

Controlling Dangerous Pathogens

*A Prototype
Protective
Oversight
System*

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..... Introduction

As has become increasingly evident in recent years, advances in biology are posing an acute and arguably unprecedented dilemma. The same basic science that could in principle be highly beneficial could also be enormously destructive, depending on how it is applied. Although the scope of actual consequence remains uncertain, the potential is clearly extraordinary with the health of individuals, the stability of societies and the viability of the global ecology all apparently at stake.

Since compelling good and appalling harm cannot be disentangled at the level of fundamental science, a burden of management is being imposed that human institutions are not currently prepared to handle. The dilemma itself has been exemplified in several widely noted experiments¹ and professionally acknowledged in reports issued by the United States National Academies of Science (NAS) and by the British Royal Society.² Not surprisingly, however, and perhaps inevitably, efforts to devise an effective response are still at an embryonic stage. The proposals separately advanced by the two scientific societies are directed at their own communities and are largely voluntary in character. Those are natural initial steps but would not alone provide robust global protection.

In an effort to encourage productive discussion of the problem and its implications, this monograph discusses an oversight process designed to bring independent scrutiny to bear throughout the world without exception on fundamental research activities that might plausibly generate massively destructive or otherwise highly dangerous consequences. The suggestion is that a mandatory, globally implemented process of that sort would provide the most obvious means of protecting against the dangers of advances in biology while also pursuing the benefits. The underlying principle of independent scrutiny is the central measure of protection used in other areas of major consequence, such as the handling of money, and it is reasonable to expect that principle will have to be actively applied to biology as well.

The monograph outlines an advanced oversight arrangement, provisionally labeled the Biological Research Security System (BRSS), which is designed to help prevent destructive applications of biology, whether inadvertent or deliberate. The arrangement is put forward with full realization that meaningful

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protection can only be achieved by imposing some constraint on freedom of action at the level of fundamental research, where individual autonomy has traditionally been highly valued for the best of reasons. Constraints of any sort on research will not be intrinsically welcome and will have to demonstrate that the protection provided justifies the costs entailed. A great deal of conceptual innovation, legal specification, institutional design and political accommodation would admittedly be required to establish such an oversight process, and there is very little precedent to work with. Because of the demands imposed and the inconvenience involved, the monograph concedes that human societies after due reflection might choose at least initially to accept lesser standards of protection and it discusses more limited incremental measures that might be undertaken. The central contention, however, is that the eventual outcome should be a fully considered choice and not the default result of inertia or neglect.

..... Context of the Problem

Because the potential consequences of advanced biology are so extraordinary, the problems of management posed are arguably becoming one of the most consequential problems of public policy ever encountered. Knowledge of fundamental life processes has progressed to the point that extensive human intervention in the course of natural evolution has apparently become feasible, not only to determine particular outcomes but to redirect the process itself. One can credibly imagine the eradication of a number of known infectious diseases. One can also credibly imagine the deliberate or inadvertent creation of new pathogens dramatically more dangerous than those that have naturally evolved. One can similarly imagine both therapeutic and destructive applications affecting basic features of cognitive, emotional, and reproductive activity. Hundreds of millions of lives might be enhanced, salvaged, manipulated, degraded, or terminated depending on how the same basic knowledge is applied. Little of that potential has yet been accomplished but none of it can be dismissed as fantasy.

Unfortunately, the capacity to alter basic life processes is not remotely matched by the capacity to understand the extended implications. For the foreseeable future, moreover, that imbalance is much more likely to accelerate than to diminish. It is not realistic to expect that the current momentum in molecular biology, in particular, will extend to the many other disciplines necessary to assess the consequences for the evolutionary process as a whole. As a result, the human species is relentlessly acquiring power far in excess of its vision and this is thereby posing monumental problems of prudential judgment – problems that society is not yet conceptually or institutionally equipped to handle. Those are the stark facts of the situation.

