations, it should be noted that institutional and/or legal enforcement of codes is possible. Nevertheless, an important objective and benefit of codes is that they catalyze discussion between the different communities involved in life sciences research and help to raise awareness of the risks. Yet, although codes of conduct have received an important amount of attention, some have provided a mixed assessment of the achievements of code-related activities until now (94, 95).

#### 2.2.5 Educational and training initiatives to raise awareness

Numerous initiatives aimed at different scientific audiences have been raising awareness on this topic across several regions (29, 96).<sup>3</sup>

<sup>1</sup> See for instance, the Antiterrorism and Effective Death Penalty Act of 1996, the Public Health Security and Bioterrorism Preparedness and Response Act of 2002 and the USA PATRIOT Act (Uniting and Strengthening America by Providing Appropriate Tools Required to Intercept and Obstruct Terrorism Act of 2001).

<sup>2</sup> See National Select Agents Registry ([www.selectagents.gov/](http://www.selectagents.gov/), accessed October 2010).

<sup>3</sup> See also the Center for International and Security Studies at Maryland, *The Controlling Dangerous Pathogens Project* ([www.cissm.umd.edu/projects/pathogens.php](http://www.cissm.umd.edu/projects/pathogens.php), accessed October 2010) and The International Council for the Life Sciences ([www.iclscharter.org/eng/index.asp](http://www.iclscharter.org/eng/index.asp), accessed October 2010).

- Educational workshops on dual-use research developed in the United Kingdom have been conducted in several regions (97).
- A course module for practising scientists, science students and laboratory technicians working on infectious diseases has been discussed in South Africa (37).
- A study has assessed education materials for biosafety, biosecurity and dual-use research at major universities in the European Union (98).
- The NSABB has recommended to the United States Government outreach and education strategies for raising awareness among various stakeholders about dual-use research of concern (99).
- On-line educational modules have been developed by:
  - the Center for Arms Control and Nonproliferation (CACNP)<sup>1</sup>
  - the Federation of American Scientists (FAS)<sup>2</sup>
  - the Southeast Regional Center of Excellence for Emerging Infections and Biodefense (SERCEB).<sup>3</sup>

A 2008 report from the American Association for the Advancement of Science (AAAS) has examined 14 programmes in the United States that educate graduate or professional students in the biomedical sciences on dual-use research issues (100). The report draws attention to the importance of education on dual-use research and the lack of funding for such activities. It also identifies gaps in current knowledge on dual-use issues and on the role of the government, research institutions and scientific organizations.

#### **Implementation of educational and training initiatives to raise awareness**

The experience of the WHO regional awareness activities raised several points (29). First, countries emphasize the importance of developing and maintaining research and laboratory capacity for public health purposes, for prevention and management of disease outbreaks, and for research

on communicable and noncommunicable diseases. This underlines the importance of access to laboratory infrastructure and biological materials, research collaboration, developing new tools for disease prevention and control, and implementation of the IHR. Another priority of many countries is addressing intellectual property rights concerning microorganisms. With the increasing number of biological laboratories worldwide and thus an increasing number of people working with biological agents and pathogenic microorganisms, there are pressing demands for teaching and training and demonstrated competency in biosafety, laboratory biosecurity and ethics. Such activities help reduce the likelihood of accidents and provide tools for scientists to discuss the complex ethical questions they encounter in their everyday work.

Second, the perception of risk associated with accidents and deliberate misuse of life sciences research differs from country to country. The knowledge and awareness of this issue are very uneven among countries and regions. Some countries are thinking of developing measures while for others the issue is novel (97).

Third, researcher expertise differs widely from country to country, as does laboratory capacity. Different approaches may be required to improve understanding and practice in different regions and countries. Some countries will opt for legislation or regulations on biosafety and biosecurity while others will focus on ethics, research and funding policy or possibly choose a different path if regulations already exist.

### **2.3 Remarks**

This section has briefly reviewed some of the research activities that have raised concerns in policy circles and within the scientific and publishing communities. Although the available evidence suggests that, so far, only a small number of published papers have raised concerns, these activities had an important impact within the media and policy communities. Many questions raised by these experiments remain unanswered (see **Table 1**) and those exposed to such experience, whether researchers or publishers, have asked for more clarity as to what should be done. Some have also put forward the need to have clear guidelines on the subject to avoid measures that would go beyond what is appropriate and put unwarranted restrictions on research activities and international collaboration (12–14).

Some have also pointed out the difficulty of

<sup>1</sup> Center for Arms Control and Non-Proliferation. Biosecurity: Risks, responses, and responsibilities ([www.armscontrol-center.org/policy/biochem/biosecurity\\_educational\\_materials/](http://www.armscontrol-center.org/policy/biochem/biosecurity_educational_materials/), accessed October 2010).

<sup>2</sup> Federation of American Scientists. Case studies in dual use biological research ([www.fas.org/biosecurity/education/dualuse/index.html](http://www.fas.org/biosecurity/education/dualuse/index.html), accessed October 2010).

<sup>3</sup> Southeast Regional Center of Excellence for Emerging Infections and Biodefense. The dual use dilemma in biological research ([www.serceb.org/dualuse.htm](http://www.serceb.org/dualuse.htm), accessed October 2010).

determining possible hazards associated with single research projects and that, instead of looking at discrete and individual activities, more attention should be devoted to the cumulative developments in the life sciences (101). Such a macro level approach would look at what trends are emerging in the life sciences and what directions of research are being funded. Whether such an approach would bring some solutions to the current problems associated with risk assessment however remains to be seen.

Others have also noted that potential risks can be found in most areas of the life sciences, leading possibly to far-fetched risk assessments. And so the focus of risk assessment ought rather to be whether the magnitude of the potential for misuse might or might not be great enough to outweigh the benefit that might be lost by closing down the research in order to negate that risk.

In any event, many questions remain open in terms of risk assessment (see **Table 1**): how best to identify what is an experiment of concern; what could be the magnitude of potential misuse; how to identify trends or path of research in the life sciences that may pose concerns; how to weigh the risks against the benefits; and who should be in charge of carrying out such assessment. On this last point, it has also been noted that adequate expert input to help carrying out risk assessment may be much harder to find than it is sometimes suggested.

The review of the different policy options shows that addressing this complex issue requires a sense of shared responsibility among different stakeholders and that an emphasis has been put until now on the role of self-governance and bottom-up mechanisms. Despite the lack of a universal agreed upon definition on dual-use research, research of concern or dangerous research, some initiatives have already been implemented at the national and local levels and some research institutions, funding bodies, publishing houses and journal editors have established review committees.

**Table 1. Key questions and concerns**

KEY QUESTIONS
<ul style="list-style-type: none"> <li>• How to identify life sciences research activities of concern?</li> <li>• How to assess benefits against risks? Based on which criteria?</li> <li>• How to address the potential risks posed by accidents or deliberate misuse of life sciences research activities?</li> <li>• How to foresee the implications of research?</li> <li>• Would legislation or self-regulation be more effective to manage these risks?</li> <li>• What is expected from the researchers, the publishers, funding bodies and the authorities?</li> <li>• Is there a need to be concerned? Is it a priority?</li> <li>• Is it a global issue? Are there global solutions? What are they?</li> <li>• Are developed and developing countries similarly concerned?</li> <li>• Are there any best practices from existing approaches?</li> <li>• Are there any assessments of different models and comparisons of approaches?</li> <li>• What are the costs and benefits of different policy options?</li> </ul>
KEY CONCERNS
<ul style="list-style-type: none"> <li>• Risks of accidents and potential misuse of research</li> <li>• Biosafety</li> <li>• Scientific value of the experiment</li> <li>• Ethical issues</li> <li>• Publications</li> <li>• Scientific freedom</li> <li>• International collaboration</li> <li>• Public health needs</li> <li>• Capacity for developing countries</li> <li>• Control measures</li> </ul>

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# 3. The biorisk management framework for responsible life sciences research

On the basis of [Section 2](#), which reviewed the available evidence of potential risks of accidents or misuse, along with the policies and positions of different stakeholders, this section focuses on the three pillars that support a biorisk management framework for responsible life sciences research, from a public health perspective (see [Box 9](#)).

Implementing the biorisk management framework for responsible life sciences research will require investing in, developing and reinforcing each of its three pillars. First, researchers, institutions and countries need to have the capacity to respond to public health needs. Second, students, researchers and laboratory staff need to receive appropriate education and training on ethics and best practices in the responsible conduct of research, and be encouraged to discuss and collab-

oratively reflect on issues related to the risks of life sciences research. Third, countries and institutions need to promote the safe and secure handling of pathogens, assess their specific needs with respect to education and safety, and implement risk-based laboratory procedures. In light of competing demands and limited resources, it is worth noting that each pillar is equally important and that safety can be achieved without major financial resources. Meanwhile, practices should be complementary and self-reinforcing and should remain focused on public health needs.

How best to do this will depend on available resources and on national, local and institutional needs, which vary greatly between countries. However, in most countries, implementation will require the involvement of different stakeholders (from policy-makers, to laboratory managers, to individual researchers) and action at all levels. Coordination among different sectors and stakeholders is essential to establish clear roles and responsibilities, and to avoid duplicating activities and overburdening existing regulatory schemes and public health activities. In this regard, a self-assessment questionnaire has been developed and is presented in [Section 4](#) to help countries and institutions assess their strengths and weaknesses and to support implementation of the biorisk management framework.

In addition, effective biorisk management policies for responsible life sciences research should be: *flexible* to incorporate new scientific developments; *sustainable* in order to meet the differing needs of countries and institutions; *viable* for countries facing competing demands with scarce resources; developed in collaboration with relevant stakeholders, particularly researchers who are the most directly affected by the policy, so that it is *acceptable* and *equitable* to all stakeholders; and built on existing frameworks and experiences (see [Box 10](#)).

The biorisk management framework has added value insofar as it incorporates a unique public

## BOX 9

### Three pillars of a biorisk management framework for responsible life sciences research

- **Pillar 1: Research excellence** – this concerns fostering quality in life science activities, which is the basis for developing new treatments and therapeutics; national health research systems (HRS) and the WHO strategy on research for health; and disease surveillance and response activities and the International Health Regulations (IHR). These elements are essential to protecting and improving the health and well-being of all people.
- **Pillar 2: Ethics** – this involves the promotion of good research practices and ethical conduct through education and training.
- **Pillar 3: Biosafety and laboratory biosecurity** – this concerns the promotion of safe and secure laboratory measures to prevent exposure to pathogens and toxins.

health approach built on elements that already exist in countries for other public health activities. Thus, the framework is a flexible, sustainable and viable way for countries to invest in reinforcing a number of core public health capacities that serve different purposes. In addition, it builds on the many options that have already been put forward by different sectors and groups to manage this issue (see **Section 2**). The biorisk management framework for responsible life sciences research helps make public health communities, policy-makers, institutions and researchers aware of the risks and encourages thinking about the wider implications of the research and about how to deal with unexpected discoveries.

Effective biorisk management policies for responsible life sciences research should, in turn, lead to:

- strengthening research capacity development
- fostering international exchange and collaboration
- fostering scientific freedom, transparency, trust and accountability
- ensuring safe and secure practices.

Effective efforts to address the potential risks arising from accidents, serendipity or intentional misuse of life sciences research activities will maintain public confidence in science, foster the responsible, ethical conduct of research, and protect laboratory workers, the environment and the community. At the same time, such investments will promote the importance of research for health and assist countries in meeting other significant public health challenges, including the containment of disease outbreaks and the development of disease surveillance mechanisms.

### 3.1 Pillar 1: Research excellence

National health research systems (HRS), the WHO strategy on research for health and the International Health Regulations (2005) can all be used to help build and enhance national research and laboratory capacities.

