

Chapter 2

Dual-Use Threats: The Case of Biological Technology

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INTRODUCTION

In February 2001, the *Journal of Virology* published the results of a scientific experiment in which Australian researchers exploring contraceptive alternatives to pesticides for controlling the mouse population unexpectedly produced a lethal mousepox virus and, in the process, demonstrated how a new, highly virulent pathogen might be constructed.¹ This work might well have gone unnoticed by most people, other than interested scientists, had it not been for the fact that seven months later, terrorist attacks were carried out on the U.S. World Trade Center and the Pentagon and a series of letters containing high-grade anthrax spores were sent to selected U.S. media outlets and members of Congress. The latter events, which killed five and injured seventeen others, unleashed an epidemic of fear that terrorists would attack America again, only this time the weapon of choice would not be a commercial airliner but a biological agent that would cause death on a massive scale. Government officials and commentators alike warned that it was not a matter of whether bioterrorists would strike but of when.

Prior to September 11 and the anthrax letters, biological threats were seen largely through the lens of biosafety or nonproliferation—that is, ensuring that scientists' use of hazardous biological materials did not threaten human health or the environment, or preventing government-led programs aimed at developing and producing biological weapons. By the end of 2001, a new threat had been added to these traditional concerns: terrorist acquisition or use of

1. Ronald J. Jackson 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* 75 (3) (February 2001): 1205–1210.

biological agents. Efforts to counter the theft, diversion, or malicious use of dangerous pathogens and toxins by terrorists came to be known as biosecurity.²

Over the past half century, many different governance measures have been adopted and still others proposed to prevent both accidental and deliberate releases of biological agents and the corresponding damage, human and financial, this would cause. These measures span multiple levels: international, national, local, and individual. They also take many forms: legally binding treaties, United Nations (UN) Security Council resolutions, and intergovernmental decisions; national laws and regulations; like-minded government policies; national and departmental policies; guidelines and standards; and scientific codes. Taken together, they help to form what some have called a “web of prevention.”³ But, like any web, there are gaps.

This chapter begins with a brief discussion of why governance of biological materials, equipment, and information is so inherently difficult. It then considers some of the most important governance measures that have been adopted at the international level, in the United States, and in other countries. These measures are grouped by their primary objectives: preventing the development and possession of biological warfare agents or weapons; controlling access to dual-use biological materials, equipment, or associated information that could be used for hostile purposes; promoting the safe and secure handling of pathogens and toxins inside and outside the laboratory; and ensuring that the risks from the most consequential types of biological research are properly identified, assessed, and mitigated before the work is carried out. The chapter then looks at two other types of governance measures that have been prominent in the dual-use biological technology debate, and concludes with a discussion of the key challenges confronting further efforts to mitigate dual-use risks in this area.

GOVERNANCE OF BIOLOGICAL TECHNOLOGY

As other studies have pointed out, governance of biological technology is inherently difficult.⁴ First, most biological agents, such as bacteria and viruses, are living organisms that replicate, so policies that focus on inventory controls and accountability, especially monitoring the quantity of materials being stored, are problematic, as small seed stocks can later be used to produce large amounts of biological agent. Most biological agents can also be found in nature—in diseased soil or animals in the case of pathogens and in other living organisms in the case of toxins. While technical proficiency is required to obtain biological

2. Jonathan Tucker, “Preventing the Misuse of Pathogens: The Need for Global Biosecurity Standards,” *Arms Control Today* 33 (5) (June 2003), http://www.armscontrol.org/act/2003_06/tucker_june03.

3. Brian Rappert and Caitriona McLeish, *A Web of Prevention: Biological Weapons, Life Sciences and the Governance of Research* (London: Earthscan, 2007).

4. See, for example, Tucker, “Preventing the Misuse of Pathogens.”

materials from these natural sources, the fact that it can be done means that policies aimed at controlling access to dangerous pathogens or toxins can also be evaded.

Second, advances in science and technology are increasing the number of biological agents of potential concern, expanding the types of equipment relevant to their development and production, and broadening the range of facilities in which work with biological agents is occurring. During the Cold War, fewer than two dozen biological agents were developed and accepted into national biological weapons programs. However, advances in genetic sequencing and in synthetic biology are now making it possible to create an almost unlimited number of modified organisms, some of which may be more dangerous than existing biological agents, harder to detect, or capable of evading existing therapeutics.

Until a decade ago, efforts to control the acquisition of equipment that could be used to make biological agents focused on items such as high containment facilities, fermenters, specialized separators and filtration equipment, and aerosol test chambers, most of which were available in a relatively small number of countries. Today, modified organisms are being created more quickly and cheaply using sophisticated gene synthesis machines and reagents that are widely available. This work is being carried out in many countries and in diverse settings—in academic institutions, in industry and other private sector facilities, in government laboratories, and, in some cases, at sites where amateur scientists work without any institutional affiliation.

Third, governance of biological technology must also grapple with intangible technology—specifically, information or knowledge. This includes, for example, technical data necessary for the development or production of biological agents; it also includes the DNA sequence databases and design software available on the Internet that are central to the synthesis of modified or novel agents. And it includes the methods and results of research that are disseminated in multiple ways—in conversations among scientists, in email exchanges, in posters or presentations at scientific conferences, and in peer-reviewed publications.

Finally, each of these items—the biological materials, equipment, and related information—is used for legitimate purposes but can also cause harm, either accidentally or deliberately. Pathogens being studied for human or animal vaccines can escape from laboratories and sicken those they were designed to protect. Equipment used to understand the underlying biological properties of existing pathogens can also be directed toward enhancing the transmissibility or virulence of those pathogens for hostile applications. Information on the synthesis of an extinct pathogen like the 1918 Spanish flu virus can be used to bolster disease surveillance as well as to resurrect and disseminate this once-lethal threat. These characteristics have had a profound impact on efforts at every level to govern dual-use biological technology.

CURRENT STATE OF INTERNATIONAL GOVERNANCE

Many efforts have been undertaken at the international level to try to manage biological threats (see Table 1). These include treaty restrictions on the development and possession of biological weapons; multilateral initiatives aimed at preventing dual-use biological material, equipment, and information from being acquired for hostile purposes; and international guidelines and policies to ensure that pathogens and toxins are handled safely and securely.

Treaty Restrictions on Biological Weapons Development and Possession

During the 1960s, controversy over the use of herbicides and riot control agents by U.S. forces in Vietnam helped stimulate international interest in banning chemical and biological weapons. This ultimately led in 1972 to the conclusion of the Biological Weapons Convention (BWC), the first international treaty outlawing an entire class of weapons of mass destruction. From the outset, the BWC's terms acknowledged the dual-use nature of biological agents: instead of prohibiting biological *weapons* specifically, it committed parties never to “develop, produce, stockpile, or otherwise acquire or retain: microbial or other biological agents, or toxins . . . of types and in quantities *that have no justification for prophylactic, protective or other peaceful purposes*,” as well as “weapons, equipment or means of delivery designed to use such agents or toxins *for hostile purposes*.”⁵ This language also ensured that the BWC's fundamental prohibitions would apply to all future scientific and technological developments in the life sciences and related fields, including in the nascent field of biotechnology. BWC parties have reaffirmed this view regarding the scope of application of the BWC at each successive review conference since the convention entered into force in 1975.

In addition to prohibiting the development and possession of biological weapons, the BWC also obligates its parties not to transfer to others and not to assist any state in producing or acquiring biological agents or toxins (as well as weapons, equipment, or delivery means) for other than peaceful purposes. At the same time, the convention commits its parties to facilitate the fullest possible exchange of materials, equipment, and information for using biological agents and toxins for peaceful purposes and to avoid hampering international cooperation in such activities. This tension between the nonproliferation and assistance provisions of the BWC has been a major source of controversy between developed and developing countries since the earliest days of the convention.

The biggest weakness of the BWC, however, is the absence of meaningful mechanisms for ensuring that countries comply with their obligations. The implications of this failure became apparent in the late 1980s as reports began to emerge from Soviet biological weapons scientists who had defected to the West. These scientists revealed that Moscow had not only maintained its biological weapons program after the conclusion of the BWC but had expanded it

5. “Convention on the Prohibition of the Development, Production and Stockpiling of Bacteriological (Biological) and Toxin Weapons and on Their Destruction” (1972), <http://www.opbw.org/convention/documents/btwcext.pdf>; emphasis added.

Table 1: International Governance of Biological Technology

Measure	Date	Current Participants	Purpose	Comments
Biological Weapons Convention	1975	173 parties, 9 signatories	Ban biological agents, toxins for other than peaceful purposes	Legally binding; no verification; tension between nonproliferation and assistance provisions
WHO Biosafety Manual	1983	194 countries	Prevent unintentional exposure to pathogens/toxins, safe use of recombinant DNA technology	Global health authority; focus on guidelines to assist members; recommendations nonbinding
WHO Biosecurity Manual	2004		Prevent intentional misuse	
WHO Responsible Life Sciences Research Guidance	2010		Promote responsible life sciences research	No guidelines for research oversight
OECD rDNA Handbook	1986	34 countries	Promote safety of rDNA work	Multilateral organizations, limited membership; recommendations nonbinding
OECD Biosecurity Guidance	2001		Provide biosecurity guidelines	
Australia Group	1992	42 countries plus European Commission	Harmonize national controls on biological materials and equipment	Informal body; political commitment
UNSCR 1373	2001	193 countries	Share information on WMD terrorism	Legally binding; no provisions for implementation
UNSCR 1540	2004	193 countries	Enact and enforce controls on biological materials, equipment, information to prevent terrorist acquisition	Legally binding; implementation of biological commitments unclear
G8 Global Partnership against the Spread of Weapons and Materials of Mass Destruction	2002	28 countries	Commit \$20 billion over 10 years to prevent terrorist acquisition of WMD /materials/info from FSU	Multilateral initiative; political not legal commitment; delay in meeting initial goals
	2011		Added implementation of UNSCR 1540, pathogen security and lab safety	Russia ousted in 2014 after Crimea annexation

Measure	Date	Current Participants	Purpose	Comments
Proliferation Security Initiative	2003	103 countries	Interdict shipment of WMD and related materials to states/nonstate actors of concern	Multilateral initiative; no implementing body; political not legal commitment
INTERPOL Bioterrorism Prevention Program	2006	190 member states	Strengthen criminal and administrative laws to prevent terrorist acquisition of biological agents;	International police organization; recommendations nonbinding
	2014		Promote security/safety of biological materials and emerging technology	
Screening of Gene Sequence Orders	2009	Major U.S. and European suppliers	Screen sequence orders to prevent customers from creating dangerous biological agents	Voluntary supplier initiative

into the largest and most sophisticated program in the world. At its peak, the Soviet program involved some 65,000 scientists, technicians, and other workers hidden in dozens of facilities operated by the KGB, the Soviet Academy of Sciences, the Soviet Academy of Medical Sciences, and the Ministries of Defense, Agriculture, Health, and Chemical Industry. Much of this illegal biological weapons program was hidden in plain sight in facilities conducting research and development (R&D) for pharmaceutical, industrial, and other civilian purposes. The real mission of the facilities operated by Biopreparat, as the civilian side of the Soviet biological weapons program was called, was R&D on human pathogens, particularly the development of antibiotic- and vaccine-resistant biological agents.⁶

The Soviet Union was not, however, the only country believed to have a biological weapons program. In the late 1980s, U.S. officials began to speak publicly about a broader proliferation problem, claiming that the number of countries with biological weapons programs had increased from four to ten in the years since the BWC had been completed. In addition to the Soviet Union, the other countries that were identified as having biological weapons programs were China, Egypt, Iran, Iraq, Libya, North Korea, South Africa, Syria, and Taiwan, almost all of which had either signed or ratified the convention.⁷ Biological weapons proliferation became an even more salient issue in the run-up to the 1991 Gulf War because of fears that Saddam Hussein would authorize the use of biological (or chemical) weapons against the coalition of military forces that had been assembled to oust Iraqi troops from Kuwait. Although this did not come to pass, UN inspectors confirmed in the years after the war that Iraq had developed and produced biological weapons during the 1980s and that biological materials and equipment from Western companies had facilitated the Iraqi program.

In the face of mounting concerns about the proliferation of biological weapons, BWC parties agreed in 1991 to study potential verification measures for the convention and in 1994 created an ad hoc group with a carefully defined mandate: to consider appropriate measures, including *possible* verification measures, to be included *as appropriate* in a legally binding protocol to strengthen the BWC. The debate over the mandate foreshadowed the positions taken by the parties in the protocol negotiations: the European Union (EU) and moderate nonaligned countries supported a variety of data declaration and on-site inspection requirements; China and the radical nonaligned countries pressed for commitments on technical assistance for developing countries and the elimination of export controls; and Russia tried to narrow the scope of the BWC's prohibitions and thus widen the definition of permitted activities. The U.S.

6. For the most authoritative study on the Soviet program, see Milton Leitenberg and Raymond A. Zilinskas, *The Soviet Biological Weapons Program: A History* (Cambridge, Mass.: Harvard University Press, 2012).

7. See Milton Leitenberg, *Assessing the Biological Weapons and Bioterrorism Threat* (Carlisle, Pa: U.S. Army War College, 2005).

government was divided: the White House was supportive of legally binding transparency measures to increase the risk and cost of cheating, whereas government departments were determined to limit the protocol's impact on sensitive biodefense and threat assessment activities and on the U.S. biotechnology and pharmaceutical industries. In July 2001, the new George W. Bush administration, whose officials had an antipathy to arms control in general and to BWC verification in particular, officially rejected the draft protocol that had been negotiated.

Following the September 11 attacks and the anthrax letters, the United States proposed, as an alternative to continuing the protocol negotiations, that state parties hold short intersessional meetings each year to exchange information on biosecurity and global health security issues, including controls on dangerous pathogens, laboratory biosafety and biosecurity, and disease surveillance. Discussions on these and related issues have continued for more than a decade, with few tangible results. Currently 173 states are party to the BWC (i.e., have both signed and ratified the convention). Nine, including Egypt and Syria, are signatories only, and fifteen, including Israel, have neither signed nor ratified the convention.

Multilateral Efforts to Control Access to Biological Material, Equipment, and Information

Since the early 1990s, a variety of international initiatives have been undertaken to try to prevent dual-use biological material, equipment, and information from being acquired for hostile purposes. Some of these initiatives have been truly international in scope, though most have been what more accurately could be called “multilateral,” since they have involved smaller groups of like-minded countries.

The first of these initiatives was the harmonization of national controls on biological-related exports by the Australia Group (AG), an informal export control coordinating body that was organized by the Australian government after Iraq's use of chemical weapons in the Iran-Iraq War. In December 1992, the twenty-two members of the AG agreed to control the export of fifty-three human and animal pathogens, ten toxins, and seven types of equipment that could be diverted to the production of biological weapons.⁸ Since that time, the AG's membership has expanded to forty-two countries (plus the European Commission), its control list for human and animal pathogens has increased to ninety microorganisms and nineteen toxins, and its equipment list has grown to include nine categories of items. The AG also has added a plant pathogens control list that as of early 2016 comprised eighteen microorganisms. Genetic elements and genetically modified organisms that contain nucleic acid sequences associated with the pathogenicity of any of the listed agents are included under the AG controls. Items not specifically on the AG control lists but for which

8. U.S. Arms Control and Disarmament Agency, *The Australia Group*, Occasional Paper (Washington, D.C.: U.S. Arms Control and Disarmament Agency, May 1993).

there is information that they may be used for biological weapons purposes also are to be controlled by member states. In addition to implementing these “catch-all” controls, AG members also have agreed that if one member denies a specific export license, the others will consult with that member before deciding whether to approve the same transaction.⁹

After September 11 and the anthrax letters, international as well as multi-lateral efforts to prevent the spread of biological weapons capabilities focused largely on terrorists and other nonstate actors. Following the 2001 attacks, the UN Security Council unanimously adopted UN Security Council Resolution (UNSCR) 1373, which, among other things, obligated all UN member states to enhance information sharing on illegal transfers of biological and other potentially deadly materials that could be used by terrorists groups. No modalities were provided, however, for implementing this commitment. Three years later, the Security Council unanimously adopted UNSCR 1540, committing all UN member states to enact and enforce laws and other measures against the spread of biological and other weapons of mass destruction and delivery means, including controls on related materials, equipment, and technology, to terrorists or other nonstate actors. Under this resolution, UN members are required to report to a dedicated UN committee on the measures they have taken or intend to take to implement these obligations. As of December 2014, 173 member states had submitted implementation reports; however, most of the measures reported were in the nuclear or chemical fields.¹⁰

Another initiative targeted against terrorist acquisition of biological and other weapons is the G8 Global Partnership against the Spread of Weapons and Materials of Mass Destruction. Under this program, which was created in June 2002, the G8 industrialized countries (Canada, France, Germany, Italy, Japan, Russia, the United Kingdom, and the United States) committed to raise up to \$20 billion over ten years to fund activities aimed at preventing terrorists or the states that support them from gaining access to weapons, material, and information that could be used in biological or other weapons of mass destruction. Much of the Global Partnership’s initial work was focused on the former Soviet Union, where it funded over four thousand research projects and related activities aimed at redirecting former Soviet scientists, including biological weapons

9. Although the AG’s focus remains national chemical and biological weapons programs, in 2014 it acknowledged the risk of diversion to nonstate actors, agreeing that members should consider the possibility of terrorist acquisition prior to approving the export of any AG-controlled item. See “The Australia Group,” 2007, <http://www.australiagroup.net/en/index.html>.