Admittedly, facts of that character and magnitude are not readily absorbed. They are being explored by some groups, but the institutions that would be responsible for managing the problem have not seriously acknowledged the situation nor fathomed the implications. They are understandably reluctant to admit problems they do not know how to solve, particularly if the requirements are as extensive and as radical as they appear to be in this case. The dominant inclination is to reduce even the most monumental questions to terms that can be managed by gradual adjustment. It is reasonable to assume that current management of advanced biology is in the early stages of such a process. It is also reasonable to assume that the adjustment eventually required will be much more extensive than currently admitted and the schedule on which it occurs more rapid.

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It is important that those who are willing to assume that much begin to anticipate the innovations likely to be necessary.

In current public discussion of the subject, fear of terrorism has been a particularly prominent theme, especially in the United States in the aftermath of the 2001 anthrax letters. That concern reflects a circumstance of obvious importance. Any individual or organization dedicated to destruction but only capable of undertaking small-scale operations might plausibly choose advanced biology as the instrument of choice. There is no indication that anyone has ever attempted wanton destruction of that sort, and there would be very appreciable practical difficulties and risks involved. Nonetheless, an attack with an especially virulent pathogen might in principle induce a disease epidemic sufficient to disorganize an entire society or degrade an entire economy. Otherwise a clandestine operation could only accomplish genuinely massive social destruction by the use of nuclear explosives, and the fissile material required is currently much more elaborately protected than are pathogens. Biotechnology is one of only two technologies that truly deserve the label “agent of mass destruction” and it is by far the more accessible of the two.

For all its current prominence, the threat of bio-terrorism, including state-sponsored terrorism, is not the exclusive or even the primary source of danger. As a practical matter, terrorist organizations by their nature are forced to evade detection and thus cannot independently generate the fundamental science required to perpetrate acts of mass destruction – as distinct from acts of mass sensation. The basic knowledge required would have to be extracted from the

legitimate research community, and the people involved would have to have been trained within that community. At the moment there is very little organized protection against the diversion of legitimate science to malicious purpose; more robust protection can be and almost certainly will be devised. In so doing, it will be necessary to address the deeper problem of inadvertence.

Precisely because the rate of discovery in biology is far outrunning the more integrated science required to assess the extended social effects, there is considerable danger that legitimate scientists pursuing compelling research ideas will initiate chains of consequence they cannot visualize and do not intend. The extensive and necessarily open process of medical and agricultural research is regularly producing results that are compellingly beneficial but that also, as an unavoidable by-product, could be exceedingly dangerous. Given that situation, protective standards will have to be developed for their own sake within the legitimate research community. That is the first, most important and most promising line of defense against deliberate maliciousness. If that line of defense is not constructed, nothing else will be effective and literally everyone increasingly will be in danger.

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The relevant biomedical research community is very extensive and globally distributed. More than a million scientific articles are published every year and seminal results are generated in all parts of the world. Information flows rapidly among leading-edge scientists and knowledge of fundamental developments also transfers rapidly to those in training. Given that situation, it seems obvious that adequate measures of protection against the misuse of biological research would have to be devised globally, not just for academic researchers but also for those working in commercial and government labs. However, current regulation of advanced biology is conducted primarily by national governments and is principally concerned with the localized containment of dangerous pathogens, the safety of research personnel, the treatment of research animals, and the preparation of distributed products such as drugs and vaccines. As discussed below, there have been as yet only embryonic efforts to organize prudential judgment at the outset of fundamental research regarding the extended implications of the knowledge to be generated. The legitimate fear of interfering with the process of scientific discovery has minimized oversight at that stage. Moreover, in areas considered to be relevant to weapons application, national governments have imposed security classification and are actively exploring the destructive application of biology under the justification of “threat assessment.” That practice is intensifying suspicion among the many governments already inclined to be suspicious of one another.