#### 3.1.1 Health research systems

Since the 1990 landmark report of the Commission on Health Research for Development, there has been growing interest in the organization and strengthening of HRS (102–107). For example, in November 2008, the “Bamako call to action” highlighted a number of priorities that are relevant to this guidance: among other things, governments

#### BOX 10

##### Hallmarks for effective management policies on responsible life sciences research

- Flexibility – adjusting for new scientific developments
- Sustainability – relevance of the policy to the needs of countries and institutions and political feasibility (or political support)
- Viability – cost of the policy
- Acceptability/equity to stakeholders
- Built on existing frameworks

#### BOX 11

##### Key considerations when implementing the biorisk management framework for responsible life sciences research

- Reinforce public health capacities in terms of research for health, biosafety and laboratory biosecurity, and ethics.
- Invest in training personnel (laboratory staff and researchers) and students in ethics, the responsible conduct of research, and biosafety and laboratory biosecurity.
- Ensure compliance with biosafety and laboratory biosecurity.
- Consider multi-stakeholder issues, with different layers of responsibilities and encourage coordination among stakeholders.
- Use existing mechanisms, procedures and systems and reinforce local institutional bodies (if they exist).

**BOX 12****Four core functions of a health research system**

**STEWARDSHIP:** Stewardship is synonymous with the oversight of a health research system (HRS). It is usually performed by governments but other stakeholders such as national health research councils or professional associations may also play a role. Stewardship covers four components:

- define and articulate the vision for a national HRS
- identify appropriate health research priorities and coordinate adherence to these
- set and monitor ethical standards for health research and research partnerships
- monitor and evaluate the HRS.

Stewardship is the most relevant function for the responsible management of life sciences research. If the function is well developed, a country would have a national policy on health research involving all key stakeholders. Partnerships and commitment between different institutions at the national and international level would be emphasized. Health priorities would be identified and funded (i.e. based on national burden of disease, political will, human resources, community participation, etc.). Ethics would constitute an important element in addressing the challenges posed by scientific advances. Ethical review boards would operate and HRS would be regularly reviewed.

**FINANCING:** Another central HRS function is to secure research funds in an accountable, transparent and efficient manner and to ensure funding matches national research priorities. This function is especially important given the financial issues regarding the funding of health research and the importance of life sciences research for economic development. Resources are needed to address infectious disease priorities (research, facilities, equipment, personnel and training), and to develop and strengthen laboratory infrastructure, equipment, manpower and training.

**CREATING AND SUSTAINING RESOURCES:** This function covers the human and physical resources necessary to conduct health research but also the importance of an enabling environment that leads to good research management, discussions of research data and availability of funding. Another aspect of this function is to ensure staff are trained and have appropriate facilities to carry out research.

**PRODUCING AND USING RESEARCH:** The production of valid research disseminated in both peer-reviewed and non-peer-reviewed literature, policy reports, books etc., is an important part of this function. The products of research – knowledge and technologies – can be deployed to inform health policies and strategies and to develop new tools (therapeutics, vaccines and other devices) for better health. One challenge is to link health research with health policy and practice. Communication between the different stakeholders (researchers, publishers, policy-makers, practitioners, the media and the public) and the role of Internet are important in linking health research with health needs.

Sources: Pang T et al. Knowledge for better health – a conceptual framework and foundation for health research systems. *Bulletin of the World Health Organization*, 2003, 81:815–820. For more information about Health Research System Analysis (HRSA) core indicators and descriptive variables, Sadana R et al. *Health Research System Analysis (HRSA) Initiative: Methods for Collecting Benchmarks and Systems Analysis Toolkit. Tool #1. A brief overview of WHO Health Research System Analysis initiative and an overview of core indicators and descriptive variables*. Geneva, World Health Organization, 2006 (WHO/EIP/IHRSA/06.1) and ([http://www.who.int/rpc/health\\_research/en/index.html](http://www.who.int/rpc/health_research/en/index.html), accessed October 2010).

committed themselves to strengthen institutional research capacity, develop and enforce ethical and regulatory frameworks, and support open access to data and sharing of health information (108, 109).

Governments and donors are increasingly focused on results-based financing for health research and demonstrating value for money.<sup>1</sup> Investing in HRS should facilitate the achievement of these objectives. Although HRS are shaped by contextual factors and existing capacities at national, subnational and institutional levels, four core functions have been identified (see **Box 12**) (7).

The main objectives of HRS are “the production of scientifically-validated research and the promotion of the use of research results, ultimately to improve health and health equity” (25, 111). At the same time, strong national HRS can also address some of the concerns about the possibility of accidents or the deliberate misuse of life sciences research highlighted in **Section 2**. Indeed, the organization and management of some research activities have been criticized not only because of potential concerns about accidents or misuse but also because of doubts about their scientific value (see **Section 2.1**). While recognizing the importance of balancing national research policy and individual leadership, HRS are one way to reinforce the management of research at national level.

### 3.1.2 Implementing the WHO strategy on research for health

In January 2009, the WHO Executive Board endorsed the organization’s strategy on research for health, which incorporates the central goal of strengthening research capacities and research governance tools (112). The resolution on WHO’s role and responsibilities in health research was then adopted by the Sixty-third World Health Assembly in resolution WHA63.21 in May 2010 (113). The WHO strategy recognizes the centrality of research for global health progress, aims to strengthen WHO’s role in research for health, and will underpin all of the Secretariat’s research-related activities (114) (see **Annex 9**). Four of the strategy’s five interrelated goals (the organization goal, the priorities goal, the capacity goal, the standards goal, and the translational goal) are important in addressing the issues and concerns arising from life sciences research (see **Box 13**).

### 3.1.3 International Health Regulations (IHR)

The IHR (2005) is a binding international legal instrument in 194 countries, including all Member States of WHO.<sup>2</sup> The aim of the regulations is to prevent and respond to the international spread of disease. The IHR (2005) entered into force on 15 June 2007 and requires countries to report public health emergencies of international concern (PHEIC) to WHO. Laboratories are a key element of the IHR. Together with WHO and other partners, countries could use this IHR (2005) requirement for national capacity to prevent the international spread of disease as an opportunity to assess their laboratory capacities and needs associated with the three pillars.

The IHR (2005) is focused on serious public health risks with the potential to spread across international borders. According to Article 2, the purpose and scope of the Regulations are:

*“to prevent, protect against, control and provide a public health response to the international spread of disease in ways that are commensurate with and restricted to public health risks, and which avoid unnecessary interference with international traffic and trade.”* [emphasis added]

Among others, one of the priority areas in the implementation of IHR (2005) is the capacity of countries to detect report, verify and control events. In this regard, Member States are expected to assess, and strengthen as necessary, national structures and resources to meet the minimum core capacity requirements under IHR (2005) (115). Having access to laboratories is critical for detecting and confirming disease outbreaks as well as chemical and radionuclear events. This underscores the importance of having reliable laboratory data, competent staff, appropriate resources and adequate infrastructure.

## 3.2 Pillar 2: Ethics

Along with good research practices and research integrity, ethical considerations are critical elements in the biorisk management framework for responsible life sciences research. This section

<sup>1</sup> Health research systems have defined as “the people, institutions, and activities whose primary purpose in relation to research is to generate high-quality knowledge that can be used to promote, restore and/or maintain the health status of populations; it should include the mechanism adopted to encourage the utilization of research.” (7, 110).

<sup>2</sup> For additional information on the International Health Regulations (<http://www.who.int/ihr/en/>, accessed October 2010).

**BOX 13****Four selected goals of the WHO strategy on research for health**

■ **The organization goal** is to strengthen the research culture across WHO. To achieve this goal, the Secretariat, in collaboration with Member States and other partners, will, for instance, develop and implement a WHO code of good research practice for those of its staff involved with research and the use of evidence; will reinforce existing mechanisms for ethical and peer-review structures and procedures; will improve the management and coordination of WHO-affiliated research; and will develop a publicly accessible repository for all such research.

■ **The capacity goal** is to support the development of robust national health research systems. To achieve this goal, the Secretariat, in collaboration with Member States and other partners, will, for instance, strengthen advocacy for robust HRS, develop guidelines in the four core functions of HRS, and develop indicators for monitoring progress.

■ **The standards goal** is to promote good research practice. Emphasizing the increasing demand for more accountability and transparency in the conduct of research, WHO is expected to promote best practices in research. In this regard, the Secretariat will, for instance, in collaboration with Member States and partners, develop norms and standards for best practice in the management of research. This will cover, for example, ethical and expert review and the accreditation of ethical review committees; the sharing of research data, tools and materials; the registration of clinical trials; and the use of evidence in the development of policy, practice and products.

■ **The translational goal** is to strengthen the links between the policy, practice and products of research. To achieve this goal, the Secretariat, in collaboration with Member States and other partners, will, for instance, support decision-making based on the best available research evidence; will promote the use of effective models of technology transfer and their evaluation; will systematically analyse barriers and encourage the creation of mechanisms to promote greater access to research results, or the enhancement of existing ones; will adopt and articulate a WHO position on open access to research outputs; and will advocate databanks, repositories and other mechanisms for maximizing the availability of health-related research findings that are freely accessible in the public domain.

**BOX 14****Summary of research excellence elements for responsible life sciences**

■ Capacity development for research is essential for reducing health inequalities and for ensuring the proper use of life sciences.

■ Use existing tools and frameworks, such as health research systems (HRS), the WHO strategy on research for health and the International Health Regulations (IHR) as these can provide useful tools for contributing to responsible life sciences research.

elaborates on these points and also develops an ethics framework to address issues associated with the potential risks posed by accidents or the deliberate misuse of life sciences research.

**3.2.1 Ethical considerations**

The importance of ethics in life sciences research is widely recognized. In the past 30 years, oversight systems have been established around the world to foster the ethical conduct of research, especially involving human and animal research subjects. More recently, ethical issues associated with genetics, cloning and stem cell research have been under the spotlight. However, aside from a debate about “environmental safety and implications for human health” in the early days of recombinant DNA research, bioethics (as a discipline) has paid relatively little attention to the safety and security issues that are central to this guidance document. The majority of ethical discourse surrounding genetics has focused on genetic therapy, genetic testing, genetic discrimination, selective reproduction, DNA fingerprinting and the patenting of genetic sequences. Discourse surrounding research ethics and practices related to ethical oversight of research, meanwhile, have traditionally focused primarily on the protection of research subjects rather than biosafety (which is most often handled by institutional biosafety committees rather than ethics committees) or risks associated with the deliberate misuse of research.

Until recently, the debate on the risks posed by accidents and deliberate misuse of research has mainly been engaged by science and secu-

rity experts rather than ethicists. However, given the potential conflicting values of promoting scientific progress and protecting public security, and the questions about responsibility that arise, the dual-use dilemma is inherently ethical in nature. Safety, meanwhile, is often treated as a technical, rather than ethical, issue. Given the potential dangers to the environment and society, however, the safety of research is obviously ethically important. Finding and maintaining the right mix of policies that will enable the benefits of life sciences research to be maximized while minimizing the risks requires efforts on the part of both the life sciences and the security communities. Developing and implementing such policies is a complex and dynamic process that calls for multifaceted solutions forged through sustained international coordination and engagement, which may uncover value conflicts in need of resolution. If the full potential of life sciences research is to be realized, the potential risks of that research must be managed. This is not just a technical challenge: it is also an ethical one. **Box 15** lists several critical ethical questions that arise from the issues raised in **Section 2**.