10. For the most recent implementation report, see Oh Joon, “Letter Dated 31 December 2014 from the Chair of the Security Council Committee Established Pursuant to Resolution 1540 (2004) Addressed to the President of the Security Council,” S/2014/958, United Nations Security Council, December 31, 2014, http://www.un.org/en/ga/search/view_doc.asp?symbol=S/2014/958.

scientists, toward sustainable civilian activities.¹¹ In May 2011, partly because of delays in meeting its original financial goal, the G8 decided to extend the Global Partnership beyond its original ten-year mandate. The G8 also agreed to expand membership in the initiative and to broaden efforts in certain priority areas, including redirecting former biological and other weapons scientists, assisting in implementation of UNSCR 1540, and working to secure dangerous pathogens and improve laboratory biosafety. Although Russia was ousted from the G8 following its annexation of Crimea in 2014, the twenty-eight remaining members of the Global Partnership appear committed to pursuing this broader agenda.¹²

In the years immediately after September 11, the United States and ten other countries also launched the Proliferation Security Initiative (PSI), which seeks to stop shipments of weapons of mass destruction, their delivery means, and related dual-use material to both state and nonstate actors of proliferation concern. Although countries like China, Iran, and North Korea view the PSI as a violation of international law protecting freedom of the seas, 103 countries, including Russia, the Republic of Korea, and many major international shipping nations, have endorsed the PSI and committed to abide by its founding principles: not to transfer proliferation-related items to countries of concern; to cooperate in searches of suspected cargoes on their own vessels or aircraft or on other vessels passing through their territory; and to share information quickly on suspicious activities that might require interdiction. Participants are expected to put in place the necessary legal authorities and operational capabilities to meet these commitments. Although the PSI has no implementing body, twenty-one of the most active PSI members exchange information and coordinate activities through an operational experts group. In May 2013, on the tenth anniversary of the founding of the initiative, seventy-two PSI participants held a high-level political meeting where they pledged to hold PSI interdiction exercises on a more regular basis, promote treaties criminalizing the illegal trade in weapons of mass destruction (WMD)–related items; cooperate in enhancing interdiction capabilities; and expand the PSI’s global outreach to other countries.¹³ Information is not available, however, about the PSI’s effect on the illegal trade in biological or other weapons-related materials.

11. G8 Global Partnership, “Assessment and Options for Future Programming: G8 Summit, May 26–27, 2011, Deauville, France,” Partnership for Global Security, <http://www.partnershipforglobalsecurity-archive.org/Official%20Documents/G-8%20Global%20Partnership/620201181141AM.html>.

12. Bonnie D. Jenkins, “The Future Role of the G-8 Global Partnership: Combatting Weapons of Mass Destruction,” Policy Analysis Brief, Stanley Foundation, June 2010; “The United States Chairmanship of the Global Partnership in 2012,” U.S. Department of State, n.d., <http://www.state.gov/t/isn/gp2013/>; and United Kingdom, “2010 to 2015 Government Policy: Weapons Proliferation,” May 8, 2015, <https://www.gov.uk/government/publications/2010-to-2015-government-policy-weapons-proliferation/2010-to-2015-government-policy-weapons-proliferation#appendix-5-global-partnership>.

13. Arms Control Association, “The Proliferation Security Initiative (PSI) at a Glance,” updated June 2013, <http://www.armscontrol.org/factsheets/PSI>.

INTERPOL, the 190-member-country international police organization, also became active on bioterrorism after the September 11 terrorist attacks and anthrax letters. INTERPOL's initial work focused largely on assisting member states to prepare for and respond to a possible bioterrorist attack. In 2006, however, under the auspices of its Bioterrorism Prevention Program, the organization launched a new project aimed at helping countries assess, strengthen, and enforce their criminal and administrative laws in order to prohibit the acquisition, transfer, and use of biological materials for hostile purposes. Little is known, however, about the impact of this effort or of a more recent INTERPOL project known as Operation S3OMMET. Under this 2014 initiative, INTERPOL announced it would work with relevant regional and international partners to raise awareness among law enforcement and public health officials, biosafety officers, and research scientists in key regions on how to improve the safety and security of dual-use biological materials and related emerging technologies so as to prevent unauthorized access to them by those who would do harm.¹⁴

Governments have not been the only actors pursuing initiatives to address bioterrorism concerns. In the mid-2000s, a number of gene synthesis companies in the United States and Europe voluntarily began to screen customer orders to ensure that the sequences they supplied could not be used to make high-risk pathogens. But the industry did not adopt a uniform approach, and some companies declined to screen at all. To help develop a more harmonized approach, various gene synthesis companies began to form international consortiums to promote greater attention to biosecurity, including the screening of orders. In 2009, the International Association Synthetic Biology, a group of largely German commercial suppliers, developed a proposal for screening sequence and customer orders. A few months later, five of the world's leading gene synthesis companies formed a competing group, the International Gene Synthesis Consortium, to develop their own screening proposal. In the end, both industry groups, which together represented most of the global gene synthesis industry, agreed to screen all synthetic gene orders they received not only for sequences of known high-risk pathogens but also for reasonably similar sequences that could be used to create novel pathogens. They also agreed to screen all customers who placed orders, to maintain sequence and customer records, and to report potentially problematic orders to the appropriate authorities.¹⁵ Some suppliers wanted to go even further, arguing that their voluntary

14. For information on INTERPOL's bioterrorism activities, see "CBRNE," INTERPOL, n.d., <http://www.interpol.int/Crime-areas/Terrorism/CBRNE/Biological-threats>.

15. Jonathan B. Tucker, "Double Edged DNA: Preventing the Misuse of Gene Synthesis," *Issues in Science and Technology* XXVI (3) (Spring 2010): 23–32, <http://issues.org/26-3/tucker-2/>.

approach should be replaced by mandatory screening requirements in Europe and the United States, backed by strong enforcement action, but this has not been done.¹⁶

International Measures Governing the Handling and Use of Biological Agents

One of the earliest international initiatives focused on the handling of dual-use biological materials was the publication of a laboratory biosafety manual by the World Health Organization (WHO) in 1983. This manual provided guidance for WHO member states on physical containment principles, technologies, and practices to prevent *unintentional* exposure to or release of biological materials. Following September 11 and the anthrax letters, WHO began to address the issue of *intentional* biological threats, releasing in 2006 a separate volume on laboratory biosecurity, including guidance for the protection, control, and accountability of biological materials.¹⁷ As the word implies, the guidance in these documents was not binding on WHO member states.

In parallel with its work on laboratory biosafety and biosecurity, WHO also began to examine the risks and opportunities of advances in the life sciences for global health security under a broader project on responsible life sciences research. In a report published in 2010, WHO recommended investing in three pillars that promote public health—research excellence, ethics, and laboratory biosafety and biosecurity—and provided a self-assessment questionnaire for public health officials, laboratory managers, and scientists to use to evaluate their strengths and weaknesses in these areas. This approach was premised on the belief that one of the most effective ways of preparing for deliberately caused disease is to strengthen public health measures for natural and accidental disease outbreaks. It also reflected the view that individual countries were in the best position to determine how to promote the safety and security of their biological research activities. The latter was a departure for the organization, which had previously issued international guidelines on both biosafety and biosecurity for member states.¹⁸

Like WHO, the Organisation for Economic Co-operation and Development (OECD) also has played a role in encouraging international harmonization of guidelines and regulations related to the handling of biological materials. In 1986, for example, the OECD issued a handbook on *Recombinant DNA Safety*

16. Jeremy Minshull and Ralf Wagner, “Preventing the Misuse of Gene Synthesis,” letter to the editor, *Nature Biotechnology* 27 (9) (September 2009): 800–801.

17. For the biosafety manual, see World Health Organization, *Laboratory Biosafety Manual*, 3rd ed. (Geneva: WHO, 2004), http://www.who.int/csr/resources/publications/biosafety/WHO_CDS_CSR_LYO_2004_11/en/. For the biosecurity guidance, see World Health Organization, *Laboratory Biosecurity Guidance* (Geneva: WHO, 2006), http://www.who.int/csr/resources/publications/biosafety/WHO_CDS_EPR_2006_6.pdf.

18. World Health Organization, *Responsible Life Sciences Research for Global Health Security: A Guidance Document* (Geneva: WHO, 2010), http://www.who.int/csr/resources/publications/HSE_GAR_BDP_2010_2/en/.

Considerations for industrial, agricultural, and environmental applications.¹⁹ In 2001, the OECD began to link various government, industry, and academic facilities that store, test, or use biological materials into a global exchange network of what it called biological resource centers (BRCs). To facilitate the sharing of biological agents among its members, the OECD also developed and issued biosecurity guidelines to prevent unauthorized access to the culture collections and other biological resources of the BRCs, including procedures for risk assessment and management, personnel security and training, and material controls. As with many of the other multilateral initiatives, the OECD's efforts apply only to its members—thirty-four as of early 2016—and are nonbinding.²⁰

CURRENT STATE OF GOVERNANCE IN THE UNITED STATES

In the United States, a wide range of laws, regulations, policies, and guidelines have been adopted in an effort to prevent biological materials, equipment, or information from causing harm. For many years, most of these measures focused on ensuring domestic implementation of the BWC's prohibitions on biological weapons development and possession, trying to prevent the spread of biological weapons to other countries, or promoting the safe handling and use of biological materials. After September 11 and the anthrax letters, many of these measures were broadened to address concerns that terrorists or other non-state actors might seek to acquire or use biological weapons (see Table 2). An unprecedented debate also began among U.S. scientists, government officials, security experts, and other stakeholders over how to prevent the accidental or deliberate misuse of advances in life sciences research—a debate that continues to this day (see Table 3).

U.S. Restrictions on Biological Weapons Development and Possession

Although the United States played a major role in the conclusion of the BWC, it did not adopt domestic legislation outlawing the development and possession of biological weapons until nearly a decade and a half after the BWC entered into force. Under the Biological Weapons Anti-Terrorism Act of 1989, it became a crime to *knowingly* develop, produce, possess, or transfer biological agents, toxins, or delivery systems *for use as a weapon* or to assist another country or organization to do so. The act provided for criminal penalties against those who

19. Organisation for Economic Co-operation and Development, *Recombinant DNA Safety Considerations* (Paris: OECD, 1986), <http://www.oecd.org/sti/biotech/40986855.pdf>.

20. Organisation for Economic Co-operation and Development, *OECD Best Practice Guidelines on Biosecurity for BRCs* (Paris: OECD, 2007), <http://www.oecd.org/sti/biotech/38778261.pdf>.

Table 2: U.S. Governance of Biological Weapons Development and Biological Materials Access and Use

Measure	Date	Title	Purpose	Comments
Federal Guidance	1976	<i>NIH Guidelines for Research Involving Recombinant DNA Molecules</i>	Outline lab practices, equipment, facilities for safety of rDNA research	Voluntary; applied only to rDNA research at institutions with NIH rDNA funding
Statute	1976	Arms Export Control Act	Control military biological exports	Legally binding; State Dept. license required
Statute	1979	Export Administration Act	Control export of dual-use biological agents	Legally binding; Commerce Dept. license required except for Australia Group/similar countries
Federal Guidance	1984	<i>HHS Biosafety in Microbiological and Biomedical Laboratories</i> Manual	Outline lab practices, equipment, facilities for laboratory biosafety	Voluntary
	2009		Added security, personnel and other aspects of laboratory biosafety	Select agent facilities and federal contractors/grantees required to follow
Statute	1989	Biological Weapons Anti-Terrorism Act	Prohibit “knowing” development and possession of agents, toxins, delivery systems for use as a weapon	Legally binding; implemented BWC in United States 14 years after ratification; included criminal penalties
Executive Actions	1990	EO 12735; Enhanced Proliferation Control Initiative	Expand controls on bioweapons-related exports	Included dual-use equipment and other exports that could facilitate weapons development or use
Statute	1991	Soviet Nuclear Threat Reduction Act (Nunn-Lugar Cooperative Threat Reduction Program)	Prevent proliferation by eliminating Soviet nuclear, chemical, and biological capabilities	Dismantled weapons facilities, redirected scientists, secured pathogens, strengthened facility safety and security
	2007		Prevent terrorist acquisition NBC capabilities	Geography and scope expanded to include countries outside former SU, biosafety & biosecurity

Measure	Date	Title	Purpose	Comments
Army Guidance	1993	Biological Defense Safety Program	Prescribe safety requirements for biological agent RDT&E	Applied to Army, contractors, subcontractors
Statute	1996	Antiterrorism and Effective Death Penalty Act	Expand BWC Act to “attempts, threats or conspiracies”; add genetically engineered items; control transfers of human pathogens	Legally binding; regulations required: select agent list of human pathogens by CDC/HHS; disclosure of agent transfers; registration of transferring/receiving facilities
Statute	2001	USA PATRIOT Act	Prohibit biological agents, toxin, or delivery systems not for peaceful purposes and possession by “restricted persons”	Legally binding; shifted burden from government to suspect to prove intent
Department Policy	2001	DOD Directive 2060	Establish process for reviewing biological research for BWC compliance	No special attention to dual-use research
	2005	DHS Management Directive 6300	Establish process for reviewing biological research and other activities for BWC and regulatory compliance	Special scrutiny of certain dual-use research to ensure BWC compliance
Statute	2002	Public Health Security and Bioterrorism Preparedness and Response Act	Strengthen select agent controls by adding: facilities that possess/use select agents, personnel checks, facility inspections; regulate select agent research	Legally binding; parallel requirements for animal and plant agents by USDA; research oversight only of proposals subject to NIH approval; compliance problems in early years
Army Guidance	2008	Biological Surety	Increase safety and security of work with biological agents	Applied to Army, contractors, subcontractors; begun after 9/11 but not implemented for 7 years
Federal Guidance	2010	Screening Framework Guidance for Providers of Synthetic Double-Stranded DNA	Advise commercial gene synthesis suppliers on screening sequence and customer orders	Voluntary; limited to select agents; weaker than industry-initiated screening protocols
Regulations	2012	Revised Select Agent Regulations	Strengthen pathogen controls by focusing on greatest threats; strengthen personnel reliability/physical security	Legally binding; removed 22 agents/toxins; added 3 viruses; designated 11 as Tier 1 (greatest risk); no official information on compliance

Table 3: U.S. Governance of Biological Research

Measure	Date	Title	Purpose	Comments
Federal Guidance	1976	<i>NIH Guidelines for Research Involving Recombinant DNA Molecules</i>	Ensure review and approval of rDNA research	Voluntary; applied only to rDNA research at institutions with NIH rDNA funding; IRBs/IRBs quickly replace RAC oversight; post-9/11 survey shows scores of institutions in noncompliance
	2010	<i>NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules</i>	Expanded to synthetic nucleic acid molecules to address biosecurity concerns	
Statute	2002	Public Health Security and Bioterrorism Preparedness and Response Act	Regulate select agent research	Legally binding; research oversight only of limited number of proposals subject to NIH approval; compliance problems in early years
CDC Guidance	2007	Oversight and Clearance of Dual-Use Research of Concern	Review intramural research using proposed NSABB framework for DURC	Voluntary; predates 2012 U.S. government-wide policy; left DURC determination to researchers; criterion subjective and vague
NIH Guidance	2008	NIH Dual-Use Screening Program	Review intramural research using proposed NSABB framework for DURC	Voluntary; predates 2012 U.S. government-wide policy; left DURC determination to researchers; criterion subjective and vague
U.S. Government Policy	2012	U.S. Government Policy for Oversight of Life Sciences Dual Use Research of Concern	Review unclassified life sciences research conducted or funded by U.S. Government for DURC	Announced 5 years after NSABB DURC proposal; applies only to research with 15 select agents; excluded privately funded and classified research; used subjective NSABB criterion
HHS Guidance	2013	HHS Framework for Funding Decisions about HPAI H5N1 Research	Strengthen oversight of H5N1 proposals by reviewing for DURC, scientific benefit, safety and security risks; later extended to H7N9 virus	Complicated, lengthy process with multiple review levels