Particularly in the United States, reaction to the 2001 terrorist events has strongly reinforced the instinct to focus on national responses. New terrorism legislation adopted in May 2002 imposed registration requirements on individuals and institutions that possess selected pathogens declared to be dangerous, under terms that have made national identity a major criterion for access. The fact that registration requirements would have to be globally enacted to be effective appears to have received no consideration. There has also been a dramatic increase in US government funding for bio-terrorism and bio-defense research, with little recognition of the need to accompany that effort with a protective oversight process. Bioterrorism funding at the National Institutes of Health (NIH), for example, has grown from a modest \$53 million in fiscal year 2001 to \$1.9 billion (requested) in fiscal year 2007.³ The Department of Homeland Security is also playing a leading role in this area, establishing, as part of its multi-million dollar National Biodefense Analysis and Countermeasures Center (NBACC), a new Biothreat Characterization Center (BTCC) to conduct studies and experiments to better understand current and future biological threats.⁴ The mission of NBACC is “to provide the nation with the scientific basis for awareness of biological threat and attribution of their use against the American public” by:

- Understanding current and future biological threats, assessing vulnerabilities, and determining potential impacts to guide the development of biodefense countermeasures; and,
- Providing national capability to conduct forensic analysis of evidence from bio-crimes and terrorism to attain a “biological fingerprint” to identify perpetrators and determine the origin and method of attack.⁵

Construction of a new facility for NBACC at Ft. Detrick began in June 2006. The 160,000 square foot facility will house the Biological Threat Characterization Center and the National Bioforensic Analysis Center (NBFAC). It will include over 70,000 square feet of laboratory space, 20% of which will be built to BL-4 standards.

This reliance on national measures was also reflected in the 2001 US decision, over broad international objection, to block efforts to develop a compliance protocol for the Biological Weapons Convention (BWC). Within the current administration especially, the largely implicit but powerfully entrenched assumptions are that the danger derives mainly from hostile foreign sources and that it can be managed primarily by controlling access to dangerous pathogens themselves. Understandable and perhaps inevitable as that reaction may be in political and emotional terms, it is highly dysfunctional in terms of scientific reality and will almost certainly intensify the underlying peril.

A collision between attitude and circumstance is a familiar human drama. It is unusually pronounced in this case but not unique. Over the longer term it is reasonable to expect that circumstances as compelling as those biology is creating will eventually conquer even the most recalcitrant attitudes, but obviously there are major questions as to how soon that might happen and in what manner. Although dysfunctional attitudes are often abandoned only in reaction to compellingly painful experience, one cannot responsibly wait for such experience in this case. Those who are able to understand the situation clearly have some responsibility to visualize an appropriate response. Although the consequences of advances in biology might turn out to be less dramatic than they currently seem, it is nonetheless necessary to explore the implications of current projections. Since that exploration will require very extensive, very demanding, and doubtless time-consuming discussion, it is quite important to begin.

The basic method of protective oversight will have to be based on systematic information disclosure and informed peer review.

In broad outline the requirements of managing advanced biology are not difficult to discern. The hard part, actually, is taking the problem seriously enough to be willing to examine the fairly obvious answer. It can be presumed that inherently dangerous areas of biological research will have to be subjected to a much more systematic process of protective oversight than is yet practiced in any country. That will have to be done globally and therefore will have to be globally formulated and globally implemented. The basic method of protective oversight will have to be based on systematic information disclosure and informed peer review. In areas of research capable of having massive consequence, it is truly a vital matter to bring independent, adequately informed, and broadly representative scrutiny to bear. No individual or research team, however competent, honorable, and patriotic, should carry the burden or be given the authority to make research decisions that might put an appreciable fraction of the human species as a whole at risk without subjecting themselves to independent oversight in advance and throughout the course of their work.

The judgments required in such an oversight process cannot be entirely derived from any set of general guidelines, although common risk-benefit assessment criteria would be an essential feature of the process. Valid judgments about the balance of benefit and risk in any specific instance can only be made in detailed context by people capable of understanding both the scientific issues in question and the social consequences. That implies a broadly representative group, including scientists, security and public health experts and public representatives not directly involved in the research in question. They would have to operate through oversight bodies of extraordinary, indeed unprecedented, credibility. That credibility would have to be established not only by the quality of the individuals but also by a highly refined specification and limitation of their powers.