Questions about values, and how to resolve value conflicts when they arise, fall directly within the realm of ethics. In addition to addressing issues of value conflict, ethical analysis is required for assessing the responsibilities of scientists, research institutions, science societies, publishers and national governments. In light of the need for more ethical input into debates about dual-use research, it is reassuring that an emerging literature is beginning to address the issues associated with the potential risks posed by the deliberate misuse of life sciences research from an explicitly ethical perspective (67, 116–122).

What can bioethics offer to address this issue? Ethics can help people identify an ethical problem and understand as fully as possible the nature of the decision they have to make (2). Ethical considerations can assist policy-makers, individual researchers and other stakeholders to discuss their differing (and sometimes competing) interests and values and use such deliberations to inform and influence policy decisions taken at the country and institutional levels. Going through this process can help resolve tensions between the responsibilities of individual researchers and the scientific community as a whole to society; the tensions between scientific freedom and security concerns; and the tensions involved in balancing potential benefits against possible risks.

#### BOX 15

#### Key ethical questions for consideration

- How to weigh the potential benefits of research against the risks for misuse? On which criteria should this assessment be based?
- How to weigh the individual interests of researchers against the common good of public health? Who should make these decisions? How can tensions between individual researcher and institutions/society best be managed?
- How to best manage the risks associated with research without hindering its beneficial application to public health?
- What are the responsibilities of individual researchers and of the scientific community as a whole to society?

#### 3.2.2 Towards an ethics framework

The development of an ethics framework should start with the recognition that the potential risks associated with accidents or the deliberate misuse of life sciences research pose dilemmas for numerous actors – with different responsibilities – at different levels of the hierarchy of scientific governance and oversight in any one country.

##### *Individual scientists*

Much of the literature on the potential risks associated with accidents or the deliberate misuse of life sciences research has thus far focused on the ethical responsibilities of (individual) scientists in particular. The dual-use phenomenon poses a dilemma for scientists who want to conduct research that will benefit humanity but who, at the same time, want to avoid projects that could potentially cause harm. Though the promotion of national security is not usually considered to be a primary responsibility of scientists (as opposed to governments) in particular, people in general have a duty of non-maleficence: the duty to do no harm (123).

Some consider scientific knowledge to be inherently good (124). Others believe that it is not scientific knowledge per se that is good or bad but rather the way that knowledge is used. Despite conflicting opinions within the life sciences community about the wisdom of restrictions on the search for new knowledge, the need to place limits on the application of that knowledge in certain

defined circumstances is broadly accepted. And there is widespread agreement that all research in the life sciences must be conducted in a safe and ethical manner. There are, however, differing views on the question of whether scientists should be held responsible for the misapplications of their research by others, whether foreseeable or not. This dispute is but one facet of the ongoing debate about the scope and limits of the responsibility of researchers.

One important and widely acknowledged duty of the individual scientist is to follow good research practices and conduct research responsibly. Good scientific practice in research is recognized as essential for the integrity of research, to nurture confidence within the research community and with society. Progress and development in scientific research also rely on the honest treatment of data and on open, transparent research that could be reproduced, thereby allowing quality control. This also includes the relevance of bringing the potential safety and security concerns associated with research activities to the attention of review committees and publishers during review processes. Good research practices generally include the conscientious avoidance of research misconduct (fabrication, falsification or plagiarism); policies for handling misconduct, conflicts of interests, data management, authorship, peer review and collaborative research; and policies regarding the protection of human and animal subjects (125, 126).<sup>1</sup> In 2007, at the first world conference “Research integrity: fostering responsible research,” participants discussed strategies for fostering responsible conduct in research and the possibilities of implementing international standards for research integrity (127). In 2010, at the second world conference on Research Integrity, a consensus emerged that research integrity needed urgent and international attention (128).

In a similar vein, another important responsibility of individual researchers is to consider the possible future implications of their work and, as far as possible, undertake such an evaluation as part of the research risk assessment. But there are some difficulties associated with this. First, enabling

individual researchers to exercise such a responsibility requires raising their awareness about those potential risks. Empirical research has shown that life scientists currently lack much awareness on this topic in general (97). Awareness-raising will not, of course, make scientists able to predict the future with certainty. Second, scientists may not have the security expertise to undertake such assessment, not to mention possible conflicts of interest that may arise. So the expectation is merely that scientists, to the best of their ability, make informed reflective judgements – taking the likelihood and magnitude of reasonably foreseeable harms and benefits of research into account – about whether or not, or the extent to which, precaution is necessary. The ability of scientists to make such judgements could, meanwhile, be enhanced via relevant education (regarding biorisks, biosafety and laboratory biosecurity, and ethics).

Additional duties of scientists include developing awareness of and maintaining compliance with existing laws, regulations and procedures applicable in their respective fields of expertise, including: those related to research review or oversight whether at a national or institutional level; safety procedures; and codes of conduct established by relevant science societies. In doing so, scientists can play a role in influencing the updating of these laws, regulations and procedures, as and when is necessary. Depending on decisions made by actors at other levels, one or more of the above (i.e. research institutions, codes of conduct, and/or national regulations) may formally require that individual scientists report potential risks to a review committee when a research proposal is submitted and/or before results are published. Scientists should also be educated and regularly trained about ethical issues that may arise in their work (see [Section 2.2.5](#)). Reflection and debate on current working practices or past experiences can help stimulate discussions on issues that are of interest to them. This could be achieved through ethics education in undergraduate and postgraduate curricula and also through ongoing professional education of scientists. Last, but not least, individual researchers may have obligations regarding whistle-blowing and playing an advocacy role in science policy debates.

### **Research institutions**

The possibility of accidents or the deliberate misuse of life sciences research also raises ethical issues for institutions where research takes place.

<sup>1</sup> See also European Science Foundation (ESF) Member Organisation Forum on Research Integrity ([www.esf.org/activities/mo-fora/research-integrity.html](http://www.esf.org/activities/mo-fora/research-integrity.html), accessed October 2010) and OECD’s Global Science Forum on *Best Practices for Ensuring Scientific Integrity and Preventing Misconduct* ([www.oecd.org/dataoecd/37/17/40188303.pdf](http://www.oecd.org/dataoecd/37/17/40188303.pdf), accessed October 2010).

Among other things, research institutions should be encouraged to have mechanisms in place to address potential risks arising from research taking place within their confines and provide relevant education, information and support for researchers. Research institutions have a responsibility to ensure that research is in accordance with national law and/or relevant codes of conduct. Though codes of conduct are often considered to be a voluntary governance mechanism, some institutions have found ways to enforce them, for instance, as a condition of employment.

A growing trend in recent years has involved increased provision of, sometimes mandatory, research ethics education to scientists. In light of the importance of the safety and security issues considered in this document, research ethics education of scientists could be expanded to ensure coverage of such topics. Research institutions should, for example, consider whether to include such education as part of the routine undergraduate and/or postgraduate training of scientists. Another possibility that has been adopted by certain countries for researchers involved in clinical trials involving human subjects is to make research ethics education a condition of research funding.

Given the importance of whistle-blowing in the event that scientific misconduct occurs, research institutions should have established procedures for whistle-blowing and provide adequate protection to whistle-blowers.

Finally, research institutions should support researchers in addressing dual-use issues if they arise. There have been recent cases of scientists seeking but receiving little, if any, guidance from research institutions about how to handle dual-use discoveries (129). Because scientists often lack expertise in matters of security, they should be provided with institutional assistance in resolving difficult questions – especially when they explicitly ask for such help. Ethics committees or biosafety committees might, in some cases, provide some support, although it is recognized that some may not (currently) have the knowledge or mandate to deal with these issues. If untoward consequences result from research, then this may adversely affect the researcher's career and damage the reputation of the research institution. These are reasons why research institutions should aim to provide competent guidance in difficult cases. In the most vexing cases, research institutions may themselves need to seek outside assistance/consultation (e.g. from government) regarding what should be done.

### *Science societies*

To date a good deal of attention has been focused on the possible incorporation within codes of conduct of guidance on the possibility of accidents or the deliberate misuse of life sciences research (see [Section 2.2.4](#)). Codes of conduct may be useful in raising awareness and also in fostering an understanding of and respect for certain norms. They can also be deployed in efforts to sensitize scientists and the public health community, and to establish public confidence and accountability. Although codes of conduct may be adopted at institutional level, they are perhaps best suited for adoption and promulgation at the scientific community level. One possibility might be the establishment of a code of conduct for scientists, or life scientists, in general. Another possibility might be the adoption of specific codes of conduct by various subspecialties of life sciences research. Relevant science societies should, therefore, be encouraged to decide whether or not to adopt such codes and/or what to include in their content. They may also consider using their professional development processes as a way to raise awareness on this issue. Likewise, a decision might be taken as to whether or not, and/or how, to promote or enforce adherence to codes on the part of their members. It is common for professional societies (like medicine) to enforce codes of conduct – i.e. as a condition of official membership and/or licensing (130). Among other things, life sciences societies must decide whether or not to go this route. Yet, many questions remain in terms of commitments, motivations and strategies to make them meaningful and effective (94, 95).

Science societies and other relevant bodies representing scientific communities, such as scientific unions, are ultimately concerned with the promotion of excellent science and of the fruits of scientific research. Raising awareness and providing guidance to researchers about issues such as the dual-use dilemma – via codes of conduct – may be one good way to achieve this aim.

### *Publishers and journal editors*

Controversy surrounding some research activities has to a large extent focused on the publication of a small number of high-profile dual-use discoveries (see [Section 2](#)). Publishers and journal editors play a crucial role in determining what becomes publicly available information and are thus ultimately accountable to the public for their decisions. Regardless of ultimate decisions about the publication of potential dual-use research findings, pub-

lishers need to be encouraged to develop criteria for deciding whether, or not, and/or how, and when to screen submissions for the risks of such findings prior to publication. Science publishers and editors have the responsibility to publish papers that will promote the advancement of science; but they also have responsibilities as publishers of papers that may have adverse societal consequences.

In 2003 a number of important life sciences journals published a joint journal statement on scientific publication and security (see [Section 2.2.2](#)), which includes provisions for the appropriate level and design of processes to accomplish effective review of papers that raise safety and security issues. Journals involved in this kind of review will need to develop mechanisms for assessing risks and benefits in difficult cases. On the one hand, science publishers should employ sufficiently vigilant measures to identify submissions that may raise concerns. On the other hand, review procedures should not be overly restrictive as this would unnecessarily hinder scientific progress and societal benefits thereby made possible. Because the assessment of risks and benefits is a complex task that is beyond the traditional scope and capacity of scientific publishers, consultation with appropriate experts is an essential part of publication processes.<sup>1</sup> Responsible publication decision-making requires adequate expert input, which may not be so easy to find.

### ***National governments, international organizations and funding bodies***

The possibility of accidents or deliberate misuse of life sciences research also poses dilemmas for policy-makers in government. On the one hand, government policy should aim to promote the advancement of science. Scientific progress usually has important societal (including economic) benefits; and promoting the good of society is a primary responsibility of government. Promotion of scientific progress partly requires provision of financial support for research, and governments are usually prudent not to overburden scientists with regulations. At the same time, safety, security and economic development are significant responsibilities of governments. Science inevitably affects society in innumerable ways, and so society (via governments) has set a number of measures to manage scientific research. Ideally, safety and security measures should help promote science to reach its social benefits and maintain public trust in science.