Measure	Date	Title	Purpose	Comments
U.S. Government Policy	2014	Deliberative Process for Gain of Function Research	Develop new U.S. government policy for conduct and funding of GOF research	Focus on research with highly transmissible pathogens—influenza, SARS, MERS viruses; accompanied by pause in funding new studies, call for voluntary pause on ongoing work
U.S. Government Policy	2014	U.S. Government Policy for Institutional Oversight of Life Sciences Dual Use Research of Concern	Outline institutional responsibility to review unclassified life sciences research for DURC if institution receives U.S. government life sciences research funding	Announced 7 years after NSABB DURC proposal; applies only to research with 15 select agents; excludes research at facilities not receiving U.S. government funding for life sciences research and classified research; uses subjective NSABB criterion; makes PI responsible for initiating DURC review

engage in prohibited activity but puts the burden of proof on the government to demonstrate hostile intent.²¹

In April 1996, following the Oklahoma City bombings and the acquisition of plague cultures through the mail by a member of the neo-Nazi organization Aryan Nation, the U.S. Congress expanded the scope of activities subject to criminal penalties under the 1989 law from *knowingly* developing, producing, possessing, or transferring biological agents for use as a weapon to *attempts, threats, or conspiracies* to do so. The April 1996 Antiterrorism and Effective Death Penalty Act, which was the source of this broader criminalization provision, also expanded the definition of a biological agent to include genetically engineered products or components thereof.²²

After September 11 and the anthrax letters, the United States modified these provisions on criminalization still further, making it a crime under the October 2001 USA PATRIOT Act for anyone to knowingly possess any biological agent, toxin, or delivery system *not reasonably justified for prophylactic, protective, bona fide research, or other peaceful purposes*. Of note, the bill shifted the burden of proof—instead of the government having to prove hostile intent, suspects now had to demonstrate that their activities were for peaceful purposes. The bill also criminalized the possession, transportation, or receipt of particularly dangerous pathogens, known as select agents, by certain restricted persons, including illegal aliens, individuals from terrorist-list countries, fugitives from justice, and individuals who are under indictment or have been imprisoned for more than one year.²³ The Federal Bureau of Investigation's (FBI) Weapons of Mass Destruction Directorate, a law enforcement unit dedicated to preventing terrorism and proliferation involving biological and other weapons of mass destruction, was given responsibility for enforcement.²⁴

21. *Biological Weapons Anti-terrorism Act of 1989*, Pub. L. 101–298, 104 Stat. 201 (1990). For a discussion of the legislation, see Ronald Atlas, Kenneth I. Berns, Gail Cassell, and Janet Shoemaker, “Preventing the Misuse of Microorganisms: The Role of the American Society for Microbiology in Protecting against Biological Weapons,” *Critical Reviews in Microbiology* 24 (3) (February 1998): 273–280.

22. *Antiterrorism and Effective Death Penalty Act of 1996*, Pub. L. 104–132, 110 Stat. 1214 (1996), sec. 511. The CDC role in implementing this legislation builds upon the responsibility given to CDC in 1971 to help ensure the safety of interstate shipments of infectious substances. See Gerald Epstein, “Controlling Biological Warfare Threats: Resolving Potential Tensions among the Research Community, Industry and the National Security Community,” *Critical Reviews in Microbiology* 27 (4) (2001): 323.

23. *Uniting and Strengthening America by Providing Appropriate Tools Required to Intercept and Obstruct Terrorism (USA PATRIOT ACT) Act of 2001*, Pub. L. 107–56 (2001), sec. 817.

24. *Ten Years after 9/11 and the Anthrax Attacks: Protecting against Biological Threats: Hearing before the Committee on Homeland Security and Governmental Affairs, United States Senate, One Hundred Twelfth Congress, First Session, 112th Cong. (2011)* (statement of Vahid Majidi, Assistant Director, Weapons of Mass Destruction Directorate, Federal Bureau of Investigation), <http://www.hsgac.senate.gov/hearings/ten-years-after-9/11-and-the-anthrax-attacks-protecting-against-biological-threats>.

As U.S. government biodefense research expanded following September 11, U.S. government agencies also put in place formal review processes to ensure that their biological research activities complied with the BWC. Since 2001, for example, the Department of Defense (DOD) has required all biological-based activities, which include both classified and unclassified biodefense research, conducted at DOD facilities or funded by DOD to be reported annually to the department and reviewed by its BWC Compliance Review Group. Dual-use research does not, however, receive special attention in the DOD BWC compliance review process.²⁵

In 2005, the Department of Homeland Security (DHS) issued its own compliance review policy for DHS biological research, development, and acquisition activities, including biodefense research. The DHS policy covers both treaty compliance and compliance with U.S. regulatory requirements, including those involving biosafety and the security of select agents. In contrast to DOD, DHS explicitly scrutinizes certain categories of dual-use biological research to ensure that it complies with U.S. BWC obligations. Under the DHS approach, all relevant projects must be submitted to the DHS Compliance Assurance Program office, which is responsible for reviewing and assessing the projects prior to their consideration by the department's Compliance Review Group (CRG). The CRG, which is chaired by the deputy secretary of DHS, must approve all such projects before they can proceed.²⁶

U.S. Measures to Control Access to Biological Materials, Equipment, and Information

For many years, the United States has undertaken a number of initiatives to try to prevent countries of proliferation concern from acquiring material, equipment, and information that could be used to develop and produce biological weapons. Under the authority of the Export Administration Act (EAA), the Commerce Department began in the 1980s to require a license for the export of several categories of biological agents, including genetically modified agents. Following revelations that U.S. and other Western companies had supplied dual-use chemical and biological materials and equipment to Iraq's weapons programs, the United States expanded its dual-use export controls under Executive Order 12735 and the Enhanced Proliferation Control Initiative. Among other things, these 1990 measures extended U.S. export controls to dual-use chemical and biological equipment and technology as well as to any other proposed export that might be related to the acquisition or use of chemical or biological weapons. Today the biological provisions of the Commerce Control List include human, plant, and animal pathogens and toxins controlled by the

25. Although the DOD BWC compliance policy dates to 1992, a more structured process does not appear to have been adopted until 2001. Center for Arms Control and Non-proliferation, *Ensuring Compliance with the Biological Weapons Convention, Meeting Report* (Washington, D.C.: Center for Arms Control and Non-proliferation, July 2009).

26. Ibid.

AG, select agent pathogens, and genetic elements for those controlled agents and toxins. Consistent with the AG, the United States also controls the export of nine types of dual-use equipment that could be used to handle biological agents. Members of the AG and other countries that have entered into agreements to control dual-use biological material and equipment are exempt from the EAA's licensing requirement.²⁷

Under the Arms Export Control Act, the State Department has similar authority to control military biological exports. Biological agents and biologically derived substances specifically developed, configured, adapted, or modified for the purpose of increasing their capability to produce casualties in human beings or livestock, to degrade equipment, or to damage crops are controlled as "significant military equipment" on the United States Munitions List and require a license for export. Both the State and Commerce Departments also control the transfer of specific technical information necessary for the development, production, or use of biological weapons to foreign nationals in the United States under a category called "deemed exports."

In the early 1990s, following the collapse of the Soviet Union, the United States sought to prevent the proliferation of former Soviet nuclear, chemical, and biological weapons capabilities to other countries through the Nunn-Lugar Cooperative Threat Reduction (CTR) program. Threat reduction activities related to biological weapons have continued since that time and, after September 11 and the anthrax letters, expanded from Russia and other former Soviet republics to the Middle East, Southeast Asia, and Africa. This multiagency U.S. effort involving the Defense, State, Energy, and Homeland Security Departments has dismantled former biological weapons facilities, redirected former weapons scientists from illicit to legitimate activities, secured collections of dangerous pathogens, carried out biosafety and biosecurity upgrades at research laboratories, and provided biosafety and biosecurity training to scientists and other laboratory personnel. Many of these projects have been spearheaded by DOD, where biological threat reduction has grown from less than 10 percent of the threat reduction budget in the 1990s to more than 60 percent today. This growth is a reflection of the expansion of the CTR program's biological mission, from preventing the spread of biological weapons capabilities from the former Soviet Union to promoting biological nonproliferation, biosafety, and biosecurity around the globe.²⁸ Much of the proliferation threat from the former Soviet biological weapons program has been eliminated; however, resid-

27. White House, Office of the Press Secretary, "Executive Order 12735: Chemical and Biological Weapons Proliferation," November 16, 1990; and White House, Office of the Press Secretary, "Fact Sheet on Enhanced Proliferation Control Initiative," December 13, 1990. For current information on U.S. dual-use biological export controls, see Department of Commerce, Bureau of Industry and Security, "Chemical and Biological Controls," updated January 2014, <http://www.bis.doc.gov/index.php/policy-guidance/country-guidance/sanctioned-destinations/16-policy-guidance/product-guidance/122-chemical-and-biological-controls>.

28. Mary Beth Nikitin and Amy Wolff, *The Evolution of Cooperative Threat Reduction: Issues for Congress*, CRS Report for Congress, R43143 (Washington, D.C.: Congressional Research Service, June 2014), <https://www.fas.org/sgp/crs/nuke/R43143.pdf>.

ual concerns remain about Russia's handful of still-secret military biological facilities and about the future of its nonmilitary biological facilities since Russia ended its participation in the CTR program in 2014.²⁹

U.S. efforts to control access to dual-use biological materials, equipment, and information have not, however, been motivated only by proliferation concerns. Fears of bioterrorism also have led to efforts to tighten controls on domestic access to biological weapons-related items. Perhaps the most important of these is the select agent program, which was established by the April 1996 antiterrorism law to strengthen the security of biological agents that could pose a severe threat to human health. Regulations to implement the new law were published by the Centers for Disease Control and Prevention (CDC) in October 1996 and took effect in April 1997 and included:

- a select agent list of approximately forty human pathogens and toxins, including genetic elements and genetically modified organisms associated with those agents;
- a registration requirement for any facility that seeks to *transfer* or *receive* select agents, including certification to the CDC that the facility and its laboratories meet the requisite biosafety standards; and
- a disclosure obligation, including information from both the transferring and receiving facility on the type and amount of agent requested and the proposed use.³⁰

After September 11 and the anthrax letters, the U.S. Congress extended these controls over facilities that *transfer* or *receive* select agents to cover facilities that *possess* and *use* them as well, and added new personnel reliability and security requirements. Under the May 2002 Public Health Security and Bioterrorism Preparedness and Response Act, anyone who was to have access to select agents was now required to register with the Department of Health and Human Services (HHS) and undergo a Justice Department background check, known as a security risk assessment. The act also directed HHS to maintain a national database of registered facilities, persons, and the select agents they possess or are transferring and to conduct inspections of relevant facilities. Civil and criminal penalties can be imposed on facilities for failing to register or for transferring select agents to an unregistered facility. The May 2002 bioterrorism law also required the secretary of agriculture to establish parallel registration,

29. Richard Weitz, "Russian-US Cooperative Threat Reduction beyond Nunn-Lugar and Ukraine," Arms Control Association, July 2, 2014, https://www.armscontrol.org/act/2014_0708/Features/Russian-US-Cooperative-Threat-Reduction-Beyond-Nunn-Lugar-and-Ukraine.

30. The law exempted clinical specimens (i.e., patient blood or tissue) being transferred for diagnostic and verification purposes and certain toxins and vaccine strains of select agents. Department of Health and Human Services, Centers for Disease Control and Prevention, "42 CFR Part 72: Additional Requirements for Facilities Transferring or Receiving Select Agents," *Federal Register* 61 (207) (October 24, 1996): 55190, <https://www.gpo.gov/fdsys/pkg/FR-1996-10-24/pdf/96-27082.pdf>.

security, record keeping, and inspection requirements to enhance the security of biological agents and toxins that could pose a severe threat to plants and animals.³¹ Final regulations to implement the May 2002 law were published in April 2005.³²

These efforts to control access to dangerous pathogens came under harsh scrutiny in late 2008 after the FBI identified Bruce Ivins, a U.S. Army biodefense scientist, as the likely perpetrator behind the 2001 anthrax letters. This led to a variety of proposals for refining the select agent list, strengthening personnel reliability, and enhancing laboratory safety and security. In May 2009, for example, the National Science Advisory Board for Biosecurity (NSABB), which had been created in 2004 to advise the U.S. government on biosecurity issues, proposed reducing or stratifying the select agent list to focus on the agents of greatest concern. The NSABB also recommended more rigorous vetting of foreign nationals with access to such agents.³³ In November 2009, the Working Group on Strengthening the Biosecurity of the United States, which had been established by President George W. Bush to review security at select agent facilities, echoed the call for a reduced or stratified select agent list as well as better coordination of U.S. government inspections and better guidance on inventory management and recordkeeping. The working group also recommended identifying or establishing a federal entity to coordinate biosecurity oversight across all relevant U.S. government agencies.³⁴

After entering office, President Barack Obama also created an interagency experts panel to provide advice on the select agent program and laboratory security. In November 2010, the Federal Experts Security Advisory Panel (FESAP) called for the removal of twenty-five agents and toxins from the select agent list and the creation of a separate list of eleven biological agents and toxins that posed the greatest risk, so-called Tier 1 agents. To strengthen personnel reliability, FESAP recommended modifying the security risk assessment process to better assess mental health, as well as providing guidance to facilities for conducting preaccess suitability and ongoing reliability assessments. Finally, to

31. *Public Health Security and Bioterrorism Preparedness and Response Act of 2002*, Pub. L. 107-188 (2002). The relevant sections of the conference report, H. Report 107-481, may be found in the *Congressional Record* 148 (66) (May 21, 2002): H2721-2724.

32. For the HHS regulations, see 42 CFR 73.12. For the USDA regulations, see 9 CFR 121.12 and 7 CFR 331.

33. National Science Advisory Board for Biosecurity, *Enhancing Personnel Reliability among Individuals with Access to Select Agents* (Washington, D.C.: NSABB, May 2009), <http://osp.od.nih.gov/sites/default/files/resources/NSABB%20Final%20Report%20on%20PR%205-29-09.pdf>.

34. The Working Group on Strengthening the Biosecurity of the United States was established pursuant to Executive Order 13486, of January 9, 2009. See “Executive Order 13486 of January 9, 2009: Strengthening Laboratory Biosecurity in the United States,” *Federal Register* 74 (9) (January 14, 2009): 2289-2291, <http://www.gpo.gov/fdsys/pkg/FR-2009-01-14/pdf/E9-818.pdf>. For the working group’s report, see *Report of the Working Group on Strengthening the Biosecurity of the United States* (Washington, D.C., 2009), <http://www.phe.gov/Preparedness/legal/boards/biosecurity/Documents/biosecreportfinal102309.pdf>.

enhance physical security, FESAP called for the development of risk assessment guidance and cybersecurity standards.³⁵

In October 2012, HHS and the Department of Agriculture (USDA) issued revised select agent regulations that reflected many of these recommendations. Three new viruses were added to the select agent list, and twenty-two other agents and toxins were removed; eleven of the remaining sixty-three select agents and toxins were designated Tier 1 because they present “the greatest risk of deliberate misuse with the most significant potential for mass casualties or devastating effects to the economy, critical infrastructure, or public confidence.”³⁶ The revised select agent rules also established new personnel and physical security requirements for facilities with Tier 1 agents, including requirements for preaccess assessments and on-going monitoring of personnel with access to Tier 1 pathogens and toxins and for bolstering the use of barriers and intrusion detection devices. New guidance documents on personnel reliability and physical security were released along with the revised regulations.³⁷ One important recommendation that the U.S. government did not implement was for the creation of a federal entity to coordinate biosecurity oversight across government agencies.