The oversight system would be tiered, matching the degree of risk with the information disclosure and review requirements. In the prototype Biological Research Security System outlined in this paper, local oversight bodies would be charged with reviewing research projects of potential concern being proposed by licensed researchers working at licensed facilities. Such research encompasses those activities that may increase the destructive potential of biological agents that otherwise would not be considered a threat. National oversight bodies would be responsible for research activity of moderate concern, such as work with anthrax and other agents already identified as having biological weapons potential. Both the local and national oversight bodies would operate on the basis of internationally agreed standards. An international body would be charged with approving and monitoring all research projects of extreme concern. That authority would be narrowly focused only on those research activities that could put an appreciable fraction of the human species at risk, such as work with smallpox or a yet more lethal contagious pathogen. Ultimately, the oversight process would have to be extended beyond individual projects involving consequential work with pathogens to address broader advances in immunology and neurobiology, for example, which may have little to do with pathogens.

Biological Research Security System
International Oversight <i>Activities of Extreme Concern</i>
National Oversight <i>Activities of Moderate Concern</i>
Local Oversight <i>Activities of Potential Concern</i>
No Oversight <i>All Other Research</i>

These oversight provisions have some precedent in current national regulatory practice. The entire arrangement constituted on an international basis has no close precedent, however, and there are many people who would summarily declare it to be impossible. Perhaps in the end it will be, but in that case the consequences are likely to be very dire indeed. If one is determined to be a hardheaded realist in this situation, it is prudent to anticipate some response commensurate with the magnitude of what is at stake. Protective oversight is the prime candidate. Whatever the eventual outcome, it will have to be seriously explored.

..... Current State of Oversight

Various treaties, laws, regulations, and other legal and political instruments govern the handling and use of pathogens. Few of these controls address the research process itself, and fewer still require an independent evaluation of the possible security and public health consequences of a given biological research project *before* the work is undertaken. This section looks at some of the more important oversight arrangements – on the international level, within the US, within the UK, and as regards the special case of smallpox research – in terms of their scope, limitations, and potential relevance to a future Biological Research Security System.

International Controls

The most significant development in the history of international efforts to prevent the misuse of biology for hostile purposes was the conclusion of the 1972 Biological Weapons Convention, which prohibits the development, production, and possession of biological agents or toxins for other than prophylactic, protective or other peaceful purposes. The BWC imposes no limits, however, on research involving biological agents and contains no provisions for verifying compliance with its obligations. In an effort to help fill these gaps, BWC States Parties agreed at past treaty review conferences that certain open-air tests fall within the scope of the BWC's prohibitions and that basic research in the biological sciences should generally be unclassified. They also adopted a series of confidence-building measures requiring the exchange of information on specific types of biological research activities and facilities.

As noted above, efforts to move beyond these politically binding arrangements toward a more robust, legally binding BWC compliance protocol collapsed in 2001, with the US citing concerns about the potential impact of the proposed declaration and inspection measures on confidential business and national security information. Although both the European Union (EU) and many moderate non-aligned (NAM) countries believed that the draft protocol contained adequate provisions for protecting such sensitive information, the Bush administration disagreed, and scuttled the protocol because of this issue. The other major stumbling block was the NAM's insistence on technical and economic assistance, including the efforts of some to try to use the protocol to eliminate existing controls on the export of biological-related materials.

To help fill the void left by the failure of the protocol negotiations, BWC States Parties agreed in November 2002 to a new process, whereby one experts meeting and one political meeting would be held each year to discuss and promote *common understanding* and *effective action* on certain agreed issues. At the insistence of the US, however each experts meeting was only two weeks long and each political meeting a week. In addition, participants were limited to

exchanging information on the agreed topics and had no decisionmaking authority. In 2003, States Parties discussed national implementing legislation and the security and oversight of pathogens. In 2004, they focused on the issues of disease surveillance and investigations of alleged use of biological weapons and suspicious outbreaks of disease. In 2005, scientific codes of conduct were discussed. These meetings helped keep the issue of strengthening the BWC on the international agenda and encouraged States Parties to share information about their national activities in each of these areas. But because of the limitations placed on the process by the US, no guidelines or best practices could be agreed and recommended for adoption by States Parties.