Governments might therefore consider what, if any, regulations associated with research oversight mechanisms might be administered by law and/or what role governmental institutions could play in the monitoring of research activities and the provision of advice and guidance to scientists and research institutions. National laws (see [Section 2](#)) already include measures to protect workers from the risks of exposure to biological agents; provisions for licensing laboratories and researchers; for the transport of biological agents; and other measures.<sup>2</sup>

Governments can also influence the direction of science when making decisions about what projects or areas of research to fund. Consonant with their aims of promoting and protecting the good of society, governments should provide more financial support to areas of research most likely to have the greatest net societal benefits. Just as scientists should weigh benefits against the risks when deciding which projects to pursue, governments should be encouraged to do the same when deciding which projects to fund. Other ways could include consideration of this issue during the setting of education agendas (e.g. ethics, biosafety and laboratory biosecurity in science undergraduate and postgraduate education programmes); the provision of resources to address this issue; and including scientists in the design of policies.

Finally, at the international level, both international organizations and funding bodies may also face dilemmas. At the same time as they promote scientific development and research, in particular in developing countries, to improve public health, these actors may consider to promote global health security and to minimize any risks to public health.

### **3.2.3 Remarks**

The preceding discussion underscores the complexity of the issues associated with the possibility of accidents or the deliberate misuse of life sciences research and highlights the ethical challenges that confront numerous actors working within different domains with different types of responsibility. The possibility of accidents or the deliberate misuse of science is not just a problem for scientists – it also poses challenges for research institutions, science

<sup>1</sup> For a list of different journal's policies, see (37).

<sup>2</sup> For additional information, see the United Nations Office at Geneva, the Biological Weapons Convention ([www.unog.ch/bwc](http://www.unog.ch/bwc), accessed October 2010).

**BOX 16****Summary of ethics elements for responsible life sciences research**

- Use existing platforms, if appropriate.
- Promote ethics education and training for students and professionals.
- Encourage discussion and reflection on research practices.
- Hold institutions and researchers to account and ensure they are aware of their responsibilities.
- Ensure institutions and researchers are aware of existing and new legislation, regulations at the country but also at the regional and international levels.

societies, publishers, journal editors, national governments, and regional and international bodies. At the international level, facilitating the sharing of experiences and best practices is important so that no incompatible measures are put forward that make international collaboration harder. Responsible decision-making is required by actors at all levels. Decision-makers will need to make judgments to resolve difficult cases of conflicting values. Scientific freedom, scientific progress, public health, safety and security are all important values, and none should be given absolute priority over the others. Conflict between these values, in any case, is not always inevitable. Wherever possible, decision-makers should aim to promote all of these values – and others – at the same time.

### 3.3 Pillar 3: Biosafety and laboratory biosecurity

Based on site-specific risk assessments, laboratory facilities that handle biological materials should develop and implement appropriate safety and security measures. These measures are critically important: they serve to minimize the risk of worker exposure to pathogens and infections, and to protect the environment and the community. Despite advances in technology and the sophistication of many instruments, laboratory-acquired infections still occur, often due to lack of training, competency and supervision and human errors. WHO has published guidelines on biosafety since 1983 and, more recently, has provided guidance for laboratory biosecurity (1). Another important

document on laboratory management has been published by the CEN (European Committee for Standardization) (4). The CEN Workshop Agreement (CWA) is based on a management system approach and promotes the adoption of recognized standards for the management of biological risks. Such standards should help an organization to identify, monitor and control the biosafety and laboratory biosecurity aspects of its activities.

Calls for the use of biosafety and laboratory biosecurity measures for addressing the risks associated with accidents and the potential misuse of research have also been emphasized in several documents, including the InterAcademy Panel statement on biosecurity (33), the International Council for Life Sciences (131), Sixth Review Conference of the BWC (132), the OECD guidelines on biosecurity (36) and the WHO laboratory biosecurity guidance (1).

#### 3.3.1 Elements of biosafety and laboratory biosecurity

Biosafety and laboratory biosecurity refer to containment principles, technologies and practices implemented to prevent unintentional exposure to pathogens and toxins, or their accidental release, as well as to protect, control and account for valuable biological materials (VBM)<sup>1</sup> within laboratories, in order to prevent their unauthorized access, loss, theft, misuse, diversion or intentional release. Concerned with the mitigation of different but related risks, both biosafety and laboratory biosecurity are based on risk assessment (3). In the WHO approach, effective biosafety practices are the foundation of laboratory biosecurity activities: indeed, the implementation of good biosafety practices also addresses certain key dimensions of laboratory biosecurity.

For any given laboratory activity, procedure or experiment with any pathogenic agent, a risk assessment should be carried out to determine the appropriate combination of risk mitigation measures which currently are captured in distinctive biosafety levels. Laboratory facilities are divided into four levels, from basic – Biosafety Level 1 – to maximum containment – Biosafety Level 4 (3). Each level has a set of particular design features, construction, equipment, containment practices, use of personal protective equipment and operational procedures ascribed to it. Risk assessments are based on a series of factors, including the

<sup>1</sup> See footnote under Definitions.

inherent properties of the agent; the consequences of any exposure and/or infection; the laboratory activity planned; and local laboratory conditions. Identified risks should be reduced to acceptable levels through appropriate risk mitigation measures. Strict adherence to the appropriate risk mitigation measures will help to minimize risks (3).

In terms of laboratory management, biosafety practices should be based on a comprehensive laboratory biorisk management system under the ultimate responsibility of the director of the laboratory. Although all laboratory workers and managers are responsible for their own safety and that of their colleagues, a laboratory biorisk management adviser<sup>1</sup> should be appointed, whenever possible, to ensure that the biosafety and laboratory biosecurity measures are followed consistently throughout the laboratory.

According to the Laboratory Biorisk Management Standard (4), the competent individual providing advice and guidance on biorisk management is often recognized as a biological safety officer or biological safety adviser. This function should be regarded as an advisory position and not directly responsible for managing biorisks, as this rests with those conducting and managing the work within the organization. The role and knowledge of the laboratory biorisk management adviser is important to develop, implement, maintain and continually improve a biosafety and biosecurity programme based on a management system. The adviser should be competent to perform the role, and allocated sufficient time and other resources to do the job effectively. In the execution of his/her biorisk management duties the adviser should be independent from those responsible for implementing the programme of work and have direct access to the top management representative when necessary.

A biosafety committee may support the biorisk management adviser. Members of this committee should cover the diverse areas of occupations and expertise of the laboratory, may be in charge of developing institutional biosafety policies and codes of practice. Such a committee may also be

<sup>1</sup> A laboratory biorisk management adviser is "an individual who has expertise in the biohazards encountered in the organization and is competent to advise top management and staff on biorisk management issues. NOTE Depending on national guidelines and institutional traditions the role of a biorisk management adviser may be differently named e.g. biosafety officer, biosecurity officer, biorisk manager or biorisk management officer." (4).

#### BOX 17

##### Elements of laboratory biorisk management system

- Biorisk management system
- Risk assessment
- Facility physical requirements
- Equipment and maintenance
- Occupational health and medical programmes
- Good microbiological techniques
- Emergency response and contingency planning
- Personnel and competency
- Biological agent and toxin inventory and information
- General safety
- Clothing and personal protective equipment
- Human factors
- Accident/incident investigation
- Decontamination, disinfection and sterilization
- Transport procedures
- Security

Source: CEN Workshop Agreement. *Laboratory biorisk management standard* (CWA15793:2008), (<ftp://ftp.cenorm.be/PUBLIC/CWAs/wokrshop31/CWA15793.pdf>, accessed October 2010).

tasked to review research protocols and may be asked to carry out other functions such as risk assessments or the development of new safety policies and the arbitration of disputes over safety matters (3).

Laboratory biosecurity, which is not only complementary to good biosafety practices, but also an integral part of an overall laboratory biorisk management system, addresses the safekeeping of all valuable biological materials (VBM), which include pathogens and toxins but also all biological materials which have a scientific, historical or economic importance (1, 133). This includes collections, reference strains, vaccines, food and pharmaceutical products, GMOs and non-pathogenic microorganisms. It is important to emphasize that implementation of biosafety and laboratory biosecurity can and should go hand-in-hand.

Based on a laboratory biosecurity risk assess-

ment, a specific laboratory biosecurity plan should be developed to manage the identified risks; such a plan should reflect the needs and requirements of each facility, the type of laboratory work undertaken and other appropriate considerations. Different actors may be part of a laboratory biosecurity assessment and may include the head of the laboratory, principal investigator, laboratory biorisk management adviser, administrators, and emergency and law enforcement agencies. Regular competency-based training of personnel regarding mitigation measures is essential for good implementation of the laboratory biorisk management system.

### 3.3.2 Biosafety, laboratory biosecurity and responsible life sciences

Safe and secure working practices associated with the conduct of research in laboratory settings are important elements for addressing the risks that could potentially arise from accidents or the deliberate misuse of life sciences research. Good laboratory biosafety practices will mitigate the risks posed by laboratory accidents while laboratory biosecurity procedures will strengthen the accountability and responsibility of laboratory workers and their managers and thereby enhance public confidence in the responsible conduct of scientific experiments.

In the future more and more laboratories will implement comprehensive systems that allow them to manage the risks associated with biological materials in the laboratories. Performance based systems based on existing international standards (e.g. ISO, CEN) have already made significant inroads in addressing key performance and quality issues (e.g. ISO 17025). On the safety and security side, the risks associated with biological materials in the laboratory can be comprehensively managed through the implementation of three key compo-

#### BOX 18

#### Summary of laboratory elements for responsible life sciences

- Conduct biosafety and laboratory biosecurity risk assessments and, based on these, apply appropriate risk reduction measures.
- Implement a laboratory biorisk management system.
- Explore the use of existing biorisk management structures (e.g. laboratory biorisk management adviser and the biosafety committee) to address issues related to the risks posed by life sciences research.
- Set performance objectives and work on continuous improvement.

nents: risk assessment, risk mitigation and performance systems (4).

There is a need for collaboration between national authorities, researchers, bioethics committees and laboratory biorisk advisers to identify the appropriate risk management measures under which activities would be performed. In addition to the role of the researcher and laboratory manager, the laboratory biorisk management adviser and the biosafety committee can also play an important role in the management of risks associated with accidents and the deliberate misuse of life sciences research.<sup>1</sup> In addition to ensuring that safe and secure practices are established and followed during the conduct of life sciences research activities, they are also involved with addressing the risks associated with research protocols and codes of practice at the laboratory level.

<sup>1</sup> See Section 1.2.1 Terminology for the use of the words “accidents and the deliberate misuse of life science research”.

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## 4. The way forward: the self-assessment questionnaire

This guidance promotes a culture of scientific integrity and excellence, distinguished by openness, honesty, accountability and responsibility. Such a culture is the best protection against accidents, the inadvertent harmful consequences of research and deliberate misuse, and the best guarantee of scientific progress and development.

This guidance has identified three pillars of a biorisk management framework for responsible life sciences research: research excellence, ethics, and biosafety and laboratory biosecurity. The self-assessment questionnaire presented below ([Section 4.3](#)) is intended to help health policy-makers, health professionals, laboratory managers, professional associations and individual scientists assess the extent to which elements related to the three pillars are in place – in the national public health system and in individual laboratories – to identify their respective strengths and weaknesses, and to build on their strengths and address their weaknesses in each of these three pillars. It can be used in a number of other ways, as explained below in [Section 4.2](#).

There is no single solution or system that will suit all countries and all laboratories. Each interested country or institution needs to assess the extent to which it has systems and practices in place to deal with this issue at local and national levels, and to decide which measures need to be reinforced.

In general, oversight, safety and public security should be pursued in a manner that maximizes scientific progress and preserves scientific freedom. This requires excellent facilities, and the management of them (including laboratories), leadership with integrity, a robust ethical framework, training and capacities development, institutional development and regular review.

### 4.1 Using the self-assessment tool

Self-assessment is a process that begins with an identification of strengths, weaknesses and gaps and concludes with action to address the gaps and weaknesses and to build on or consolidate the strengths.