In December 2014, FESAP issued new recommendations on laboratory biosafety and biosecurity³⁸ in response to disclosures the previous summer of three other incidents involving select agents: the accidental exposure of some eighty-four CDC laboratory workers to live anthrax; CDC’s shipment of a relatively benign bird flu (H9N2) that had been contaminated with the highly lethal H5N1 influenza virus; and the discovery of vials of smallpox and other infectious agents that had been left in an unsecured storage area in an NIH lab for more than fifty years.³⁹ To help prevent similar incidents in the future, FESAP recommended that HHS and USDA establish a review body to validate the policies and protocols being used at select agent research facilities to

35. “Executive Order 13546 of July 2, 2010: Optimizing the Security of Biological Select Agents and Toxins in the United States,” *Federal Register* 75 (130) (July 8, 2010): 39, 439–442, <http://www.gpo.gov/fdsys/pkg/FR-2010-07-08/pdf/2010-16864.pdf>; and Federal Experts Security Advisory Panel, *Recommendations Concerning the Select Agent Program* (revised) (Washington, D.C., June 13, 2011), <http://www.phe.gov/Preparedness/legal/boards/fesap/Documents/fesap-recommendations-101102.PDF>. The FESAP report was originally released November 2, 2010.

36. Department of Health and Human Services, Centers for Disease Control and Prevention, “42 CFR Part 73: Possession, Use, and Transfer of Select Agents and Toxins; Biennial Review,” *Federal Register* 77 (194) (October 5, 2012): 61084, <http://www.gpo.gov/fdsys/pkg/FR-2012-10-05/pdf/2012-24389.pdf>.

37. For the full text of the select agent regulations, see *ibid.*, 61084–115.

38. Report of the Federal Experts Security Advisory Panel, December 2014, <http://www.phe.gov/s3/Documents/fesap.pdf>

39. Dina Fine Maron, “CDC Botched Handling of Deadly Flu Virus,” *Scientific American*, July 11, 2014, <http://www.scientificamerican.com/article/cdc-botched-handling-of-deadly-flu-virus/>.

inactivate, sterilize, and decontaminate hazardous biological materials. They also called for greater transparency in government reporting about laboratory incidents involving select agents and for a federal review to determine how many U.S. high-containment laboratories are needed for research on select agents.

In 2014, the most recent year for which data are available, 316 facilities and some eleven thousand individuals were approved to work with select agents.⁴⁰ But limited information is available from the U.S. government about the compliance of these facilities and individuals with the select agent regulations, as the last U.S. government audits appear to have been done in 2006, when ten out of ten institutions subject to USDA regulations and eleven out of fifteen institutions subject to HHS regulations were found by their respective agencies to be in violation of at least one aspect of the select agent rules.⁴¹ A 2015 investigation by a U.S. newspaper found that since 2003, HHS and USDA have cited more than one hundred laboratories for serious safety and security lapses. Of the labs subject to HHS oversight, seventy-nine have been referred for potential enforcement action, including nineteen who have been fined over \$2.4 million. Since 2008, thirty-three labs have agreed to participate in performance improvement programs after repeated failures to correct past biosafety and security problems or to comply with security requirements for working with the most dangerous select agents. For its part, USDA has conducted forty-eight investigations of laboratories subject to its oversight, and has levied fines of about \$117,000.⁴²

Even as controls on select agents were first being implemented, attention began to focus on the risk that advances in gene synthesis technology might make possible the creation of select agents *de novo*, without naturally occurring nucleic acids or pathogens. In a report in 2006, the NSABB pointed to the global availability of gene synthesis suppliers, equipment, and reagents, as well as the diversity of practitioners, some of whom, such as high school students or engineers, had little exposure to biosafety rules. As noted earlier, although some commercial suppliers of gene sequences had begun to screen

40. Lori J. Bane, Associate Director for Policy, CDC Division of Select Agents and Toxins, personal correspondence, November 14, 2014.

41. Department of Agriculture, Office of Inspector General Southeast Region, *Audit Report: Animal and Plant Health Inspection Service Evaluation of the Implementation of the Select Agent or Toxin Regulations Phase II*, Report no. 33601-3-AT (Washington, D.C.: Department of Agriculture, January 2006), <http://www.usda.gov/oig/webdocs/33601-3-AT.pdf>; and Department of Health and Human Services, Office of Inspector General, *Summary Report on Universities' Compliance with Select Agent Regulations*, A-04-05-02006 (Washington, D.C.: Department of Health and Human Services, June 2006), <http://oig.hhs.gov/oas/reports/region4/40502006.pdf>. A 2014 audit of over 4,000 facilities found 27 instances in which select agents had not been registered properly. But the audit focused only on inventory controls at U.S. government facilities. "FACT SHEET: Biosafety and Biosecurity in the United States," December 16, 2014, http://www.cdc.gov/about/pdf/lab-safety/external-usg-wide-fact-sheet_bsat-safety-stand-down-and-summary-table_final_12-16-2014.pdf.

42. Alison Young and Nick Penzenstadler, "Inside America's Secretive Biolabs," *USA Today*, May 28, 2015, <http://www.usatoday.com/story/news/2015/05/28/biolabs-pathogens-location-incidents/26587505/>.

customer orders voluntarily, suppliers were uncertain about what actually fell within U.S. select agent laws and regulations. In order to prevent synthetically derived sequences from evading the select agent rules, the NSABB recommended that the U.S. government develop a process for commercial suppliers to use to determine which sequences to screen for—select agent or otherwise—as well as standards and practices for how to screen, including record keeping. The NSABB also called for the development and implementation of universal standards and practices for screening sequences and, longer term, an effort to replace the existing list of specific select agents with a broader sequence-based system focused on the predicted properties of select agents.⁴³

In October 2010, nearly four years after the NSABB report and a year after the International Association Synthetic Biology and the International Gene Synthesis Consortium had issued their own proposals for sequence and customer screening, the U.S. government released its guidance for commercial gene synthesis suppliers. This guidance was weaker than the approaches recommended by the NSABB and by the gene synthesis industry because it was both voluntary and focused on screening customer orders only for sequences associated specifically with select agents. In addition to outlining steps for sequence and customer screening, the guidance also addressed record keeping and screening software.⁴⁴

U.S. Measures Governing the Handling and Use of Biological Agents

U.S. efforts to govern the handling and use of biological agents date to the mid-1970s, when concerns about the potential risks of the new field of biotechnology led the National Institutes of Health (NIH) to create the Recombinant DNA Advisory Committee (RAC) to develop guidelines for the conduct of recombinant DNA (rDNA) research. The first *NIH Guidelines for Research Involving Recombinant DNA Molecules (NIH Guidelines)* classified agents into four risk groups based on their relative pathogenicity for healthy human adults and outlined the combination of laboratory practices, equipment, and facilities appropriate both for the agent and the proposed experiment. For rDNA research, this was supplemented by the use of biological barriers to limit the infectivity of a vector for specific hosts or to limit its dissemination and survival in the environment. Specific plant and animal pathogens also had special handling conditions. Research facilities were required to establish institutional biosafety committees (IBCs) to ensure that their rDNA work was done in accordance with the *NIH Guidelines*, which applied to all rDNA research conducted at institutions in the United States and abroad that received funds from NIH

43. National Science Advisory Board for Biosecurity, *Addressing Biosecurity Concerns Related to the Synthesis of Select Agents* (Washington, D.C.: NSABB, December 2006), http://osp.od.nih.gov/sites/default/files/resources/Final_NSABB_Report_on_Synthetic_Genomics.pdf.

44. Department of Health and Human Services, *Screening Framework Guidance for Providers of Synthetic Double-Stranded DNA* (Washington, D.C.: Department of Health and Human Services, October 2010), <http://www.phe.gov/Preparedness/legal/guidance/syndna/Documents/syndna-guidance.pdf>.

for such research. The guidelines were voluntary but included penalties for noncompliance, including the loss of NIH funds for rDNA research.⁴⁵

In 1984, HHS published the first consolidated U.S. safety guidelines for laboratory activities involving biological agents. Like the *NIH Guidelines*, the HHS manual on *Biosafety in Microbiological and Biomedical Laboratories* (BMBL) categorizes agents into four classes or levels depending upon their degree of risk and describes the combination of laboratory practices, equipment, and facilities recommended to work safely with those agents. Following the adoption of the select agent program, the BMBL began to address laboratory biosecurity as well, providing guidance not only on risk assessment methodology but on physical security, personnel management, inventory controls, and other aspects of a laboratory biosecurity plan. As with its approach to biosafety, the BMBL's biosecurity guidance links the protection of biological agents and toxins to their identified risks. Although the BMBL represents voluntary guidelines, U.S. government contractors and grantees as well as facilities registered to work with select agents are required to follow the manual.⁴⁶

Beginning in 1993, the U.S. Army published detailed guidance for Army personnel, contractors, and subcontractors engaged in biological research, development, test, and evaluation (RDT&E) activities under its biological defense program.⁴⁷ Shortly after the anthrax letters, the Army began to develop a biological surety program to strengthen the safety and security of dangerous pathogens and toxins at its facilities. This "biosurety" program, which was not implemented formally until 2008, was based on those the military already had developed for nuclear and chemical weapons and focused on laboratory safety, physical security, agent accountability, and personnel reliability.⁴⁸ Later that year, following the anthrax charges against Army biodefense scientist Ivins, the DOD Inter-Service Council for Biosecurity and Biosafety recommended upgrading background-check requirements, increasing supervisor review and control of after-hours access to labs, and improving control over select agent stocks at DOD facilities.⁴⁹ A Defense Science Board task force on biosafety and

45. Department of Health and Human Services, National Institutes of Health, *NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules (NIH Guidelines)* (Washington, D.C.: Department of Health and Human Services, November 2013), http://osp.od.nih.gov/sites/default/files/NIH_Guidelines_0.pdf.

46. Department of Health and Human Services, *Biosafety in Microbiological and Biomedical Laboratories*, 4th ed. (Washington, D.C.: U.S. Government Printing Office, 2009); and Frank Gottron and Dana A. Shea, *Oversight of High-Containment Biological Laboratories: Issues for Congress*, CRS Report for Congress, R40418 (Washington, D.C.: Congressional Research Service, May 2009), 8.

47. Department of the Army, "Biological Defense Safety Program, Technical Safety Requirements," Army Regulation 385-69, December 31, 1993, at 32 CFR 627.

48. Department of the Army, "Biological Surety," Army Regulation 50-1, July 28, 2008.

49. Government Accountability Office, *High Containment Laboratories: National Strategy for Oversight Is Needed*, GAO-09-574 (Washington, D.C.: GAO, September 2009), <http://www.gao.gov/new.items/d09574.pdf>.

biosecurity further recommended improving the video monitoring of DOD labs and better coordination of laboratory inspections.⁵⁰

U.S. government regulations also address other aspects of the handling of biological agents in an effort to prevent harm to human beings, animals, plants, and the environment. For example, under the Toxic Substances Control Act, the Environmental Protection Agency (EPA) regulates commercial research and development with new microorganisms and any other microorganisms the agency determines are for a significant new use.⁵¹ Under USDA regulations, any person wishing to import, move, or release genetically engineered plant pests must either provide notification to or obtain a permit from the USDA.⁵²

Research Oversight

U.S. efforts to oversee consequential biological research have followed two distinct but parallel tracks. The first track involves the *NIH Guidelines*, which in addition to prescribing physical containment requirements for rDNA research also originally prohibited six types of rDNA experiments because of biosafety concerns.⁵³ In the late 1970s, these restrictions in the guidelines began to be loosened as concerns about the risks of biotechnology research diminished. By 1982 the research prohibitions in the original guidelines had been eliminated, and local IBCs and institutional review boards (IRBs; for overseeing human subject research) had replaced the RAC as the primary authority for reviewing and approving most rDNA research.⁵⁴ Serious questions, however, began to be raised about compliance with these local review requirements after a 2004 study of U.S.-based IBCs revealed that scores of U.S. biotechnology companies had no IBC registered with NIH and that many of the university and other IBCs that were registered either did not meet or issued blanket approvals rather than review each research project separately.⁵⁵

By comparison, oversight of the rDNA experiments that remain subject to NIH approval under the *NIH Guidelines* has been made even stronger since

50. Department of Defense, Defense Science Board, *Report of the Defense Science Board Task Force on Department of Defense Biological Safety and Security Program* (Washington, D.C.: Department of Defense, May 2009), <http://www.acq.osd.mil/dsb/reports/ADA499977.pdf>.

51. New microorganisms are defined as microorganisms “formed by the deliberate combination of genetic material originally isolated from organisms of different taxonomic genera.” 15 USC 2604 and 40 CFR 725.3. See also *Fact Sheet—Microbial Products of Biotechnology: Final Regulations under the Toxic Substances Control Act* (n.d.).

52. 7 CFR 340.3 and 7 CFR 340.4.

53. Donald Fredrickson, *The Recombinant DNA Controversy, a Memoir: Science, Politics, and the Public Interest, 1974–1981* (Washington, D.C.: ASM Press, 2001), 39–40.

54. Epstein, “Controlling Biological Warfare Threats,” 338; and Ronald M. Atlas, “Applicability of the NIH Recombinant DNA Advisory Committee Paradigm for Reducing the Threat of Bioterrorism” (draft paper prepared for the Controlling Dangerous Pathogens Project, April 2002), 3–8.

55. Sunshine Project, *Mandate for Failure: The State of Institutional Biosafety Committees in an Age of Biological Weapons Research* (Austin: Sunshine Project, October 2004).

2001. Under the May 2002 bioterrorism bill, any rDNA experiment that must be approved by NIH also has to be approved by the secretary of HHS or the administrator of USDA's Animal and Plant Health Inspection Service if it involves agents or toxins on either department's select agent list. From January 2006 to December 2013, ninety-one of these so-called restricted experiments were proposed to HHS, of which thirty-one were approved. The remaining sixty experiments, all of which involved inserting drug-resistance traits into select agents, were not approved because they posed potentially serious risks to public health and safety. In recent years there have been four violations of the legal requirements governing HHS's oversight of restricted experiments, two of which resulted in civil penalties ranging from \$40,000 to \$1 million.⁵⁶ No comparable data on restricted experiment proposals or violations have been released by USDA.

In April 2010, the NSABB proposed expanding the *NIH Guidelines* to include synthetic biology, which seeks to create novel biological structures with predictable properties and functions, either by reengineering existing organisms or genomes or assembling nonliving biological components in novel ways. Governance of this evolving field, as the NSABB noted in a report at the time, is challenging because of the difficulty of predicting the biological characteristics of the new systems being created; the pace of developments and volume of information being produced; the diversity of disciplines involved, which includes the life sciences, engineering, chemistry, materials science, and computer modeling; and the variety of practitioners, not only university and high school students but also private sector and amateur scientists. Despite these challenges, the NSABB recommended establishing oversight arrangements for research with synthetic nucleic acids, including by explicitly adding synthetic nucleic acids to the *NIH Guidelines*.⁵⁷ NIH implemented the NSABB recommendation two years later, expanding the guidelines to include research with synthetic nucleic acid molecules even if rDNA techniques are not used.⁵⁸

The second track of U.S. efforts to oversee biological research has focused on the security concerns raised by dual-use research. This began in the summer of 2001 when, spurred in part by the Australian mousepox experiment, the U.S. National Academy of Sciences convened an expert panel chaired by Massachusetts Institute of Technology professor Gerald Fink to examine the risks from dual-use biotechnology research. The Fink Committee, as it came to be called,

56. Jacinta Smith, Denise Gangadharan, and Robbin Weyant, "Review of Restricted Experiment Requests, Division of Select Agents and Toxins, Centers for Disease Control and Prevention, 2006–2013," *Health Security* 13 (5) (2015): 307–316.

57. National Science Advisory Board for Biosecurity, *Addressing Biosecurity Concerns Related to Synthetic Biology* (Washington, D.C.: NSABB, April 2010), http://osp.od.nih.gov/sites/default/files/resources/NSABB%20SynBio%20DRAFT%20Report-FINAL%20%282%29_6-7-10.pdf.

58. For information on the *NIH Guidelines*, see National Institutes of Health, "Biosafety: NIH Guidelines," n.d., <http://osp.od.nih.gov/office-biotechnology-activities/biosafety/nih-guidelines>.

issued its aptly titled report, *Biotechnology Research in an Age of Terrorism*, in October 2003. The report emphasized that dual-use biotechnology research has the capacity “to cause disruption or harm, potentially on a catastrophic scale”; it also pointed out that U.S. and international measures governing such research do not address this security threat, in that they focus largely on biosafety and nonproliferation.