The questionnaire that follows allows users to assess the extent to which structures, mechanisms and processes are in place that will facilitate and ensure excellence in science, safety and security. The second part of the process of self-assessment requires users to consider those areas that have been identified as weaknesses or gaps through answering the questions. This second stage may involve meetings with others who are involved in laboratory management or policy formulation. The final aspect of self-assessment is corrective action to address gaps or weaknesses identified.

The questionnaire can be used as a quick assessment for individuals in senior government positions, or even laboratory managers. It can also be completed by employees at a research facility as a process of assessing the institution.

Aside from its primary purpose of assessment, the questionnaire is also intended to stimulate discussion and debate about the issues raised, to raise awareness about the three pillars of the biorisk management framework, and to provide a basis for thinking about what is necessary to ensure good quality, responsible activities in the life sciences.

### 4.2 Interpreting the results of the self-assessment tool

If the questionnaire is to be used as a quick assessment for individuals in senior government positions, or laboratory managers the user may find that the first time they try to answer the questions, many of the answers will be “don’t know”. In other words, it is likely that many respondents, particularly senior government officials, may not have an overview of the detailed implementation of systems for safety, security and ethics at public

health facilities. An answer of “don’t know” on any of the questions should indicate to the user that they need to find out more information about that particular issue.

So, answering the questionnaire quickly, before consulting laboratory managers or public health care facility managers will enable the user to identify those areas where she or he requires more information. After consultations to gather information the user may wish to fill in the questionnaire once again. This time there may be fewer “don’t know” responses and more that fall into the categories “agree” or “disagree”. Where the answers are “disagree” the user should be alerted to the fact that action may need to be taken to address the situation. For example, if the answer to the question “Facilities and equipment are appropriate to the level of work being done and are adequately maintained” is “disagree” or “strongly disagree” it is clear that the facilities and equipment are not appropriate to the level of work being done, or are not adequately maintained. This may present a safety risk, both to the public and to those working in the laboratory and suggests that measures need to be taken to address the problem. On the other hand, a response of “agree” or “strongly agree”

shows that appropriate measures are already in place.

If the questionnaire is completed by a group of laboratory scientists the results may be interpreted slightly differently. In this case a large number of “don’t know” answers to any one of the questions may indicate that staff is uninformed about the particular issues being probed. For example “don’t know” responses to the question “Research priorities are in line with national health needs” suggests that laboratory staff do not know what the national health needs are, or may suggest that when research projects are initiated consideration is not given to whether the research is in line with national health needs. Whichever of the two it is, the answer “don’t know” should indicate to managerial staff that there is a need to discuss the issue further with their staff.

In general, for all users of the questionnaire, answers of “agree” or “strongly agree” to the questions identify strengths; answers of “disagree” or “strongly disagree” indicate weaknesses and answers of “don’t know” indicate gaps in knowledge (in other words issues for which more information may be required).

### 4.3 The self-assessment questionnaire

#### Self-assessment: Responsible life sciences research

Good quality, ethical research activities that are conducted in safe and secure facilities strengthens public health

##### PILLAR 1: RESEARCH EXCELLENCE (see Section 3.1)<sup>1</sup>

Answers to the questions in this section will assess the extent to which the basic requirements for excellent public health research are in place

- |   |  |
|---|--|
| <p>1.1 Scientific collaboration <b>within</b> institutions is encouraged and facilitated</p> <p><input type="checkbox"/> Strongly agree</p> <p><input type="checkbox"/> Agree</p> <p><input type="checkbox"/> Disagree</p> <p><input type="checkbox"/> Strongly disagree</p> <p><input type="checkbox"/> Don't know</p> <hr/> <p>1.2 Scientific collaboration <b>between institutions and countries</b> is encouraged and facilitated</p> <p><input type="checkbox"/> Strongly agree</p> <p><input type="checkbox"/> Agree</p> <p><input type="checkbox"/> Disagree</p> <p><input type="checkbox"/> Strongly disagree</p> <p><input type="checkbox"/> Don't know</p> <hr/> <p>1.3 Research funding is transparent (i.e. it is known who funds research, and what research is funded at institutional level)</p> <p><input type="checkbox"/> Strongly agree</p> <p><input type="checkbox"/> Agree</p> <p><input type="checkbox"/> Disagree</p> <p><input type="checkbox"/> Strongly disagree</p> <p><input type="checkbox"/> Don't know</p> <hr/> <p>1.4 Accountability is required (e.g. through regular reporting of financial expenditure as well as scientific progress)</p> <p><input type="checkbox"/> Strongly agree</p> <p><input type="checkbox"/> Agree</p> <p><input type="checkbox"/> Disagree</p> <p><input type="checkbox"/> Strongly disagree</p> <p><input type="checkbox"/> Don't know</p> <hr/> <p>1.5 Research priorities are in line with national health needs</p> <p><input type="checkbox"/> Strongly agree</p> <p><input type="checkbox"/> Agree</p> <p><input type="checkbox"/> Disagree</p> <p><input type="checkbox"/> Strongly disagree</p> <p><input type="checkbox"/> Don't know</p> | <p>1.6 Research matches research priorities</p> <p><input type="checkbox"/> Strongly agree</p> <p><input type="checkbox"/> Agree</p> <p><input type="checkbox"/> Disagree</p> <p><input type="checkbox"/> Strongly disagree</p> <p><input type="checkbox"/> Don't know</p> <hr/> <p>1.7 Research findings are routinely published</p> <p><input type="checkbox"/> Strongly agree</p> <p><input type="checkbox"/> Agree</p> <p><input type="checkbox"/> Disagree</p> <p><input type="checkbox"/> Strongly disagree</p> <p><input type="checkbox"/> Don't know</p> <hr/> <p>1.8 Good communication exists between policy-makers and the research community</p> <p><input type="checkbox"/> Strongly agree</p> <p><input type="checkbox"/> Agree</p> <p><input type="checkbox"/> Disagree</p> <p><input type="checkbox"/> Strongly disagree</p> <p><input type="checkbox"/> Don't know</p> <hr/> <p>1.9 On-going research training takes place</p> <p><input type="checkbox"/> Strongly agree</p> <p><input type="checkbox"/> Agree</p> <p><input type="checkbox"/> Disagree</p> <p><input type="checkbox"/> Strongly disagree</p> <p><input type="checkbox"/> Don't know</p> <hr/> <p>1.10 Junior researchers are nurtured and supported</p> <p><input type="checkbox"/> Strongly agree</p> <p><input type="checkbox"/> Agree</p> <p><input type="checkbox"/> Disagree</p> <p><input type="checkbox"/> Strongly disagree</p> <p><input type="checkbox"/> Don't know</p> <hr/> <p>1.12 Education and/or training is offered on dual-use issues</p> <p><input type="checkbox"/> Strongly agree</p> <p><input type="checkbox"/> Agree</p> <p><input type="checkbox"/> Disagree</p> <p><input type="checkbox"/> Strongly disagree</p> <p><input type="checkbox"/> Don't know</p> |
|---|--|

<sup>1</sup> For more information about Health Research System Analysis (HRSA) core indicators and descriptive variables, see (111).

1.13 Skilled researchers are valued and retained

- Strongly agree  
 Agree  
 Disagree  
 Strongly disagree  
 Don't know

1.14. National legislation and policy fosters scientific development and freedom

- Strongly agree  
 Agree  
 Disagree  
 Strongly disagree  
 Don't know

#### **PILLAR 2: ETHICS** (see Section 3.2)

*Answers to the questions in this section will assess the extent to which measures to ensure that research conducted is ethical are in place*

2.1 Education and/or training is offered on research ethics

- Strongly agree  
 Agree  
 Disagree  
 Strongly disagree  
 Don't know

2.2 Appropriate ethical research guidelines and practices have been published and implemented

- Strongly agree  
 Agree  
 Disagree  
 Strongly disagree  
 Don't know

2.3 Adequate mechanisms exist for investigating and responding to non-adherence to ethical standards

- Strongly agree  
 Agree  
 Disagree  
 Strongly disagree  
 Don't know

2.4 Research is subject to a risk assessment that includes the societal impact of the research

- Strongly agree  
 Agree  
 Disagree  
 Strongly disagree  
 Don't know

2.5 Researchers are competent to assess the potential societal impact of research Strongly

- Strongly agree  
 Agree  
 Disagree  
 Strongly disagree  
 Don't know

2.6 Research is subject to a risk assessment that includes potential environmental impact

- Strongly agree  
 Agree  
 Disagree  
 Strongly disagree  
 Don't know

2.7 Researchers are competent to make the assessment of the potential environmental impact of research

- Strongly agree  
 Agree  
 Disagree  
 Strongly disagree  
 Don't know

2.8 Potential for misuse of the research is considered at all stages and appropriate action taken if necessary

- Strongly agree  
 Agree  
 Disagree  
 Strongly disagree  
 Don't know

2.9 Researchers know how to assess whether the risk outweighs the benefit of continuing with their research or activities

- Strongly agree  
 Agree  
 Disagree  
 Strongly disagree  
 Don't know

2.10 A code of conduct/practice for life scientists exists at national or institutional level

- Strongly agree  
 Agree  
 Disagree  
 Strongly disagree  
 Don't know

2.11 Researchers are aware of and informed about national and international conventions, laws and regulations related to their research

- Strongly agree
- Agree
- Disagree
- Strongly disagree
- Don't know

2.12 An ethics committee assesses research proposals involving human subjects

- Strongly agree
- Agree
- Disagree
- Strongly disagree
- Don't know

2.13 A review process exists to assess ethical issues raised by research proposals not involving human or animal subjects

- Strongly agree
- Agree
- Disagree
- Strongly disagree
- Don't know

2.14 Information about the national and international conventions and regulations related to all fields of science is easily accessible

- Strongly agree
- Agree
- Disagree
- Strongly disagree
- Don't know

2.15 National legislation and policy relevant to the life sciences provides protection against the misuse of science

- Strongly agree
- Agree
- Disagree
- Strongly disagree
- Don't know

**PILLAR 3: BIOSAFETY AND LABORATORY BIOSECURITY** (see Section 3.3)

*Answers to the questions in this section will assess whether measures to ensure laboratory safety and security are in place*

3.1 Facilities and equipment are appropriate to the level of work being done and are adequately maintained

- Strongly agree
- Agree
- Disagree
- Strongly disagree
- Don't know

3.2 Researchers have somewhere to turn to get competent advice if they have safety or security questions relating to their research

- Strongly agree
- Agree
- Disagree
- Strongly disagree
- Don't know

3.3 National legislation/regulation exists that sets safety and security practices and procedures for laboratories

- Strongly agree
- Agree
- Disagree
- Strongly disagree
- Don't know

3.4 An assessment of the risk associated with research activities is conducted

- Strongly agree
- Agree
- Disagree
- Strongly disagree
- Don't know

3.5 Risk assessments are able to identify requirements for risk reduction measures including the level of containment required

- Strongly agree
- Agree
- Disagree
- Strongly disagree
- Don't know

- 3.6 Biosafety and laboratory biosecurity training is provided to all those working in laboratories
- Strongly agree  
 Agree  
 Disagree  
 Strongly disagree  
 Don't know
- 
- 3.7 Biosafety and laboratory biosecurity training includes a test of competence
- Strongly agree  
 Agree  
 Disagree  
 Strongly disagree  
 Don't know
- 
- 3.8 Standard Operating Procedures have been developed (at institutional level)
- Strongly agree  
 Agree  
 Disagree  
 Strongly disagree  
 Don't know
- 
- 3.9 Staff are trained to work according to the Standard Operating Procedures
- Strongly agree  
 Agree  
 Disagree  
 Strongly disagree  
 Don't know
- 
- 3.10 Staff are regularly tested to ensure competence in the Standard Operating Procedures
- Strongly agree  
 Agree  
 Disagree  
 Strongly disagree  
 Don't know
- 
- 3.11 Legislation/regulations exist to address hazardous waste disposal
- Strongly agree  
 Agree  
 Disagree  
 Strongly disagree  
 Don't know
- 3.12 Legislation/regulations regarding hazardous waste disposal are followed
- Strongly agree  
 Agree  
 Disagree  
 Strongly disagree  
 Don't know
- 
- 3.13 Health surveillance mechanisms exist and are followed (at institutional level)
- Strongly agree  
 Agree  
 Disagree  
 Strongly disagree  
 Don't know
- 
- 3.14 Health reporting mechanisms exist and are effective at institutional level
- Strongly agree  
 Agree  
 Disagree  
 Strongly disagree  
 Don't know
- 
- 3.15 Staff are required to report laboratory accidents, incidents and near misses
- Strongly agree  
 Agree  
 Disagree  
 Strongly disagree  
 Don't know
- 
- 3.16 A record of research projects exists and is maintained at institutional level
- Strongly agree  
 Agree  
 Disagree  
 Strongly disagree  
 Don't know
- 
- 3.17 A record of valuable biological materials exists and is maintained at institutional level
- Strongly agree  
 Agree  
 Disagree  
 Strongly disagree  
 Don't know
- 3.18 Valuable biological material is safely and securely stored
- Strongly agree  
 Agree  
 Disagree  
 Strongly disagree  
 Don't know

3.19 Mechanisms exist for staff to report unlawful or irregular conduct (i.e. whistle-blowing mechanisms exist)

- Strongly agree
- Agree
- Disagree
- Strongly disagree
- Don't know

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3.20 Measures exist to protect staff who report unlawful or irregular conduct from occupational detriment

- Strongly agree
- Agree
- Disagree
- Strongly disagree
- Don't know

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# Annexes



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# Annex 1

## Contributors

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This guidance has been prepared by Dr Emmanuelle TUERLINGS.

Dr Chandre GOULD worked on the self-assessment questionnaire (Section 4) and Dr Michael SELGELID worked on the ethics section (Section 3.3).

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# Annex 2

## Declaration of interests

In line with WHO policy, participants of the “Guidelines review group workshop on responsible life sciences research, 22–24 June, 2009, Geneva” have completed and signed a declaration of interests. The WHO Secretariat reviewed these declarations and concluded that there were no conflict of interests.

### **Guidelines review group workshop on responsible life sciences research, 22–24 June 2009, WHO, Geneva**

#### **Participants**

Professor Peter Ian FOLB, University of Cape Town, South Africa  
Dr David FRANZ, Midwest Research Institute, United States of America  
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#### **Videoconference**

**22 June, E232, 15:00–17:00**

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## Annex 3

# Guidelines review group workshop on responsible life sciences research, WHO, Geneva, 22–24 June 2009

### Executive summary

1. The meeting recognized that good science and sound scientific research are inextricably linked with the health, development and good policies of a country. Moreover, the confidence of the people and their trust in government and policies depends to a large extent on trustworthy science. Achieving this involves partnerships, a partnership that includes the World Health Organization.
  2. The World Health Assembly resolution WHA55.16 of 18 May 2002 drew attention to the converse of this: the accidental or deliberate misuse of biological and chemical agents or radionuclear materials that affect adversely health, including the dual use potential of these agents, and the enormous public health implication of this – nationally and globally.
  3. The readership of this document is envisaged to be health policy makers and those who implement policy, health professionals, scientific community, the general public including educators, the WHO itself and governments. It is clear that the scope of the document goes beyond the health sector to industry, trade and commerce and the government departments that manage those activities.
  4. The purpose of the document is to balance maximum scientific potential and freedom against the need for scrutiny, safety and public security. The pillars on which such an approach rest include the following: excellent facilities, and the management of them (including laboratories); leadership; a robust ethical framework; training and capacities development; institutional development; and review. Success will depend on a range of mechanisms.
  5. In the end, the document aims at the culture of scientific integrity and excellence characterized by openness, honesty (which is paramount), accountability, responsibility and relevance.
- These are the best protection against accidents and potential misuse, and the best guarantees of progress and development.
6. The document identifies the following key activities in attaining these objectives: review including self-assessment, strengthening systems (including laboratories and their operations), capacity development, including facilities and human potential, robust ethical frameworks and the central role of the WHO.
- Underlying principle governing these considerations is that one size does not fit all, and neither should it; that the uniqueness of countries and their specific needs should be respected and cherished, and that each country would have its own vision on where it wishes to go and how to get there. At the same time, it has to be understood, that in the national and global interest, certain essential standards of the pursuit of science and of scientific research need to be in place.
7. A process for review and assessment, including self-assessment, is set out in the document that will enable countries and their policy makers to identify their respective strengths and weaknesses, and to build on their strengths and address their weaknesses. It includes human resources, operational issues, training, filling the gaps, funding strategies, standards of performance and ethics. Encompassed here is human subject research, animal experiments and basic science. A conceptual matrix has been developed (and will need to be further developed by a small expert group) that will make possible a process of measurement and scoring to allow for evaluation of progress and responsiveness.
  8. With regard to ethics, it is acknowledged that there has been some neglect of this issue, which call out to be addressed at a number of levels: individual, institutional, science community, journals and editors, national gov-

- ernments and international organizations. All these affect codes of conducts, requirements of the law, the ethics of policy, resolution of the inherent tensions between the primacy of the individual and utilitarian public imperatives of security, safety and scientific progress. This document argues that one should build on what is already in place, and that the system should be alert of serendipitous discoveries and capable of responding to it.
9. These considerations apply as much to research applied in the private sector and industry as they do to public scientific and health institutions. (The private sector is vast and growing in this regard).
  10. Two points in particular are argued in the ethics section of the paper; namely,
    - i. the importance and value of an independent ombudsman; and,
    - ii. ethics alone will not be sufficient; ethics is a crucial element but not the whole story.
  11. The implications of not getting this right are several and severe: poor science, public health risks, policy failure, a defective culture of research, weak public confidence, impaired funding opportunities and lack of development, and, inevitably the potential risk of misuse.
  12. The document briefly considers case examples such as avian flu, smallpox, mousepox and others as illustrative of the potential global impact of misusing science.
  13. The World Health Organization should lead the way for reasons that were developed at a previous meeting held on 16 October 2006, which identified 5 priorities areas leading to a five points plan set out in a note for the record of the internal meeting held at WHO on 6 February 2009. This plan was guided by the following principles:
    - i. work should be done with the regions;
    - ii. working with countries is a two way street;
    - iii. efforts should be evaluable;
    - iv. evaluation tools presently available are insufficient and should be developed
    - v. an important element of this activity is capacity development that would include ethics, leadership, networks and surveillance.
  14. In its conclusions, the meeting identified the potential value and importance of centers of excellence; that countries with an interest in responding to these challenges and at varying stages of their development should be identified in the first instance (altogether 6, one from each region would be ideal); the need to identify best practices from experience; identification and fostering of expertise, including those with potential expertise in the country; and capacity assessment and ways of filling the gaps.

# Annex 4

## The NSABB's proposed framework for the oversight of dual-use research

The NSABB's proposed system for the oversight of dual-use life sciences research that has been recommended to the United States Government includes:

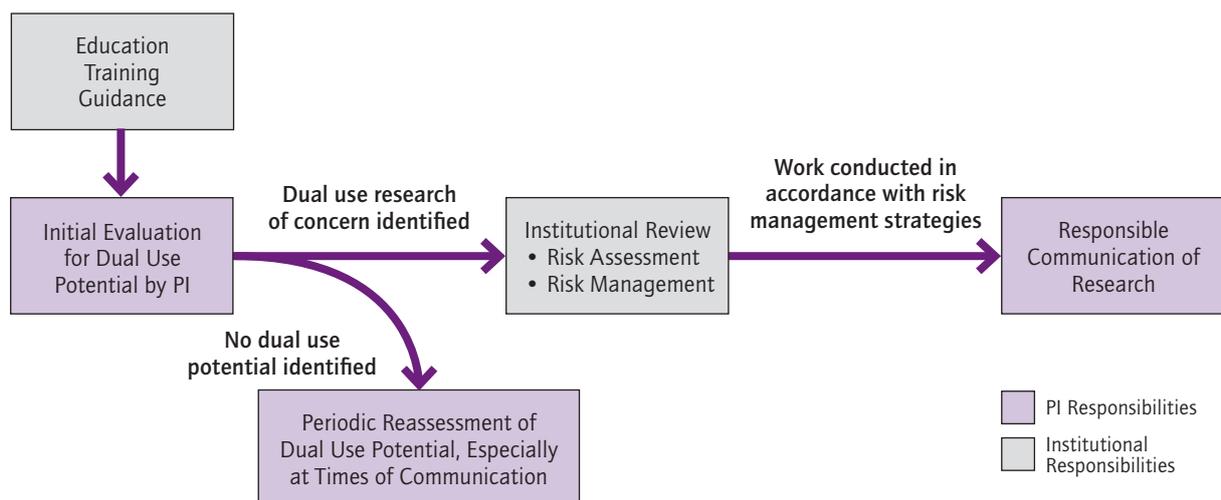
- the development of federal guidelines for the oversight, conduct and responsible communication of dual-use research;
- raising researchers' awareness about dual-use research issues;
- ongoing and mandatory education about dual-use research issues and policies;
- local evaluation and review of research with dual-use potential by the investigator and the research institution;
- risk assessment and risk management as a foundation for oversight;

- compliance and enforcement;
- evaluation of the efficacy, impact, and burden of the oversight system.

The NSABB proposed framework<sup>1</sup> focuses on the local oversight of dual-use research, on researchers who continually assess their work for dual-use potential, and on institutional review of research that includes risk assessment and risk management (see below).

Within this framework, researchers are considered the most critical element of oversight as they are likely to be most familiar with their work and its potential applications. To assist in the assessment of research for its dual-use potential, the NSABB developed a criterion for identifying research that constitutes "dual use research of concern." The

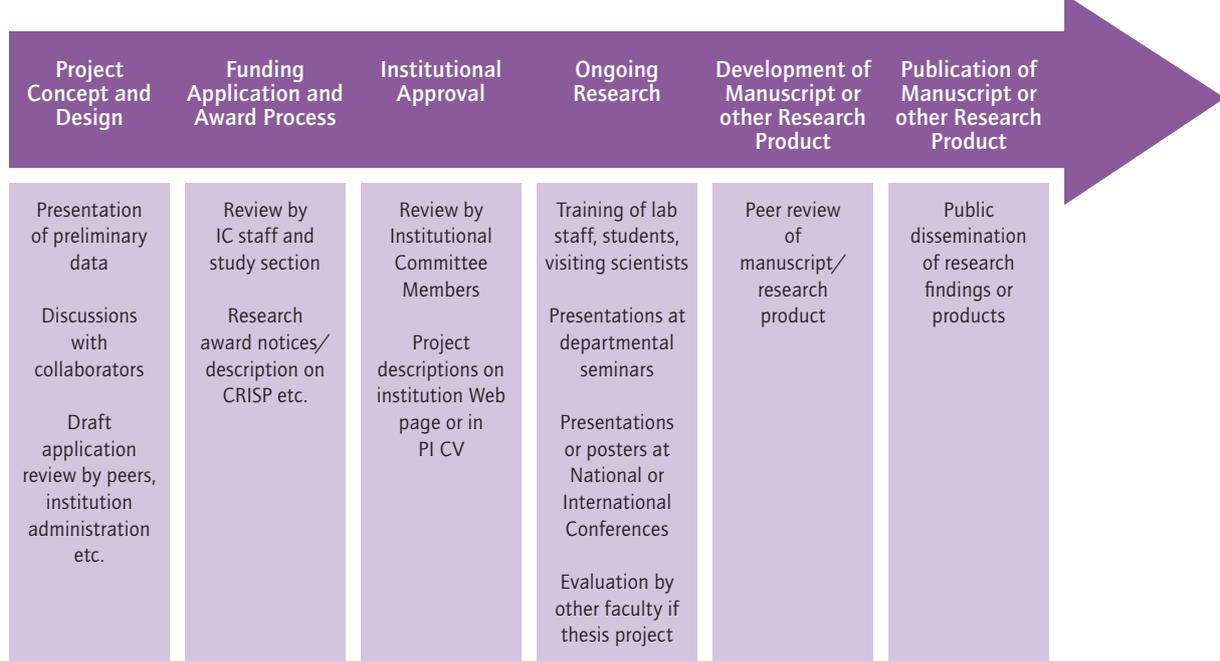
### Proposed steps in local oversight of dual-use research



Source: Adapted, with permission, from National Science Advisory Board for Biosecurity. *Proposed framework for the oversight of dual use life sciences research: strategies for minimizing the potential misuse of research information. A report of the National Science Advisory Board for Biosecurity (NSABB)*, June 2007.