To help fill this gap, the Fink Committee proposed adding seven types of what it called “experiments of concern” to the research oversight process already in place under the *NIH Guidelines*. Specifically, it called for local IBC review followed, if necessary, by further review by the RAC or the NIH director, of any experiment that would

- demonstrate how to render a vaccine ineffective;
- confer resistance to antibiotic or antiviral agents;
- enhance the virulence of a pathogen or render a nonpathogen virulent;
- increase the transmissibility of a pathogen;
- alter the host range of a pathogen;
- enable evasion of diagnosis or detection methods; or
- enable weaponization of a biological agent or toxin.

The committee noted that these seven types of experiments represented current dangers but that additional types of experiments would need to be included in the future to address other potential threats. The committee also acknowledged that although oversight would initially apply only to research at facilities that were subject to the NIH guidelines, eventually *all* relevant research, including in private-sector and non-NIH government facilities, should be included in the oversight process. To help address these issues, the Fink Committee proposed the establishment of a national science advisory board for biodefense within HHS.⁵⁹ The creation of the NSABB in March 2004 was a direct result of the Fink Committee’s recommendations.

In June 2007, after more than three years of deliberations, the NSABB released a proposed framework for oversight of dual-use research. The NSABB proposal differed from the Fink Committee’s approach in a number of important respects. First, the NSABB focused on dual-use research of concern (DURC), a subset of dual-use research. Second, rather than have IBCs make the initial determination of whether research was of potential concern, the NSABB proposed that researchers do this themselves. Third, the NSABB proposed a single criterion for researchers to use to determine if their work met the definition of DURC—whether, based on current understanding, the research can be “*reasonably anticipated* to provide knowledge, products, or technologies that *could*

59. National Research Council, Committee on Research Standards and Practices to Prevent the Destructive Application of Biotechnology, *Biotechnology Research in an Age of Terrorism* (Washington, D.C.: National Academies Press, 2003), http://www.nap.edu/openbook.php?record_id=10827.

be directly misapplied by others to pose a threat to public health and safety, agricultural crops and other plants, animals, the environment, or material.”⁶⁰ Finally, recognizing that determining the applicability of this criterion would be a “subjective and challenging task,” the NSABB outlined seven broad categories of experimental effects (similar to the Fink Committee’s experiments of concern) that, if generated by the proposed research, *might* mean that it met the DURC criterion and thus required further institutional review or oversight by an IBC or other expert review committee.⁶¹

Although the NSABB initially recommended applying its oversight framework to federally funded research only, it later shifted position, arguing in its April 2010 synthetic biology report that dual-use oversight should be uniform and comprehensive, extending beyond the life sciences and academia to include other practitioners, including in the private sector.⁶² The NSABB was silent, however, on the issue of classified biodefense research, which was explicitly outside the scope of its responsibilities. This was especially unfortunate, given that the biodefense research program then being developed by DHS for its new National Biodefense Analysis and Countermeasures Center fell squarely within the Fink Committee’s seven experiments of concern.⁶³

Even before the NSABB oversight framework was released publicly in June 2007, CDC put in place a DURC review process for its own research activities, known as *intramural* research, based on the NSABB’s recommendations.⁶⁴ NIH did the same in 2008.⁶⁵ In presentations at a biosafety conference in 2010, NIH researchers reported that a retrospective review of NIH intramural research projects approved between 2004 and 2009 showed that only a small subset of biomedical research raised potential dual-use concerns in their *initial* screening (101 of 3,444 in one study and 12 of 734 in another) and that further expert review determined that only two projects actually met the definition of DURC. The NIH review also concluded that dual-use review was “easily incorporated” into existing IBC review processes and resulted in “no additional cost”

60. 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* (Washington, D.C.: NSABB, 2007), <http://osp.od.nih.gov/sites/default/files/resources/Framework%20for%20transmittal%20duplex%209-10-07.pdf>; emphasis added.

61. *Ibid.*

62. NSABB, *Addressing Biosecurity Concerns Related to Synthetic Biology*.

63. Milton Leitenberg, James Leonard, and Richard Spertzel, “Biodefense Crossing the Line,” *Politics and the Life Sciences* 22 (2) (2003): 2–3, <http://www.politicsandthelifesciences.org/Contents/Contents-2003-9/PLS2003-9-22-02-0002.pdf>.

64. Centers for Disease Control and Prevention, *Oversight and Clearance of Dual-Use Research of Concern*, CDC-SM-2007-01 (Atlanta, GA: CDC, March 23, 2007).

65. Megan C. Morgan, “Evaluation of a First-Tier Screening Program for Dual-Use Research of Concern” (presentation at the 53rd Annual Biological Safety Conference, Denver, October 5, 2010), <http://www.absaconference.org/pdf53/Session11-Morgan.pdf>.

and “no adverse effects” on research progress.⁶⁶ A CDC review of manuscripts from its intramural research program found that from 2007 to 2010, only eight manuscripts raised DURC questions, out of an annual publication rate of approximately 3,000 articles. After additional review, all eight manuscripts were published substantively “as is.”⁶⁷ Neither NIH nor CDC has released information since 2010 on the impact of their respective DURC review processes.

Despite CDC and NIH’s efforts to review their own intramural research, nearly five years passed before a broader policy for *U.S. government DURC* was announced. The release of this policy in March 2012 was a direct result of controversy over two external or *extramural* research projects on the H5N1 influenza virus, which had been funded by NIH without considering dual-use concerns. The new policy, which applied only to unclassified life sciences research funded or conducted by the U.S. government, drew heavily on both the Fink Committee’s original experiments of concern and the NSABB’s single, proposed criterion for assessing research. But it also narrowed the NSABB approach by adding a requirement that the research also had to involve one of fifteen specific agents or toxins from the select agent list. Agencies were ordered to review their intramural and extramural research projects to determine whether they involved DURC and, if so, to conduct risk-benefit assessments, develop risk mitigation plans, and provide periodic reports on the projects.⁶⁸

Concern over the H5N1 influenza research projects (one of which had been conducted by Dutch scientists)—including questions about the scientific value of the research, the biosafety conditions under which the projects were undertaken, and the dissemination of the results—continued to draw attention to the adequacy of U.S. oversight policies for dual-use research. But instead of examining the effectiveness of its approach more broadly, the U.S. government reacted in a piecemeal way, outlining first, in February 2013, a complicated and lengthy process by which HHS would make future *funding* decisions on certain highly pathogenic avian influenza (HPAI) research proposals. These studies were called “gain of function” (GOF) research, because they involved modifying already dangerous pathogens in order to increase their transmissi-

66. Morgan, “Evaluation of a First-Tier Screening Program for Dual-Use Research of Concern”; and Molly S. Stitt-Fischer, “The National Institutes of Health Dual Use Screening Program: A Proposed Quality Control Model” (presentation at the 53rd Annual Biological Safety Conference, Denver, October 5, 2010), <http://www.absaconference.org/pdf53/Session11-Stitt-Fischer.pdf>.

67. Mary D. Ari, PhD, “CDC’s Implementation of Dual-Use Research of Concern (DURC) Oversight” (presentation at the Council of Science Editors Annual Meeting, Seattle, May 20, 2012), http://www.resourcenter.net/images/cse/files/2012/annmtg/handouts/03_ari_3.pdf.

68. *United States Government Policy for Oversight of Life Sciences Dual Use Research of Concern* (Washington, D.C., March 2012), <http://www.phe.gov/s3/dualuse/documents/us-policy-durc-032812.pdf>.

bility or pathogenicity or to alter their host range.⁶⁹ Six months later, HHS extended the H5N1 funding review process to proposed experiments with the H7N9 influenza virus after twenty-two scientists published letters in *Nature* and *Science* seeking support for conducting GOF experiments with H7N9, which had emerged earlier in the year in China and was believed to pose a potential pandemic risk.⁷⁰

Despite, or perhaps because of these piecemeal steps, the controversy over GOF research did not end. In early 2014, other work to create new virus strains similar to the 1918 pandemic virus and to enable the H1N1 virus to evade the human immune system produced an outcry among scientists that spread quickly to the mainstream press in the United States and abroad.⁷¹ Concerns about the safety and security of research with highly dangerous pathogens were reinforced at the same time by the reports that had come to light regarding the mishandling of anthrax, the H5N1 influenza virus, and smallpox at government research facilities.

In July 2014, a call to curtail experiments involving the creation of potential pandemic pathogens pending further analysis and the convening of a meeting to discuss such work was issued by eighteen leading scientists and quickly endorsed by nearly three hundred other U.S. and foreign scientists and policy experts. Other scientists more positively disposed toward GOF research also endorsed the meeting idea.⁷² In October 2014, the White House Office of Science and Technology Policy responded, announcing that the U.S. government would undertake a deliberative process on GOF experiments with help from the NSABB and the National Research Council of the National Academies in order to develop a new U.S. policy on the conduct and funding of such research. The White House also announced a funding pause on new GOF studies involving influenza, severe acute respiratory syndrome (SARS), and Middle East respira-

69. Department of Health and Human Services, *A Framework for Guiding U.S. Department of Health and Human Services Funding Decisions about Research Proposals with the Potential for Generating Highly Pathogenic Avian Influenza H5N1 Viruses That Are Transmissible among Mammals by Respiratory Droplets* (Washington, D.C.: HHS, February 2013), <http://www.phe.gov/s3/dualuse/Documents/funding-hpai-h5n1.pdf>.

70. David Malakoff, "Critics Skeptical as Flu Scientists Argue for Controversial H7N9 Studies," *Science* 341 (6146) (August 9, 2013): 601; and Harold Jaffe, Amy P. Patterson, and Nicole Lurie, "Extra Oversight for H7N9 Experiments," *Science* 341 (6147) (August 16, 2013): 713–714.

71. See, for example, "Scientists Condemn 'Crazy, Dangerous' Creation of Deadly Airborne Flu Virus," *Guardian*, June 11, 2014; and Steve Connor, "Exclusive: Controversial US Scientist Creates Deadly New Flu Strain for Pandemic Research," *Independent*, July 1, 2014.

72. "Cambridge Working Group Consensus Statement on the Creation of Potential Pandemic Pathogens (PPPs)," July 14, 2014, <http://www.cambridgeworkinggroup.org/>; and "Scientists for Science," *Virology Blog*, July 28, 2014, <http://www.virology.ws/2014/07/28/scientists-for-science/>.

tory syndrome (MERS) viruses and encouraged those already conducting such work to pause voluntarily until a new policy was in place.⁷³ (The White House subsequently lifted the pause on five MERS and two influenza studies.⁷⁴)

Over the next eighteen months, the NSABB held five meetings and commissioned both a risk-benefit assessment study and an analysis of the ethical issues surrounding GOF research.⁷⁵ The former, a \$1 million, one-thousand-page contractor effort, was highly criticized by opponents of GOF research on technical and analytical grounds, including the study's failure to calculate the probability of an enhanced pathogen escaping the laboratory, a key variable in the calculation of pandemic risk. The study was also criticized for bias, in that 80 percent of the scientists interviewed about the benefits of GOF research were either scientists who conducted such research or representatives of agencies who funded it.⁷⁶ The ethical study, by comparison, provided a comprehensive, balanced discussion of the various ethical and decision-making frameworks of potential relevance to evaluating GOF proposals. Of particular importance was the study's suggestion that a federal advisory body like the NSABB might play a role in reviewing GOF research.⁷⁷

The NSABB also prepared a draft working paper outlining its initial thoughts on a conceptual approach for reviewing proposed GOF studies. As in its earlier work on dual-use research, the NSABB recommended focusing GOF oversight on research that posed the greatest risk, or what it called GOF studies of concern. The working paper also recommended that oversight for these studies should be incorporated into existing policy frameworks (for example, the NIH Guidelines and the oversight policies for DURC), although it

73. Department of Health and Human Services, *U.S. Government Gain-of-Function Deliberative Process and Research Funding Pause on Selected Gain-of-Function Research Involving Influenza, MERS and SARS Viruses: Frequently Asked Questions* (Washington, D.C.: HHS, November 2014), <http://www.phe.gov/s3/dualuse/Documents/gof-qanda.pdf>.

74. Nell Greenfieldboyce, "NIH Allows Restart of MERS Research That Had Been Questioned," *Shots: Health News from NPR*, December 18, 2014, at <http://www.npr.org/sections/health-shots/2014/12/18/371686933/nih-allows-restart-of-mers-research-that-was-deemed-too-risky>.

75. Joseph Kanabrocki, "NSABB Working Group Report: Preliminary Findings and Draft Recommendations," PowerPoint presentation for National Science Advisory Board for Biosecurity meeting, January 7–8, 2016, <http://osp.od.nih.gov/sites/default/files/NSABB%20Working%20Group%20-%20Preliminary%20Findings%20and%20Draft%20Recommendations.pdf>.

76. Gryphon Scientific, "Risk and Benefit Analysis of Gain of Function Research," Draft Final Report, December 2015, <http://osp.od.nih.gov/sites/default/files/Risk%20and%20Benefit%20Analysis%20of%20Gain%20of%20Function%20Research%20-%20Draft%20Final%20Report.pdf>. For public comments on the report, see <http://dels.nas.edu/resources/static-assets/bls/agenda/Compiled%20Public%20Comments%20to%20NAS%20and%20NSABB%20-%20ALL%20COMMENTS.pdf>.

77. Michael J. Selgelid, "Gain of Function Research: Ethical Analysis," White Paper, n.d., http://osp.od.nih.gov/sites/default/files/Gain-of-Function%20Research%20Ethical%20Analysis%20White%20Paper%20by%20Michael%20Selgelid_0.pdf.

recognized that additional oversight might be required in some cases.⁷⁸ The National Research Council contributed to the NSABB's work by holding two symposiums to elicit input from the scientific community and the public. The first symposium focused on scientific and technical questions related to the conduct of risk-benefit assessments of GOF research. The second symposium examined possible oversight policies, including the recommendations in the draft NSABB working paper.⁷⁹

In the coming months, the NSABB is expected to refine and elaborate its proposed recommendations and, ultimately, submit a final report to the federal government for consideration. But whether the policy that emerges from the U.S. deliberative process is effective will depend not only on the details of the oversight arrangements but also on the policy's scope: whether it applies only to U.S. government funded research, as currently planned, or is used to review all relevant research in the United States and, eventually, other countries.

In parallel with the 2014 announcement of the GOF deliberative process, the U.S. government also finally released in September 2014, nearly seven years after the NSABB oversight proposal, a new policy on the responsibilities of *research institutions* involved in dual-use research. Like the 2012 policy for U.S. government DURC, this new policy applies only to unclassified research involving one or more of fifteen specific select agents and toxins. But it also is somewhat broader than the 2012 policy in that it covers relevant research at any institution (e.g., government, academic, or private) that receives federal funding for life sciences research, even if the U.S. government is not funding the project in question. However, both research at institutions that do not receive federal funds for life sciences research and classified research (including for biodefense) remain outside the scope of U.S. DURC oversight requirements.

Under the new U.S. policy, the DURC review process begins only after a research project has secured funding. The primary investigator (PI) is expected to initiate the DURC review and to work with an institutional review entity (IRE), such as an IBC, to conduct a risk-benefit assessment and, if appropriate, to develop a draft risk mitigation plan. The IRE is responsible for making the final determination of whether the research is DURC, for ensuring that an appropriate risk mitigation plan is in place, and for reviewing both the plan and the research on an annual basis. The institution where the DURC is to be carried out is responsible for notifying the appropriate U.S. government agency of the DURC determination and for submitting the draft risk mitigation plan

78. National Science Advisory Board for Biosecurity, "Working Paper Prepared by the NSABB Working Group on Evaluating the Risks and Benefits of Gain-of-Function Studies to Formulate Policy Recommendations," Deliberative Draft, December 23, 2015, http://osp.od.nih.gov/sites/default/files/NSABB%20WG%20Working%20Paper%20on%20Gain-of-Function%20Studies%2012-23-2015_0.pdf.

79. For the report from the first symposium, see <http://dels.nas.edu/Workshop-Summary/Potential-Risks-Benefits-Gain/21666?bname=bls>; for information on the second symposium, see <http://dels.nas.edu/Upcoming-Event/Gain-Function-Research-Second/AUTO-9-61-70-Q>.

for final approval. Although the policy is not legally based, failure to comply could lead to the loss of existing or future U.S. government research funds.⁸⁰

Current State of Governance in Other Countries

As in the United States, other countries also have adopted measures aimed at preventing the spread of biological weapons capabilities or ensuring the safety and security of work involving dangerous biological materials (see Table 4). For example, EU members have enacted national legislation to implement the BWC's prohibitions against biological weapons development and acquisition. Since 1994, EU member states also have approved various regulations and directives designed to control exports of dual-use items, including those related to biological weapons. These regulations and directives are binding on every EU country. Under European Council regulation (EC) 3381/94, member states must require a license for exports outside the EU of biological materials, equipment and technical information. Consistent with AG controls, the regulation also includes a "no-undercut" policy as well as catch-all controls requiring the licensing of any nonlisted dual-use items that pose a proliferation risk. Biological agents adapted for use in war and equipment specifically designed for biological weapons purposes are controlled by EU members under the EU's list of common military goods, which is based on the munitions list of the Wassenaar Arrangement, the multilateral export control regime that succeeded the Cold War-era Coordinating Committee for Multilateral Export Controls, known as CoCOM.⁸¹

Because of concerns about the safety of genetic modification techniques generally and genetically modified foods specifically, EU member states also have enacted directives on the safe handling of genetically modified organisms (GMOs). For example, under European Council Directive 90/219/EEC, facilities must notify their relevant government authority before using GMOs for the first time. The notification must include a description of the proposed work, an assessment of the risks to human health and the environment, and other information depending on the characteristics of the organism and level of containment required. Activities requiring Level 3 containment or above may

80. *United States Government Policy for Institutional Oversight of Life Sciences Dual Use Research of Concern* (Washington, D.C., September 24, 2014), <http://www.phe.gov/s3/dualuse/Documents/durc-policy.pdf>.

81. (EC) 3381/94 established the general principles while Annex I of 94/942/CFSP contained the original control lists. These were later combined in (EC) 1334/2000. The most recent version of which is (EU) 388/2012. See "Report to Parliament and the Council on the Implementation of Council Regulation (EC) No 1334/2000 Setting Up a Community Regime for the Control of Exports of Dual-Use Items and Technology, October 2000 to May 2004," 20 September 2004, http://trade.ec.europa.eu/doclib/docs/2004/september/tradoc_118993.pdf; and German Ethics Council, *Biosecurity—Freedom and Responsibility of Research* (Berlin: Deutscher Ethikrat, May 2014), <http://www.ethikrat.org/files/opinion-biosecurity.pdf>. For the EU munitions list, see "Common Military List of the European Union," *Official Journal of the European Union*, C 90 (March 27, 2013): 1–37, <http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:C:2013:090:0001:0037:EN:PDF>.

Table 4: Biological Technology Governance In Other Countries

Measure	Date	Country	Purpose	Comments
90/219 EEC	1990	EU members	Control contained use of GMOs; prenotify first use; prior approval for Level 3 work or above	Legally binding; continues to be revised
90/220 EEC	1990	EU members	Control release of GMOs; prenotify release; prior approval by EC	Legally binding; penalties for violations; continues to be revised
3381/94 EC	1994	EU members	Control exports of biological agents, toxins, related equipment to proliferant countries	Legally binding; follows Australia Group control lists; continues to be revised
Anti-Terrorism, Crime and Security Act	2001	UK	Control access to human pathogens and toxins: notification and security requirements; background checks	Legally binding
	2007			Added plant pathogens
Code of Conduct for Biosecurity	2007	Netherlands	Guidance for screening dual-use research & facility access	Not legally binding; proposed by KNAW at government request; subsequently determined not sufficient
Act on Securing Biological Substances, Delivery Systems, Related Materials	2008	Denmark	Control access to biological substances, delivery systems and related materials; oversight of dual-use research	Legally binding; penalties for violations; dual-use review process relegated to subsidiary documents
Executive Order	2009		Requires licensing, vulnerability assessment, security plan, access controls, and recordkeeping	
Laboratory Biorisk Management Standard	2008	EU	Guidance for handling biological materials in labs and other facilities	Politically binding; little information on national implementation
Regulation of Research into Biological Disease Agents Act	2008	Israel	Control access to biological agents by facility authorization; oversight of dual-use research by institutional committees	Legally binding; national-level council assists implementation
Human Pathogens and Toxin Act	2009	Canada	Strengthen controls on access to human pathogens and toxins by facility licensing, security clearances for high-risk agents, and inspections	Legally binding
Chemical, Biological, Radiological, Nuclear Action Plan	2009	EU members	Prevent unauthorized access to materials of concern	Politically binding; no information on implementation
	2011		Agree on common control lists	

not proceed without prior government approval.⁸² Under European Council Directive 90/220/EEC, before deliberately releasing a GMO into the environment, a manufacturer or importer must submit a notification to the government containing a full assessment of the risks to human health, animal health, and the environment of the proposed release, as well as detailed information on the GMO, the release plans and receiving environment, and monitoring and control arrangements. Final authority for approving the release resides with the European Commission.⁸³ Violators may be subject to penalties within EU member states.

Members of the EU also have taken steps to prevent terrorists or other nonstate actors from acquiring or using biological agents, although few of these measures are legally binding. One exception is the Anti-Terrorism, Crime and Security Act of 2001 (ATCSA), which was adopted by the UK after September 11 and the anthrax letters to control access to biological agents that could be used against human beings, including genetic elements and genetically modified organisms associated with those agents. Under the ATCSA, facilities that possess or plan to possess these agents are required to notify the government and comply with any reasonable security enhancements imposed after an inspection of the site. They also are required to comply with official requests for information about security at their facility and about persons who have or are proposed to have access to controlled pathogens. Background checks may be conducted by the government, which may also deny individuals access to controlled pathogens or facilities where they are located. In 2007, following a foot-and-mouth disease outbreak in Surrey, the ATCSA was extended to include animal pathogens as well.⁸⁴

82. “Council Directive of 23 April 1990 on the Contained Use of Genetically Modified Micro-organisms (90/219/EEC),” *Official Journal of the European Union*, L 117 (May 8, 1990): 1–14, <http://www.biosafety.be/GB/Dir.Eur.GB/Cont.Use/90.219/TC.html>. For the amended version, 2009/41/EC, see “Directive 2009/41/EC of the European Parliament and of the Council of 6 May 2009 on the Contained Use of Genetically Modified Micro-organisms (Recast),” *Official Journal of the European Union*, L 125 (May 21, 2009): 75–97, http://www.biosafety.be/PDF/2009_41_EN.pdf?REQUEST=Seek-Deliver&COLLECTION=oj&SERVICE=eurlex-&LANGUAGE=en&DOCID=20011073p0032. The EU’s “Level 3” corresponds to biosafety level (BSL) 3 in the United States. The biosafety level refers to the level of physical containment required for work with biological materials in a laboratory facility. The levels are designated in ascending order from BSL-1 (the lowest) to BSL-4 (the highest), with each level building on the previous level’s requirements for laboratory practices, safety equipment, and facility design.

83. “Council Directive of 23 April 1990 on the Deliberate Release into the Environment of Genetically Modified Organisms (90/220/EEC),” *Official Journal of the European Union*, L 117 (May 8, 1990): 15–27, <http://www.biosafety.be/GB/Dir.Eur.GB/Del.Rel./90.220/TC.html>. For the amended version, 2001/18/EC, see “Directive 2001/18/EC of the European Parliament and of the Council of 12 March 2001 on the Deliberate Release into the Environment of Genetically Modified Organisms and Repealing Council Directive 90/220/EEC,” *Official Journal of the European Union*, L 106 (April 17, 2001): 1–39, http://eur-lex.europa.eu/resource.html?uri=cellar:303dd4fa-07a8-4d20-86a8-0baaf0518d22.0004.02/DOC_1&format=PDF.

84. Statutory Instrument 2001 (no. 4019), *Anti-terrorism, Crime and Security Act 2001*, http://www.opbw.org/nat_imp/leg_reg/uk/ATCS.pdf. The 2007 revisions are described in “Pathogens and Toxins Guidance ATCSA 2001 Schedule 5 Order 2007 Notes (SI 2007/929)” (n.d.), <http://www.cf.ac.uk/osheu/resources/Schedule%20%20pathogens%20and%20toxins%20list%20and%20guidance.pdf>.

In 2009, EU members adopted an action plan that, among other things, seeks to block unauthorized access to biological and other materials of concern. In 2011, members agreed on a common control list for each type of material, including a list of high-risk biological agents. EU members also agreed to implement the European Committee for Standardization's Laboratory Biorisk Management Standard, which provides guidance for handling biological materials in laboratories and other facilities based on WHO biosafety and biosecurity guidelines.⁸⁵ EU member states have released relatively little information about their implementation of these measures, which are politically but not legally binding.

Outside of the EU, Canada has strengthened its domestic controls on access to biological materials, which originally applied only to human pathogens and toxins that were being imported into the country. In 2009, the Canadian Parliament adopted the Human Pathogens and Toxin Act, which revised Canadian law to include all risk group 2, 3, and 4 human pathogens and toxins, natural or synthetic, whether imported or acquired domestically.⁸⁶ Under recent implementing regulations, no person may possess, produce, store, transfer, release, or dispose of high-risk pathogens or toxins without first obtaining a government license. Before a license is issued, facilities are required to designate a biosafety officer, and facilities conducting scientific research are required to submit information on their biosafety and biosecurity procedures. The regulations also require that any person entering a facility area handling so-called security sensitive biological agents (a subset of risk group 3 and 4 human pathogens) must have a security clearance or be accompanied by someone with a clearance. Compliance monitoring through inspections, as well as enforcement actions, are also authorized under the law and regulations.⁸⁷

Progress in strengthening oversight of dual-use life sciences research has been more limited, with few countries outside the United States having adopted research oversight policies. One that has is Denmark, which in June 2008 passed an Act on Securing Specific Biological Substances, Delivery Systems and Related Materials. Under the Danish law, dual-use research that can be used directly for the development of biological weapons or for offensive purposes is considered a type of technology and thus a "related material." The law applies to all entities,

85. Commission of the European Communities, "On Strengthening Chemical, Biological, Radiological and Nuclear Security in the European Union—an EU CBRN Action Plan," COM(2009) 273 final, June 24, 2009, <http://www.bureaubiosecurity.nl/dsresource?type=pdf&disposition=inline&objectid=rivmp:243738&versionid=&subobjectname>; European Commission, "Progress Report on the Implementation of the EU CBRN Action Plan, May 2012," n.d., http://ec.europa.eu/dgs/home-affairs/what-we-do/policies/crisis-and-terrorism/securing-dangerous-material/docs/eu_cbrn_action_plan_progress_report_en.pdf; and European Committee for Standardization, *Laboratory Biorisk Management Standard*, CWA 15793:2008 (Brussels: European Committee for Standardization, February 2008), http://www.absa.org/pdf/CWA15793_Feb2008.pdf.

86. "Risk group" refers to the classification of a biological agent based on its ability to cause disease. The risk groups are designated in ascending order from risk group 1, for agents that pose no or low risk, to risk group 4, for agents that pose the greatest risk.

87. "Human Pathogens and Toxin Regulations," *Canada Gazette* 148 (25) (June 21, 2014), <http://www.gazette.gc.ca/rp-pr/p1/2014/2014-06-21/html/reg2-eng.php>.

public or private, military or civilian, that handle, use, or store controlled items and thus combines in a more robust way the U.S. laws on select agents and U.S. policies on DURC.⁸⁸

To ensure prompt implementation of the Danish biosecurity law as well as the flexibility to respond to future technological developments, both the lists of controlled items and the basic requirements were included in a separate executive order, which was adopted in 2009. Under the executive order, any entity that possesses or plans to possess a controlled item must obtain a license from the Danish biosecurity agency, known as the Center for Biosecurity and Biopreparedness (CBB). Such entities must prepare a vulnerability assessment and security plan for their site and appoint a biosafety officer to keep records of all individuals given access to controlled biological materials. Once licensed, they must maintain an inventory of all controlled items and submit to inspections by Danish authorities. Violations may result in fines, imprisonment, or criminal penalties.⁸⁹

Because the 2009 executive order could not address every implementation detail, other CBB documents provide additional guidance, including on the process for evaluating research proposals for dual-use concerns. Scientists are responsible for conducting the initial screening of their research to determine whether it has dual-use potential, using a CBB questionnaire. If one or more of eleven possible research outcomes applies, the scientist must contact CBB so the agency can decide how possible risks should be addressed and whether a license or other form of regulation, such as restrictions on participation in the research or on its publication, is required.⁹⁰

In November 2008, Israel adopted similar biosecurity legislation in response to a report by the Steering Committee on Biotechnological Research in an Age of Terrorism (COBRAT), a special committee created by the Israeli Academy of Sciences and Humanities and the Israeli National Security Council. Although modeled on the U.S. Fink Committee, COBRAT went much further than its American counterpart, recommending mandatory research oversight in

88. For a detailed discussion of the Danish approach, see Centre for Biosecurity and Biopreparedness, *An Efficient and Practical Approach to Biosecurity* (Copenhagen: CBB, 2015), https://www.biosikring.dk/fileadmin/user_upload/PDF_FILER/Biosecurity_book/An_efficient_and_Practical_approach_to_Biosecurity_web1.pdf.

89. Danish Ministry of Health and Prevention, “Act on Securing Specific Biological Substances, Delivery Systems and Related Materials,” ACT no. 474, June 17, 2008, https://www.biosikring.dk/fileadmin/user_upload/PDF_FILER/Biosikringsdokumenter/ACTNo474of17_June2008.pdf; and Danish Ministry of Health and Prevention, “Executive Order on Securing Specific Biological Substances, Delivery Systems and Related Materials,” EO no. 981, October 15, 2009, <https://www.biosikring.dk/499/>.

90. Centre for Biosecurity and Biopreparedness, *An Efficient and Practical Approach to Biosecurity*, 115–16, 239–43; and Centre for Biosecurity and Biopreparedness, “Questionnaire about Dual Use Research of Concern for Companies, Project Managers, Etc.,” August 18, 2015, https://www.biosikring.dk/fileadmin/user_upload/PDF_FILER/UK_forms_and_guides/Questionnaire_about_dual-use_research_of_concern.pdf.

all facilities, including government laboratories, as well as controls on dangerous biological agents.⁹¹

Under Israel's 2008 Regulation of Research into Biological Disease Agents Act, the Ministry of Health must authorize any institution or laboratory that possesses, conducts research on, or works with certain listed biological agents. Such institutions and laboratories are required to establish an institutional committee of scientists, security experts, and safety personnel to review research proposals for biosafety and biosecurity, including dual-use concerns. The law also provides for the creation of an interdisciplinary council to advise the Ministry of Health on the formulation and implementation of the necessary operating rules and regulations, including those governing the list of controlled agents, the proceedings of the institutional committees, and related issues.⁹²

Recommendations also have been made in two other countries for research oversight policies, but as of early 2016 these have yet to be adopted. The first is the Netherlands, where in 2007 a biosecurity working group established by the Royal Netherlands Academy of Arts and Sciences (KNAW) proposed a code of conduct to prevent life sciences research from contributing to activities prohibited under the BWC or to any other misuse of biological agents or toxins. The KNAW *Code of Conduct for Biosecurity* outlines rules related to a number of issues, including screening for dual-use research as well as access to facilities involved in such work.⁹³ However, following the 2011 controversy over U.S. and Dutch research with the H5N1 virus, a separate KNAW biosecurity committee concluded that the code was not sufficient for addressing dual-use concerns and recommended the creation of an independent Biosecurity Advisory Committee for Research in the Life Sciences to advise researchers and institutions on relevant research proposals, including the conduct of the research and possible publications restrictions. The Dutch government has not responded to the biosecurity committee's report, although it has organized biosecurity workshops and published an online biosecurity questionnaire for use by those working with dangerous pathogens.⁹⁴

The second country is Germany, where in 2014 the German Ethics Council released a report with two key research oversight recommendations. The first was to establish a national German code of conduct for responsible research to

91. Steering Committee on Issues in Biotechnological Research in an Age of Terrorism, *Biotechnology Research in an Age of Terrorism* (Jerusalem: Israel Academy of Sciences and Humanities and Israel National Security Council, 2008).

92. David Friedman, "Israel," in *Education and Ethics in the Life Sciences: Strengthening the Prohibition of Biological Weapons*, ed. Brian Rappert (Canberra: Australian National University Press, 2010), esp. 82–85, <http://press.anu.edu.au?p=51221>.

93. Royal Netherlands Academy of Arts and Sciences (KNAW), Biosecurity Working Group, *A Code of Conduct for Biosecurity* (Amsterdam: KNAW, 2008).