<sup>1</sup> National Science Advisory Board for Biosecurity. *Proposed framework for the oversight of dual use life sciences research: strategies for minimizing the potential misuse of research information. A report of the National Science Advisory Board for Biosecurity (NSABB)*, June 2007.

## Examples of points of communication of dual-use research during the research process



Key: IC: Institutes and Centers; CRISP: As of December 30, 2009, the CRISP database, a NIH system, has been replaced with the Research Portfolio Online Reporting Tools (RePORT) Expenditures and Results (RePORTER) <http://projectreporter.nih.gov/reporter.cfm>, accessed October 2010); PI CV: Principal Investigator Curriculum Vitae

Source: Adapted, with permission, from National Science Advisory Board for Biosecurity. *Proposed framework for the oversight of dual use life sciences research: strategies for minimizing the potential misuse of research information. A report of the National Science Advisory Board for Biosecurity (NSABB)*, June 2007.

NSABB's criterion for identifying dual-use research of concern is "research that, based on current understanding, can be reasonably anticipated to provide knowledge, products, or technologies that could be directly misapplied by others to pose a threat to public health and safety, agriculture, plants, animals, the environment, or materiel." The NSABB also identified seven categories of experiments that describe information, products or technologies that if produced from life sciences research mean the research warrants careful consideration for its dual-use potential (see box below). These categories are informed by the NRC experiments of concern.

The NSABB report also provides tools to assist in the responsible communication of research results throughout the research continuum (see figure below) and considerations for the development of codes of conduct for life sciences researchers.

**NSABB categories of research that warrant careful consideration for dual-use potential**

1. Enhance the harmful consequences of a biological agent or toxin.
2. Disrupt immunity or the effectiveness of an immunization without clinical and/or agricultural justification.
3. Confer to a biological agent or toxin, resistance to clinically and/or agriculturally useful prophylactic or therapeutic interventions against that agent or toxin or facilitate their ability to evade detection methodologies.
4. Increase the stability, transmissibility, or the ability to disseminate a biological agent or toxin.
5. Alter the host range or tropism of a biological agent or toxin.
6. Enhance the susceptibility of a host population.
7. Generate a novel pathogenic agent or toxin or reconstitute an eradicated or extinct biological agent.

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## Annex 5

### A decision-making tool from the Centre for Applied Philosophy and Public Ethics, Australia

The identification of several salient experiments of concern (see box below) prompted the Center for Applied Philosophy and Public Ethics in Australia to develop a decision-making tool regarding dual-use dilemmas in the biological sciences (see table below).<sup>1</sup>

#### **Experiments of concern**

According to the Center for Applied Philosophy and Public Ethics, experiments of concern are those that attempt to do any one of the following:

1. demonstrate how to render a vaccine ineffective;
2. confer resistance to therapeutically useful antibiotics or antiviral agents;
3. enhance the virulence of a pathogen or render a non-pathogen virulent;
4. increase the transmissibility of a pathogen;
5. alter the host range of a pathogen;
6. enable the evasion of diagnosis and/or detection by established methods;
7. enable the weaponization of a biological agent or toxin;
8. sequence the genes of a pathogen;
9. synthesize a pathogenic microorganism;
10. experiment in any way with variola virus (smallpox);
11. attempt to recover/revive past pathogens.

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<sup>1</sup> Miller S and Selgelid MJ. *Ethical and philosophical consideration of the dual-use dilemma in the biological sciences*. Dordrecht NE, Springer, 2008. Report prepared by the Centre for Applied Philosophy and Public Ethics at the Australian National University for the Australian Department of Prime Minister and Cabinet, National Security Science and Technology Unit, November 2006.

**Decision-making for dual-use dilemmas in the biological sciences**

DECISIONS	OPTIONS				
	OPTION 1 THE COMPLETE AUTONOMY OF THE INDIVIDUAL SCIENTIST	OPTION 2 INSTITUTIONAL CONTROL	OPTION 3 INSTITUTIONAL & GOVERNMENTAL CONTROL	OPTION 4 AN INDEPENDENT AUTHORITY	OPTION 5 GOVERNMENTAL CONTROL
Who are the decision-makers regarding im/ permissible research?	Individual researcher	i) Scientists in university (collegial) (ii) Corporation (iii) Govt. Res. Centre	i) Scientists in university (collegial) (ii) Corporation (iii) Govt. Res. Centre	Independent authority	Government
Should compliance with physical safety & security regulation be mandatory?	No	Yes	Yes	Yes	Yes
Should dual-use technology be licensed?	No	No	Yes	Yes	Yes
Should education & training be mandatory?	No	No	Yes	Yes	Yes
Should personnel security regulation be mandatory?	No	No	Yes	Yes	Yes
Who are the decision-makers regarding censorship/constraint of material proposed for dissemination?	Individual editor	i) Individual editor (ii) Corporation (iii) Govt. Res. Centre	(i) Individual editor (ii) Corporation (iii) Govt. Res. Centre	Independent Authority	Government

NB: The decision-making in question pertains only to dual-use research in the biological sciences identified as potentially problematic by virtue of coming under one of the pre-established headings of Experiments of Concern

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# Annex 6

## A model from the Center for International and Security Studies

The prototype oversight system, known as the Biological Research Security System, developed by the Center for International and Security Studies (CISSM) at the University of Maryland, USA, rests on two key elements: national licensing of personnel and research facilities and independent peer review of relevant projects before their initiation. As the table on “Illustrative categories of research activities” shows, for the activities of extreme concern, there would be a global standard setting and review body – the International Pathogens Research Authority. This body would oversee those activities and would be in charge of defining the research activities falling under the different categories of oversight. At the next level, there would be a national review body – the National Pathogens Research Authority – to oversee activities of moderate concern. The national body would also oversee the work of local review bodies and the licensing of researchers and facilities. Finally, the local review body – the Local Pathogens Research Committee – would be in charge of overseeing activities of potential concern. According to CISSM, most of the microbiological research would either fall under this last category or not be covered at all.

### Illustrative Categories of Research Activities

#### ACTIVITIES OF EXTREME CONCERN (AEC)

Work with eradicated agents;<sup>a</sup> work with an agent assigned as BL-4/ABL-4; *de novo* synthesis of above; expanding the host range of an agent to a new host (in humans, other animals and plants) or changing the tissue range of a listed agent;<sup>b</sup> construction of antibiotic- or vaccine-resistant listed agent.

#### ACTIVITIES OF MODERATE CONCERN (AMC)

Increasing virulence of listed agent or related agent; insertion of host genes into listed agent or related agent; increasing transmissibility or environmental stability of listed agent or related agent; powder or aerosol production of listed agent or related agent; powder or aerosol dispersal of listed agent or related agent; *de novo* synthesis of listed agent or related agent; construction of antibiotic- or vaccine-resistant related agent; genome transfer, genome replacement, or cellular reconstitution of listed agent or related agent.

#### ACTIVITIES OF POTENTIAL CONCERN (APC)

Work with listed agents – or exempt avirulent, attenuated, or vaccine strain of a listed agent – not covered by AEC/AMC; Increasing virulence of non-listed agent; increasing transmissibility or environmental stability of non-listed agent; powder or aerosol production of non-listed agent; powder or aerosol dispersal of non-listed agent; *de novo* synthesis of non-listed agent; genome transfer, genome replacement, or cellular reconstitution of non-listed agent.

<sup>a</sup> This would include, for example, activities with the 1918 influenza virus and chimeric influenza viruses with at least one gene from the 1918 influenza virus.

<sup>b</sup> This would include, for example, activities with chimeric influenza viruses with at least one gene from a human influenza virus and at least one gene from an avian influenza virus.

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<sup>1</sup> Steinbruner J et al. *Controlling dangerous pathogens. A prototype protective oversight system.* The Center for International and Security Studies at Maryland (CISSM), The University of Maryland, College Park, Maryland, March 2007.

**Table Definitions**

**Agent:** fungus, protozoan, bacterium or archaeon, virus, viroid, or prion; or genetic element, recombinant nucleic acid, or recombinant organism.

**Listed Agent:** agent on CDC Select Agent list, USDA High-Consequence Livestock Pathogens list, or USDA/APHIS/PPQ Plant Pathogens list.

**Related agent:** for fungi, protozoans, or bacteria or archaea, an agent that currently is, or in the last two years was, assigned to the same genus as a listed agent; for viruses, viroids, or prions, an agent that currently is, or in the last two years was, assigned to the same family as a listed agent; for genetic elements, recombinant nucleic acids, or recombinant organisms, an agent orthologous to a listed agent. (This includes any avirulent, attenuated, or vaccine strain of a listed agent, if said strain is exempt under the CDC Select Agent list, USDA High-Consequence Livestock Pathogens list, or USDA/APHIS/PPQ Plant Pathogens list.)

**Non-listed agent:** agent other than a listed agent or related agent.

**Eradicated agent:** agent previously in circulation in nature but not within the last decade, as determined by cases of or isolation from humans, animals, or plants, or by detection of antibodies to the agent from individuals younger than the time-span elapsed since the last recorded isolation.

**De novo synthesis:** construction of agent using synthetic genomic nucleic acid (non-prion agents) or synthetic protein (prions), irrespective of whether said construction require additional reagents, extracts, cells, or 'helper' entities. For purposes of this definition, 'synthetic genomic nucleic acid' refers to nucleic acid that corresponds to an agent genome and that is prepared using, in any step or set of steps, chemically synthesized oligonucleotides, corresponding to at least 5% of said agent genome.

**Powder:** powder other than lyophilized reference specimen (<10 mg).

**Antibiotic:** antibiotic of therapeutic utility against listed agent.

**Vaccine:** vaccine of therapeutic utility against listed agent.

Source: Steinbruner J et al. *Controlling dangerous pathogens. A prototype protective oversight system.* The Center for International and Security Studies at Maryland (CISSM), The University of Maryland, College Park, Maryland, March 2007.