94. As described in German Ethics Council, *Biosecurity—Freedom and Responsibility of Research* (Berlin: German Ethics Council, 2014), <http://www.ethikrat.org/files/opinion-biosecurity.pdf>. Copies of the KNAW reports are available at <https://www.knaw.nl/en/news/publications/improving-biosecurity>.

sensitize researchers and others to the risk of misuse and to define what constitutes responsible conduct. The council emphasized that the code should apply to all public and private facilities doing relevant research and should obligate researchers, after suitable training, to screen and monitor their own research for DURC. The council also recommended the adoption of legislation providing a legal definition of dual-use research of concern, establishing a national-level dual-use research interdisciplinary commission with the authority to vote on research projects, and requiring researchers to consult with the commission prior to and during the conduct of their research. To give its recommendations greater force, the council proposed that German funding bodies fund proposals only from researchers who comply with the code of conduct and have received a positive vote by the dual-use research commission. The council also proposed that the German government take the lead in trying to secure adoption of a similar dual-use research policy within the EU and of the code and definition of dual-use research of concern on a global level.⁹⁵ The German government has not responded to the Ethics Council report.

Other Measures for Managing Biological Technology

While many proposals have been made over the last decade and a half for managing the risks from biological technology, two types warrant particular attention. The first, scientific codes, have received strong support from across the scientific community. The second, restrictions on the dissemination of sensitive dual-use research information, have elicited the opposite reaction, notwithstanding periodic debates over the need for a mechanism to that effect.

Codes for Scientists

Since the collapse of the BWC protocol negotiations, significant attention has focused on the utility of scientific codes in helping address dual-use concerns. Much of this discussion has focused on ethical codes, which describe personal and professional standards; or on codes of conduct, which provide guidelines on appropriate behavior. Little attention, however, has been given to codes of practice, which outline enforceable procedures and rules.⁹⁶

At the suggestion of the United States, codes of conduct were a major topic of discussion in the BWC intersessional meetings in 2005. One important non-governmental participant was the InterAcademy Panel (IAP), a global network of science academies from around the world. The IAP proposed five principles to guide the development of codes of conduct: (1) awareness of dual-use risks; (2) safe and secure laboratory practices; (3) education and information about

95. German Ethics Council, *Biosecurity—Freedom and Responsibility of Research*, <http://www.ethikrat.org/files/opinion-biosecurity.pdf>.

96. Brian Rappert, "Towards a Life Sciences Code: Countering the Threat from Biological Weapons," Strengthening the Biological Weapons Convention Briefing Paper no. 13 (2nd ser.), University of Bradford, Bradford, UK, September 2004, http://www.brad.ac.uk/acad/sbtwc/briefing/BP_13_2ndseries.pdf.

dual-use laws, regulations, and policies; (4) the accountability of scientists to report violations of rules against using biology for destructive purposes; and (5) the promotion of these principles within oversight arrangements for dual-use research and publications. More than seventy member academies have endorsed the IAP approach.⁹⁷

In the United Kingdom, the Royal Society has supported codes of conduct both as a means of raising consciousness among scientists about the potential for misuse of their work and as a focal point for training and education on relevant national and international obligations. The society also has argued for more-detailed codes of practice built on existing biosafety laws and regulations to help prevent the misuse of scientific research.⁹⁸ Codes of conduct also have been proposed by national science bodies in Germany and the Netherlands. In the United States, the NSABB outlined the possible elements of a code of conduct in an appendix to its 2007 dual-use oversight framework, identifying the most important individual, group, and institutional responsibilities at each stage of the research process. The NSABB later developed an education module on dual-use research for scientists and a toolkit to help scientists formulate and disseminate a code of conduct.⁹⁹

Professional associations such as the International Union of Microbiological Societies and the American Society of Microbiology (ASM) also have adopted codes of conduct. These codes have several common features: a commitment to biosafety, support for the ethical conduct of research, and opposition to the misuse of microbiology, including for development of biological weapons.¹⁰⁰ All of these codes, however, are general in nature.

The same is true of the only government code known to have been developed and promulgated for scientists and scientific institutions, the British code of ethics. This voluntary code, which was issued in 2007, contains a small num-

97. The InterAcademy Panel, “IAP Statement on Biosecurity,” November 7, 2005, <http://www.interacademies.net/10878/13912.aspx>; and Jo L. Husbands, “Engaging the International Scientific Community in Issues of Dual-Use Research: The Experience of the NAS and the Inter-Academy Panel” (presentation at The Advancement of Science and the Dilemma of Dual Use: Why We Can’t Afford to Fail, Warsaw, November 9–10, 2007).

98. See, for example, Royal Society, *The Roles of Codes of Conduct in Preventing the Misuse of Scientific Research* (London: Royal Society, June 2005), https://royalsociety.org/~media/Royal_Society_Content/policy/publications/2005/9645.pdf.

99. National Science Advisory Board on Biosecurity, *Enhancing Responsible Science—Considerations for the Development and Dissemination of Codes of Conduct for Dual Use Research* (Washington, D.C.: NSABB, February 2012), http://osp.od.nih.gov/sites/default/files/resources/COMBINED_Codes_PDFs.pdf.

100. Australian Society for Microbiology, “Ethics” (1979), <http://www.theasm.org.au/about-us/governance/>; American Society for Microbiology, “Code of Ethics” (2005), <http://www.asm.org/index.php/governance/code-of-ethics>; and International Union of Microbiological Societies, “Code of Ethics” (2008), <http://www.iums.org/index.php/code-of-ethics>.

ber of broad principles: rigor, honesty, and integrity; respect for life, the law, and the public good; and, responsible communication, listening, and informing.¹⁰¹

Restrictions on the Dissemination of Information

Since September 11 and the anthrax letters, both scientists and scientific journals have been concerned about the possibility of restrictions on the dissemination of scientific findings that could have security implications. U.S. scientific journals have tried to forestall government-imposed restrictions, offering instead to establish their own review processes for handling sensitive manuscripts. The first to do so were the scientific journals published by the ASM, which in August 2002 began to require peer reviewers to inform journal editors of any manuscript that contained information on methods or materials that might be misused or pose a threat to public health or safety. The manuscripts would then be reviewed by the editor in chief in consultation with the ASM publications board. A few months later, the *Proceedings of the National Academy of Sciences* quietly adopted a similar process for reviewing manuscripts involving select agents. This was followed in January 2003 by a statement from thirty journal editors and scientists calling for the development of processes for considering the security implications of proposed manuscripts and, where necessary, for modifying or refraining from publishing papers whose potential harm outweighed their potential benefits. None of these initiatives, however, included guidance for reviewers on how to identify information that constituted a potential threat.¹⁰²

In 2005 the limits of the journal editors' approach was put to the test when research involving the 1918 H1N1 virus was submitted to *Science* for publication. The NSABB was asked for its opinion and recommended publishing the paper after adding information on the public health benefits of the research. However, Donald Kennedy, *Science's* editor in chief, later made clear that unless the paper had been classified he would have proceeded with publication, irrespective of the NSABB's recommendation.¹⁰³ Michael Osterholm, an NSABB member at the time, subsequently regretted the NSABB decision, arguing that if the reconstructed H1N1 virus had escaped the lab it could have caused a 1918-like pandemic, contrary to the NSABB's original assessment.¹⁰⁴

In 2011, the NSABB again was asked for publication advice, this time on the work involving the construction of modified H5N1 viruses capable of respiratory transmission in mammals. But instead of supporting full publication, the NSABB recommended redacting methodological and other experimental

101. United Kingdom, Government Office for Science, *Rigour, Respect and Responsibility: A Universal Ethical Code for Scientists* (London: Government Office for Science, September 2007), <http://virtualbiosecuritycenter.org/wp-content/uploads/2012/07/UK-ethical-code.pdf>.

102. As discussed in Elisa Harris and John Steinbruner, "Scientific Openness and National Security after 9-11," *CBW Conventions Bulletin* (67) (March 2005): 1–6.

103. Donald Kennedy, "Better Never than Late," *Science* 310 (5746) (October 14, 2005): 195.

104. Michael T. Osterholm to Amy Patterson, April 12, 2012, https://labs.fhcrc.org/cbf/Papers/H5N1_docs/Osterholm_Letter_April_2012.pdf.

details that could enable the modified viruses to be recreated and used to cause harm.¹⁰⁵ The NSABB also called for an international meeting of experts to discuss H5N1 research policy. Although WHO quickly organized the meeting, the participants were, as Osterholm later noted, from the “involved influenza research community, telling us what they should and shouldn’t be allowed to do” based on their own self-interest.¹⁰⁶ The WHO experts group concluded that trying to limit access to the complete manuscripts would pose insurmountable practical problems, though it acknowledged the potential value of developing a mechanism for controlling access to other dual-use research information in the future.

After the WHO meeting, the U.S. government asked the NSABB to reconsider the two H5N1 manuscripts, which had been edited at the request of NIH to clarify the public health benefits of the research and the laboratory safety measures taken with the virus. Given what was in effect a choice between publishing the full manuscripts or none at all, the NSABB voted unanimously in one case and 12–6 in the other for publication. Paul Keim, another former NSABB member, later commented that disinterested parties needed to be part of the process, as scientists could not be expected to assess the risks of their research on their own. Osterholm was more scathing, charging that the NSABB was continuing to “kick the can down the road” instead of figuring out how to manage DURC and its dissemination.¹⁰⁷

Following the H5N1 controversy, NIH agreed to explore the feasibility of a mechanism for restricting access to sensitive dual-use information. This apparently was done as part of the review process that led to the U.S. government policies for oversight of DURC.¹⁰⁸ But rather than a mechanism for controlling access, NIH instead developed guidance for communicating DURC responsibly, including points for institutions and researchers to consider in assessing the risks and benefits of communicating their work. The guidance included an option for restricting access to sensitive information, but was silent on how institutions and researchers should do this.¹⁰⁹

105. For a discussion of the handling of these manuscripts, see *Biological Security: The Risk of Dual-Use Research: Hearing before the Committee on Homeland Security and Governmental Affairs, United States Senate, One Hundred Twelfth Congress, Second Session*, 112th Cong. (2012) (statement of Anthony S. Fauci, Director, National Institute of Allergy and Infectious Diseases, National Institutes of Health), <http://www.hsgac.senate.gov/download/2012-04-26-fauci-testimony-biological-security>.

106. Osterholm to Patterson.

107. Brendan Maher, “The Biosecurity Oversight,” *Nature* 485 (7399) (May 24, 2012): 431–434; and Osterholm to Patterson.

108. Kathryn Harris, Biosecurity and Biosafety Program, National Institutes of Health, personal correspondence, July 13, 2015.

109. National Institutes of Health, *Tools for the Identification, Assessment, Management, and Responsible Communication of Dual Use Research of Concern: A Companion Guide to the United States Government Policies for Oversight of Life Sciences Dual Use Research of Concern* (Washington, DC: National Institutes of Health, September 2014), 48–53, <http://www.phe.gov/s3/dualuse/Documents/durc-companion-guide.pdf>.

ASM journal editors also have acknowledged the difficulties of identifying and handling dual-use research information. In 2013–2014 the journals used the new U.S. government DURC policy to review several HPAI gain of function manuscripts. They concluded that determining whether an experiment meets the U.S. government definition of DURC is a judgment call and thus problematic for journal editors and IBCs. Presumably the same is true, but to an even greater extent, for researchers. In an unprecedented step, the editors, two of whom had served on the NSABB, called in April 2014 for the creation of a federal advisory board similar to the RAC to provide a more organized approach to managing DURC and its dissemination.¹¹⁰

GOVERNANCE CHALLENGES

Governments have traditionally viewed the risks posed by advances in the life sciences as a biosafety matter involving legitimate scientists or as a proliferation problem focused on national biological weapons programs. The former is reflected in the variety of international and national measures governing the handling and use of biological agents, such as the WHO biosafety manual, the *NIH Guidelines*, and the EU's biosafety regulations and directives. The latter is reflected in the conclusion of the BWC and in the subsequent multilateral and national efforts to deny proliferators access to biological materials, equipment, and related information through initiatives such as the Australia Group, export controls, and threat reduction programs in the former Soviet Union.

However, the September 11 terrorist attacks and the anthrax letters profoundly altered perceptions of the biological threat. To a greater degree than ever before, advances in the life sciences were viewed as not only a force for public good but also as a potential source of harm, particularly if used by terrorists or other nonstate actors. In response, further governance efforts concentrated first on what could be achieved most quickly: preventing unauthorized access to the most dangerous biological agents and toxins. In the United States, this meant stronger laws (the 2001 PATRIOT Act and 2002 bioterrorism bill) criminalizing biological weapons development and possession and regulating individuals and facilities that possess or use select biological agents or toxins. Over time, it also meant trying to keep pace with advances in technology (by screening gene sequence orders and including synthetic nucleic molecules in the *NIH Guidelines*) and with the diffusion of technology (by expanding threat reduction programs beyond the former Soviet Union). Internationally, it resulted in similar measures aimed at controlling access to specified biological agents and toxins (e.g., the 2001 UK antiterrorism law) and at strengthening

110. Arturo Casadevall, Terence S. Dermody, Michael J. Imperiale, Rozanne M. Sandri-Goldin, and Thomas Shenk, "On the Need for a National Board to Assess Dual Use Research of Concern," *Journal of Virology* 88 (12) (2014): 6535–6537.

the security of biological agents and toxins (e.g., UNSCR 1540, the OECD's biosecurity guidelines, and the INTERPOL bioterrorism prevention program).

On its own, each of the governance measures discussed in this chapter has a role to play in helping address one or more of the risks posed by dual-use biological materials, equipment, and related information. Together, they help create a web of prevention—against accidental harm to human beings or the environment from the research activities of legitimate scientists, as well as against deliberate harm to human beings, animals, or plants from the acquisition and use of biological agents or toxins by national governments, terrorists or other nonstate actors.

Few question the harm that could be caused by a dedicated national biological weapons program. A landmark 1993 U.S. Office of Technology Assessment proliferation study, for example, estimated that 1,000,000 to 3,000,000 deaths could result in a metropolitan area like Washington, D.C., if one hundred kilograms of anthrax spores were delivered as an aerosol from a single aircraft, under optimal dispersal and weather conditions, against an unprotected population.¹¹¹

Of course deaths are not the only measure of harm. A proliferator's use of biological weapons could also have a severe economic impact, depending on the agent used, the delivery conditions, and the availability of post-attack prophylaxis. CDC scientists estimated in 1997 that the cost of an aerosol release of anthrax spores in the suburbs of a major city could be up to \$26.2 billion for every one hundred thousand people exposed. This estimate included only the casualty-related costs: lost future earnings, hospitalization, treatment, and so on. It did not include the decontamination or other costs associated with remediation after an attack or the broader costs to businesses and the economy from the disruption caused by the attack.¹¹²

No terrorist group or nonstate actor is known to have the technical and operational capabilities required to prepare and disseminate a large quantity of anthrax or other biological agent in an aerosol form. However, a more rudimentary terrorist capability, like that considered in a 2004 U.S. Homeland Security Council scenario, would still result in significant human and economic costs. Under this scenario, five cities were attacked sequentially by a truck disseminating an anthrax aerosol from a concealed, improvised spraying device. These attacks resulted in an estimated 328,848 exposures, 13,208 fatalities, and a further 13,342 casualties.¹¹³

111. U.S. Congress, Office of Technology Assessment, *Proliferation of Weapons of Mass Destruction: Assessing the Risks*, OTA-ISC-559 (Washington, D.C.: U.S. Government Printing Office, 1993), 52–54.

112. A. F. Kaufmann, M. I. Meltzer, and G. P. Schmid, "The Economic Impact of a Bioterrorist Attack: Are Prevention and Postattack Intervention Programs Justifiable?" *Emerging Infectious Diseases* 3 (2) (April–June 1997): 83–94, <http://wwwnc.cdc.gov/eid/article/3/2/97-0201>.

113. Homeland Security Council, "Scenario 2: Biological Attack—Aerosol Anthrax," in *Planning Scenarios: Executive Summaries*, 2–1–2 (Washington, DC: Homeland Security Council, July 2004), www.globalsecurity.org/security/library/report/2004/hsc-planning-scenarios-jul04.htm#toc.

Proliferators and terrorists are not the only potential sources of harm. Today, scientists have the capacity to resurrect extinct pathogens, as U.S. scientists did in the case of the 1918 H1N1 virus, which is estimated to have killed some 50 million people during the 1918 pandemic. Scientists can also modify existing pathogens to make them more dangerous, as Dutch scientists did when they made the highly lethal H5N1 avian influenza virus capable of respiratory transmission in mammals. And they can use synthetic biology to create novel pathogens, either by reengineering existing pathogens or by assembling non-living biological components in novel ways. The accidental release of such pathogens could lead to devastating losses, human and financial.

This last source of potential harm is now overtaking biological weapons proliferation and bioterrorism as a primary concern. The latest U.S. government report on arms control treaty compliance, released in June 2015, raises questions about biological research and development activities in Russia and Iran and about whether North Korea and Syria still consider the use of biological weapons as a military option. But no country is charged with maintaining a biological weapons program.¹¹⁴ Similarly, eight years after the Commission on the Prevention of Weapons of Mass Destruction Proliferation and Terrorism predicted that a terrorist incident with biological weapons would likely occur by the end of 2013, concerns about bioterrorism gradually are being replaced by broader concepts of biorisk and health security, which bring together all biological threats, whether deliberate, accidental, or natural in origin.¹¹⁵

What may now be the most serious source of potential harm is also subject to the weakest governance efforts. Despite more than a decade of meetings, discussions, and reports, little progress has been made toward achieving effective national measures or common international policies for overseeing the most consequential areas of dual-use life sciences research. Proposals have been made by the Fink Committee, the NSABB, and others in the United States, as well as by science and ethics bodies in the United Kingdom, the Netherlands, and Germany to include all relevant research in the oversight process and to work to harmonize these policies internationally. But thus far, serious challenges have prevented these proposals from being adopted.

The first and perhaps most important challenge is from scientists themselves. Surveys from 2004 to 2007 found that U.S. scientists believe the select agent requirements pose a burden, affecting their ability to collaborate domestically and internationally and increasing the time and financial costs of conduct-

114. Department of State, “2015 Report on Adherence to and Compliance with Arms Control, Nonproliferation, and Disarmament Agreements and Commitments,” June 5, 2015, <http://www.state.gov/t/avc/rls/rpt/2015/243224.htm#BWC2>.

115. In addition to predicting a biological weapons terrorist attack, the commission also emphasized that, given the technical expertise required to carry out a large-scale biological attack, the United States should “be less concerned that terrorists will become biologists and far more concerned that biologists will become terrorists.” Commission on the Prevention of Weapons of Mass Destruction Proliferation and Terrorism, *World at Risk* (New York: Vintage Books, 2008), xv, 11; and Al Mauroni, “Gauging the Risk from Bioterrorism,” *War on the Rocks*, June 2014, <http://warontherocks.com/2014/01/gauging-the-risk-from-bioterrorism/>.

ing research.¹¹⁶ Fears that scientists would abandon much-needed life sciences research, including work with select agents, led many scientists to endorse self-governance of life sciences research as an antidote to government regulation. In the United States, this bias toward self-governance was a dominant feature of the NSABB's initial recommendations for oversight of dual-use research. As Paul Keim later observed in response to criticism over the NSABB's handling of the H5N1 manuscripts, "We're accused of being the bad guys. But most of what we've done is to push back against harsher regulations."¹¹⁷ Self-governance has also been at the heart of the limited policies that the U.S. government finally began to put in place in 2012, more than five years after the NSABB released its DURC oversight recommendations. Internationally, the challenge from scientists can be seen in the priority given by WHO and other science bodies to raising awareness among life scientists through training and education in biosafety and biosecurity as well as through voluntary codes of conduct. Scientists, the argument went, were in the best position to assess the risk of their own work, and creating a culture of responsibility would facilitate this process.

Many of the predicted negative effects on select agent research in the United States that helped encourage the push for self-governance of dual-use research do not seem to have been borne out. In a study published in 2010, investigators reported an overall stimulus to the field after 2002, based on an archival review of the number of *Bacillus anthracis* and Ebola virus "papers published per year, number of researchers authoring papers, and influx rate of new authors." Even after controlling for the increased funding available for select agent research after 2001, the study found an increased propensity for U.S. authors to begin select agent research. Domestic collaborations on select agent research also increased, as did international partnerships with certain foreign research institutions. The most significant negative effect was a loss of efficiency: the number of research papers published per million dollars of select agent funding declined two- to five-fold.¹¹⁸

In the United States, effective governance of biotechnology research has also been challenged by the sharp increase in biodefense spending since September 11. Much of this funding has been for research on medical countermeasures to protect against deliberate biological attacks. At the NIH, for example, funding for civilian biodefense, which excludes military biodefense spending, increased from a modest \$53 million in fiscal year (FY) 2001 to \$6.72 billion

116. As discussed in M. Beatrice Dias, Leonardo Reyes-Gonzalez, Francisco M. Veloso, and Elizabeth A. Casman, "Effects of the USA PATRIOT Act and the 2002 Bioterrorism Preparedness Act on Select Agent Research in the United States," *Proceedings of the National Academy of Sciences* 107 (21): 9556–9561.

117. Heidi Ledford, "Call to Censor Flu Studies Draws Fire," *Nature* 481 (7379) (January 5, 2012): 9–10.

118. Beatrice Dias et al., "Effects of the USA PATRIOT Act."

(budgeted) for FY 2016.¹¹⁹ In the first few years of this expansion, from 2001 to January 2005, the number of NIH-funded research grants on anthrax, plague, and other potential biological warfare agents jumped to almost five hundred from thirty-three between 1996 and 2000.¹²⁰ NIH also created a broad network of facilities to support its biodefense work, including eleven Regional Centers of Excellence (RCEs) for biodefense and emerging infectious diseases research; two national and twelve regional biocontainment laboratories for research requiring high levels of containment; and, most recently, fourteen Centers of Excellence for Translational Research (CETR) on medical countermeasures or related technology, which have replaced the RCEs. These laboratories were part of a broader expansion of U.S. high-containment laboratories from slightly more than four hundred in 2004 to an estimated fifteen hundred today.¹²¹ Across the U.S. government, funding for civilian biodefense exceeded \$90 billion from FY 2001 to FY 2016.¹²²

Although the Fink Committee singled out biodefense research as raising particular dual-use concerns, neither the oversight approach it recommended nor that proposed by the NSABB clearly apply to military biodefense work, given the decision by both to link dual-use oversight only to academic or other institutions formally subject to the *NIH Guidelines*. One of the RCEs established by NIH to conduct biodefense research, the Southeast RCE (SERCEB), initiated its own dual-use review process in 2004 for proposals it intended to fund. SERCEB identified two important issues in the course of its dual-use reviews: (1) that few investigators were aware of the dual-use problem; and (2) that technical expertise was critical to dual-use risk assessment. For these reasons, SERCEB cautioned against making researchers solely responsible for

119. Tara Kirk Sell and Matthew Watson, “Federal Agency Biodefense Funding, FY2013–FY2014,” *Biosecurity and Bioterrorism* 11 (3) (September 2013): 196–216; and Crystal Boddie, Tara Kirk Sell, and Matthew Watson, “Federal Funding for Health Security in FY2016,” *Health Security* 13 (3) (2015): 186–206. The figure of \$6.72 billion for FY 2016 includes \$1.37 billion for civilian biodefense and \$5.35 billion for multiple hazard and preparedness line items previously included as civilian biodefense funding by Boddie, Sell, and Watson.

120. *Biodefense: Next Steps: Hearing before the Subcommittee on Bioterrorism and Public Health Preparedness of the Committee on Health, Education, Labor, and Pensions, United States Senate, One Hundred Ninth Congress, First Session*, 109th Cong. (2005) (prepared statement of Anthony S. Fauci, Director, National Institute of Allergy and Infectious Diseases, National Institutes of Health), <https://www.gpo.gov/fdsys/pkg/CHRG-109shrg98930/pdf/CHRG-109shrg98930.pdf>.

121. As the Government Accountability Office has repeatedly pointed out, the exact dimensions of this laboratory expansion are not known, as only facilities that possess or transfer select agents must register with a government agency. Government Accountability Office, *High Containment Laboratories: Assessment of the Nation’s Need Is Missing*, GAO-13-466R (Washington, D.C.: GAO, February 25, 2013), <http://www.gao.gov/assets/660/652308.pdf>.

122. Sell and Watson, “Federal Agency Biodefense Funding, FY2013–FY2014”; and Boddie, Sell, and Watson, “Federal Funding for Health Security in FY 2016.” The \$90 billion figure includes \$78.82 billion reported in Sell et al. for FY 2001 through FY 2014; \$3.05 billion reported in Boddie Sell, and Watson for FY 2015 and FY 2016; and \$10.11 billion reported in Boddie Sell, and Watson for FY 2015 and FY 2016 “multiple hazard and preparedness” line items previously included as civilian biodefense funding by the authors.

identifying whether their own research posed dual-use risks, noting that dual-use awareness is highly subjective.¹²³

Classified biodefense work was explicitly exempted not only from the scope of the NSABB's work but, ultimately, from the dual-use oversight policies promulgated by the U.S. government in 2012 and 2014. According to the DOD, classified projects are not reviewed for dual-use concerns because the information and products from those projects are controlled through the classification process.¹²⁴ This reflects a profound misunderstanding of the purpose of dual-use review, which is to identify and mitigate risks not only from research results but from the research process itself. Whether DHS includes classified research projects in its dual-use review process is not known.

Finally, differing national perceptions of the risk from biotechnology research and of the importance of the issue in national policy have been a challenge to effective national and international governance efforts. For developing countries, the possible misuse of dual-use biological materials, equipment, or information is an abstract problem compared to the millions of people who die each year from naturally occurring diseases such as tuberculosis, malaria, and hepatitis. For these countries, the global diffusion of dual-use technology is critical not only to their ability to fight indigenous disease threats but to their economic and technological development more broadly. Concerns about the potential impact of biotechnology research are seen as a preoccupation of Western countries and, in some cases, as a veiled excuse for technology denial.

While developing countries generally do not share the West's dual-use concerns, even developed countries have been slow to embrace effective governance of all aspects of the dual-use problem. Long-standing biosafety measures coupled with efforts aimed at preventing national biological weapons programs were supplemented after September 11, 2001, with other initiatives designed to deny terrorists access to dangerous pathogens and toxins or equipment that could enable their production. National oversight of biotechnology and other research being conducted as part of the evolving revolution in the life sciences has been much more limited, emerging in only a few countries. Efforts to develop common international policies and procedures for overseeing the most consequential areas of dual-use research have been even less successful. This has been the case despite the fact that virtually every report by a scientific body on the dual-use biotechnology research issue over the past decade has underscored the international dimension of the problem and the corresponding need for an international response. From the Fink Committee to the British Royal Society to the WHO, the importance of harmonized international standards for managing dual-use research of concern has been repeatedly highlighted.

123. E. Megan Davidson, Richard Frothingham, and Robert Cook-Deegan, "Practical Experiences in Dual-Use Review," *Science* 316 (5830) (June 8, 2007): 1432–1433.

124. Walter B. Chase III, CTR OSD OUSD ATL, personal communication, June 19, 2015.

Many important steps have been taken over the past half-century to try to respond to the complex and multifaceted risks posed by dual-use biological materials, equipment, and related information. Although direct links cannot be drawn between specific measures and outcomes, most observers are likely to agree that, taken together, these measures have contributed to progress in preventing the acquisition of biological weapons, controlling access to biological weapons-related capabilities, and promoting the safe handling of dangerous biological materials. Most of these measures emerged in response to specific controversies or concerns. Opposition to the use of herbicides and riot control agents in Vietnam contributed to the conclusion of the BWC. Fears of recombinant DNA technology led to the *NIH Guidelines* and to EU directives controlling GMOs. Western assistance to Iraq's chemical and biological weapons programs resulted in the creation of the AG and the adoption of national controls on biological weapons-related capabilities. And post-Cold War worries about the proliferation of material and expertise from the former Soviet weapons program stimulated the CTR.

The September 11 terrorist attacks and subsequent anthrax letters were directly responsible for a wide array of other national and international measures. These include the U.S. select agent regulations and biological weapons criminalization provisions, the UK antiterrorism act, Danish and Israeli laws controlling dangerous pathogens and high-consequence research, and the Canadian law regulating human pathogens. Internationally, these measures include UNSCR 1540, the G8 Global Partnership, the Proliferation Security Initiative, the INTERPOL bioterrorism prevention program, and the WHO and OECD biosecurity guidelines.

Even the limited measures that have been adopted in the United States to manage the risks from dual-use research emerged only after other controversies. The NSABB provided its recommendations on dual-use oversight in June 2007 but not until March 2012 did the U.S. government publish its first policy on the issue—and only then after controversy had erupted over the U.S. and Dutch H5N1 projects, which had been funded by NIH without considering dual-use concerns. The U.S. government's September 2014 institutional DURC policy was released in the midst of an unprecedented debate within the scientific community over GOF research and after a summer of revelations regarding U.S. laboratory incidents involving dangerous pathogens.

Given the wide range of challenges to effective oversight, it is difficult to imagine that policy-makers in the United States or other countries will support a robust approach to oversight of DURC in the absence of an event that makes effective oversight a more salient political issue. But perhaps that is too pessimistic. It is possible that the “deliberative process” now underway in the United States to develop a policy on the conduct and funding of GOF research will result in stronger oversight measures, at least for this particular type of research. In the near term, the most direct and expeditious way of achieving this is by adding GOF studies of concern to the restricted experiments section of the select

agent regulations, which not only outline clear oversight requirements but are legally based. The possibility that other types of experiments might require more stringent scrutiny and need to be added to the restricted experiments was in fact explicitly acknowledged by both HHS and USDA in their regulations.¹²⁵

Ultimately, however, more robust oversight arrangements need to be adopted for other types of DURC as well. To encourage compliance and adequate funding for implementation, the oversight requirement should be mandatory. To make it more effective, it should apply to all relevant research, whether academic, industry, or government, including classified biodefense or other projects. And to help researchers determine whether their proposed work is subject to oversight, the affected categories of research should be clearly defined. The Danish approach to dual-use research is one example of how this could be done: outlining the basic obligation, including the scope of application, in legislation but using executive actions (such as executive orders and policy guidance), which provide more flexibility for responding to technological developments, to enumerate the implementation details.

The oversight arrangements also should be coordinated by an independent federal entity, as the biosecurity working group established by President George W. Bush recommended in 2009. To build confidence, it should consult with but not be based within any of the government agencies that are responsible for funding or conducting dual-use research. It should oversee and assess the progress and impact of the oversight requirements and, as the GOF ethical study suggested, provide an additional level of review of proposed research projects that raise the most serious concerns.

Finally, consistent with the globally distributed nature of life sciences research, the U.S. government should seek to establish common DURC rules and procedures internationally. This means going beyond mere discussions of biosecurity and biosafety in various international fora, as has been done for many years, and developing a concrete strategy for pursuing international harmonization of laws, regulations, and policies for the most consequential types of life sciences research. As the Fink Committee pointed out, this is essential if the risks from dual-use research are to be managed effectively. It also is essential to avoid U.S. scientists being put at a competitive disadvantage in relation to life sciences researchers in other countries.

125. This idea comes from Richard Ebright. See <https://fas.org/blogs/secrecy/2015/10/restricted-experiments/>.

Chapter 3

Governance of Information Technology and Cyber Weapons

Herbert Lin

FRAMING THE PROBLEM

In the twenty-first century, information is the key coin of the realm. Nations rely on information and information technology (IT) to ever-increasing degrees. Computers and networks are integral for most business processes, including payroll and accounting, tracking of sales and inventory, and research and development (R&D). Delivery of food, water, energy, transportation, healthcare, and financial services all depend on IT, which is itself a major sector of the economy. Modern military forces use weapons that are computer controlled. Coordination of actions of military forces depends on networks that allow information about the battlefield to be shared. Logistics for both civilian and military activities depend on IT-based scheduling and optimization.

But bad guys also use IT. Criminals use IT to steal intellectual property and commit fraud. Terrorists use IT for recruitment, training, communications, and public outreach, often in highly sophisticated ways, although to date they are not known to have used IT to commit destructive acts. And as the U.S. government is exploring various ways of using cyberspace as an instrument of national policy to create political, military, diplomatic, economic, or business advantages, other nations—some of them with interests that do not align with those of the United States—are doing the same.

One commonly used definition of *dual-use technology* is “technology intended for beneficial purposes that can also be misused for harmful purpos-