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# Annex 7

## Implementation of oversight mechanisms

A report of practical experiences in dual-use review published by the Southeast Regional Center of Excellence for Emerging Infections and Biodefense (SERCEB) in Chapel Hill, North Carolina<sup>1</sup> has identified two significant issues: the lack of awareness about the dual-use dilemma and the need for technical expertise when assessing dual-use risks. Through its Policy, Ethics, and Law (PEL) Core, the centre reviews all proposals for dual-use issues, using the criteria of the Fink report (see **Box 7**) and the NSABB (see **Annex 4**).<sup>2</sup> The Center has developed an online module on the dual-use dilemma in biological research aimed at graduate and post-doctoral students, faculty members and biosafety professionals involved in the conduct, oversight or analysis of life sciences research.<sup>3</sup> According to the Center, “incorporating dual-use training and oversight mechanisms into existing programs, regulations, and requirements may be the most

practical approach to devising a process for dual-use review”.

The US Centers for Disease Control and Prevention (CDC) has implemented several processes for dual-use review.<sup>4</sup> It has, for instance, developed a policy brief for reviewers and an on-line training module that addresses these issues. The Coordinating Center for Infectious Diseases (CCID) reviews all research documents before their submission for publication, including for dual-use concerns. The publication of the two papers on the characterization of the 1918 influenza virus in 2005 (see **Box 4**) led to the pre-publication review by CCID and to the establishment of the Institutional Biosecurity Board (IBB), which reviews proposals that may raise dual-use issues with the help of a risk-benefit analysis questionnaire. However, the paucity of proposals raising concerns has often led to the cancellation of the IBB monthly meetings.

Finally, proposals for self-governance have also been put forward by those working in synthetic biology. These include proposals for firms to screen orders of synthetic DNA, to license DNA synthesizers, to educate users of synthetic DNA, and to peer review experiments.<sup>5</sup> Private synthetic biology companies in some high-income countries have also started to voluntarily screen DNA orders. They are using specific programmes to look for certain sequences of DNA. Some of these companies find it difficult to identify which criteria should be used to screen orders and recognize that not all companies currently screen orders and customers.

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<sup>1</sup> Davidson EM et al. Practical experiences in dual-use review. *Science*, 2007, 316:1432–1433.

<sup>2</sup> National Science Advisory Board for Biosecurity. *3rd International roundtable. Sustaining progress in the life sciences: strategies for managing dual use research of concern*. National Science Advisory Board for Biosecurity, Bethesda, Maryland, 5–6 November 2008.

<sup>3</sup> Southeast Regional Center of Excellence for Emerging Infections and Biodefense. *The dual use dilemma in biological research* ([www.serceb.org/dualuse.htm](http://www.serceb.org/dualuse.htm), accessed October 2010).

<sup>4</sup> National Science Advisory Board for Biosecurity. *3rd International roundtable. Sustaining progress in the life sciences: strategies for managing dual use research of concern*. National Science Advisory Board for Biosecurity, Bethesda, Maryland, 5–6 November 2008.

<sup>5</sup> Check E. Synthetic biologists try to calm fears. *Nature*, 441:388–389; Garfinkel MS et al. *Synthetic genomics: Options for governance*. The J. Craig Venter Institute, Massachusetts Institute of Technology & Center for Strategic and International Studies, 2007; Bugl et al. DNA synthesis and biological security. *Nature Biotechnology*, 2007, 25:627–629; National Science Advisory Board for Biosecurity. *3rd International roundtable. Sustaining progress in the life sciences: strategies for managing dual use research of concern*. National Science Advisory Board for Biosecurity, Bethesda, Maryland, 5–6 November 2008.

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# Annex 8

## Codes of conduct

The following examples of codes of conduct are in addition to the codes described in Section 2.2.4.

- The World Medical Association urges “all who participate in biomedical research to consider the implications and possible applications of their work and to weigh carefully in the balance the pursuit of scientific knowledge with their ethical responsibilities to society.”<sup>1</sup>
- The American Medical Association’s Council on Ethical and Judicial Affairs has guidelines to prevent malevolent use of biomedical research. These are now part of the AMA’s code of medical ethics.<sup>2</sup>
- The British Medical Association has stated: “Professional scientists and physicians have an ethical responsibility to reinforce the central norm that biological and genetic weapons are unacceptable. This should be explicitly stated in codes of professional conduct in order to safeguard the public interest in matters of health and safety.”<sup>3</sup>
- In November 2005, the Interacademy Panel (IAP) issued a statement on biosecurity, which was endorsed by 68 national academies of science.<sup>4</sup> This statement noted: “Scientists have a special responsibility when it comes to problems of ‘dual use’ and the misuse of science and technology.” The statement presents several guiding principles for individual scientists and local scientific communities who wish to develop codes of conduct. These principles include awareness, safety and security in laboratories, education and information, accountability and oversight.
- The American Society for Microbiology (ASM) has added the following statement to its code of ethics: “ASM members are obligated to discourage any use of microbiology contrary to the welfare of humankind, including the use of microbes as biological weapons and will call to the attention of the public or the appropriate authorities misuses of microbiology or of information derived from microbiology.”<sup>5</sup>
- The Chinese Academy of Sciences (CAS), a leading academic institution and comprehensive research and development centre in natural science, technological science and high-tech innovation in China, published in 2007 the Statements on the Notion of Science to guide the scientific and technical community in forming a correct scientific value system, to promote and develop a scientific spirit, to abide by scientific ethics and moral standards, and to fulfil its social responsibility. CAS also established biosafety committees and started biosafety training programmes at all its life sciences institutes.
- The Royal Netherlands Academy of Arts and Sciences has developed a national biosecurity code of conduct for scientists.<sup>6</sup> The code puts forward several provisions that would need to be applied at the individual level and at the research institutions, financing, publishing and monitoring levels. The implementation of the provisions

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<sup>1</sup> The World Medical Association. *The World Medical Association Declaration of Washington on biological weapons*. Adopted by the WMA General Assembly, Washington 2002; editorial changes made during the May 2003 Council Session, (Document 17.400).

<sup>2</sup> Green SK et al. Council on Ethical and Judicial Affairs of the American Medical Association. Guidelines to prevent the malevolent use of biomedical research. *Cambridge Quarterly of Healthcare Ethics*, 2006, 15:432–447.

<sup>3</sup> British Medical Association (BMA). *Biotechnology, weapons and humanity*. London, Harwood Academic Publishers, 1999.

<sup>4</sup> The InterAcademy Panel on International Issues (IAP). *IAP Statement on Biosecurity*. 7 November 2005.

<sup>5</sup> American Society for Microbiology (ASM). *Code of ethics (Revised and Approved by Council 2005)*. 2005 (<http://forms.asm.org/ASM/files/ccLibraryFiles/FILENAME/00000001596/ASMCCodeofEthics05.pdf>, accessed October 2010).

<sup>6</sup> Royal Netherlands Academy of Arts and Sciences. *A Code of Conduct for Biosecurity. Report by the Biosecurity Working Group*. Amsterdam, Royal Netherlands Academy of Arts and Sciences, August 2008.

– which cover raising awareness, research and publication policy, accountability and oversight, internal and external communication, accessibility, shipment and transport – will need to be tailored to the needs of organizations and will remain under their responsibility. The Royal Netherlands Academy of Arts and Sciences also noted that the most important objective of the Code of Conduct for Biosecurity is to raise awareness and to prompt debate on the topic of dual-use research.

- The Royal Society in the United Kingdom has emphasized that codes may raise awareness and foster discussion on the subject and that codes should be based where possible on existing guidelines and principles: “Introducing extended codes of conduct or practice based on existing health and safety regulations will provide an opportunity for education and training to reinforce these regulations.”<sup>1</sup>
- Other related developments include:<sup>2</sup>
  - the NSABB’s recommendations for the development of a code of conduct for scientists and laboratory workers;<sup>3</sup>
  - the code of ethics for the life sciences that has been proposed by individual scientists Margaret Somerville and Ronald Atlas;<sup>4</sup>
  - the International Union of Biochemistry and Molecular Biology (IUBMB) has a code of ethics which makes reference to the misuse of science;
  - the International Union of Microbiological Societies (IUMS) has a very general statement on ethics;<sup>5</sup>
  - in 2006, the China Association for Science and Technology published the Code of Conduct for Chinese Scientists to uphold the ethics of scientific research and maintain academic self-discipline;
  - the International Centre for Genetic Engineering and Biotechnology (ICGEB) is assisting the United Nations Secretariat in fulfilling a mandate received by the Security Council to reinforce ethical norms and advocate the creation of national codes of conduct for scientists;
  - the International Committee of the Red Cross (ICRC) has been working with scientists in the life sciences to adopt “profession-

al and industrial codes of conduct aimed at preventing the abuse of biological agents”.<sup>6</sup>

- Although not promoting the idea of a universal code of conduct on this subject, the International Council for Science (ICSU) has also linked scientific rights and freedoms with responsibilities. Researchers have an individual responsibility to conduct research with honesty, integrity, openness and respect and a collective responsibility to maximize the benefits and minimize risks of the misuse of science for society.<sup>7</sup>

<sup>1</sup> The Royal Society. *The roles of codes of conduct in preventing the misuse of scientific research*. RS policy document 03/05, June 2005.

<sup>2</sup> National Science Advisory Board for Biosecurity. *3rd International roundtable. Sustaining progress in the life sciences: strategies for managing dual use research of concern*. National Science Advisory Board for Biosecurity, Bethesda, Maryland, 5–6 November 2008.

<sup>3</sup> National Science Advisory Board for Biosecurity. *Proposed framework for the oversight of dual use life sciences research: strategies for minimizing the potential misuse of research information. A report of the National Science Advisory Board for Biosecurity (NSABB)*. June 2007.

<sup>4</sup> Atlas RM, Somerville M. Life sciences or death sciences: tipping the balance towards life with ethics, codes and laws. In: Rappert B, McLeish A (eds). *A web of prevention: biological weapons, life sciences and the governance of research*, London, Earthscan, 2007:15–33; and Somerville MA, Atlas RM. Ethics: A weapon to counter bioterrorism. *Science*, 2005, 307:1881–1882.

<sup>5</sup> National Science Advisory Board for Biosecurity. *3rd International roundtable. Sustaining progress in the life Sciences: strategies for managing dual use research of concern*. National Science Advisory Board for Biosecurity, Bethesda, Maryland, 5–6 November 2008.

<sup>6</sup> International Committee of the Red Cross (ICRC). *Responsibilities of actors in the life sciences to prevent hostile use*. Geneva, ICRC, 2004.

<sup>7</sup> International Council for Science (ICSU). *Freedom, responsibility and universality of science*. Paris, International Council for Science (ICSU), 2008.

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## Annex 9

### WHO strategy on research for health

The WHO strategy on research for health defines a common framework for how research is approached in WHO and the role WHO is taking in global health research. The resolution on WHO's role and responsibilities in health research was endorsed by the Sixty-third World Health Assembly in resolution WHA63.21 in 2010.<sup>1</sup>

The box below highlights the actions that the resolution specifically recommends for Member States.

#### **Highlights from the World Health Assembly resolution on WHO's role and responsibilities in health research**

The Sixty-third World Health Assembly,

1. Endorses the WHO strategy on research for health;
2. Urges Member States:
  - to recognize the importance of research for improving health and health equity and to adopt and implement policies for research for health;
  - to consider drawing on the strategy on research for health according to their own national circumstances and contexts;
  - to strengthen their national health research systems;
  - to establish, as necessary and appropriate, governance mechanisms for research for health;
  - to improve the collection of reliable health information and data and maximize, where appropriate, their free and unrestricted availability in the public domain;
  - to promote intersectoral collaboration and high-quality research;
  - to initiate or strengthen intercountry collaboration;
  - to consider, where appropriate, the establishment of regional collaborating mechanisms, such as centres of excellence;
  - to continue to pursue financing of research for health.

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<sup>1</sup> For additional information, see ([http://www.who.int/rpc/research\\_strategy/en/index.html](http://www.who.int/rpc/research_strategy/en/index.html), accessed October 2010).