At the Sixth Review Conference in December 2006, States Parties agreed to hold a new round of annual experts and political meetings between 2007 and 2010. Of particular importance are the topics to be considered in 2008: national, regional and international measures to improve biosafety and biosecurity; and oversight, education, and other measures aimed at preventing the misuse of advances in the biosciences and biotechnology research. Unfortunately, the time for the experts meeting on these issues was halved, from two weeks to one. Moreover, the US again rejected efforts to give these inter-sessional meetings decisionmaking authority, thus raising questions about their ultimate impact.⁶

Other international instruments also have been adopted to deal with concerns about the environmental and public health implications of advances in biotechnology, in particular.⁷ In 1992, a Code of Conduct for the Release of Organisms into the Environment was developed by the United Nations Industrial Development Organization (UNIDO).⁸ The UNIDO Code, which is voluntary in nature, called for the establishment of national risk assessment and decision-making structures to provide scientific judgments concerning the use and release of genetically modified organisms (GMOs). It also called for linking safety precautions and monitoring arrangements to the level of assessed risk, based on the biological properties of the organism and the receiving environment. Under the 1992 Biodiversity Convention, countries are legally required to regulate the use and release of genetically modified organisms that could have an adverse impact on biodiversity and to provide information on their regulations to other States Parties to whom such organisms are being transferred.⁹ The International Technical Guidelines for Safety in Biotechnology, which were adopted by the United Nations Environment Programme (UNEP) in December 1995, also emphasize the importance of effective oversight of activities involving organisms with novel traits. Under the UNEP Guidelines, such oversight is defined as including risk assessment, disclosure of relevant information and careful record keeping. It can also include prior notification of certain contained uses and releases of organisms with novel traits and prior approval by relevant national authorities.¹⁰

Finally, the World Health Organization published the first edition of its *Laboratory biosafety manual* in 1983 to provide guidance to countries on the safe handling of pathogenic microorganisms. A third edition was published in 2004 that included new sections on biosecurity, risk assessments, and the safe use of recombinant DNA technology.¹¹

US Controls

As on the international level, both security considerations and environmental and public health concerns have shaped US policy on the handling and use of dangerous pathogens. Prior to the conclusion of the BWC, President Richard Nixon decided, in 1969, that the US should unilaterally renounce the possession of biological weapons and confine the US biological weapons program to research and development for defensive purposes only. But this policy, which is still in effect, permits research into those offensive aspects of biological agents necessary to determine defensive requirements, thus underscoring the difficulties of distinguishing between legitimate and illegitimate activities in this area.¹²

Over the past decade, a variety of measures have also been adopted to strengthen controls on access to dangerous pathogens. Under the Antiterrorism and Effective Death Penalty Act of 1996, any facility involved in the *transfer* of a “select agent” from a list of human pathogens developed by the Centers for Disease Control and Prevention (CDC) must register with CDC and notify it of all proposed transfers.¹³ In the aftermath of the anthrax letters, new legislation was adopted in October 2001 prohibiting the knowing possession of any biological agent, toxin or delivery system that is not reasonably justified for prophylactic, protective, bona fide research, or other peaceful purposes. The law, known as the USA Patriot Act also makes it a crime for certain restricted persons, including illegal aliens and individuals from terrorist-list countries, to possess, transport, or receive select agents.¹⁴

In May 2002, additional bio-terrorism legislation extended the registration requirement for facilities that *transfer* select agents to include facilities that *possess* select agents as well. Under the Public Health Security and Bioterrorism Preparedness and Response Act of 2002, government background checks are required for anyone that is to be given access to select agents. In addition, the Department of Health and Human Services (HHS) is required to develop a national database of registered persons and the select agents they possess, including strain and other characterizing information if available, and to carry out inspections of relevant facilities. The US Department of Agriculture (USDA) is required to develop parallel registration, security, record keeping, and inspection measures for facilities that transfer or possess specific plant and animal pathogens.¹⁵ Under the final regulations to implement the legislation, all affected facilities are also required to develop a biosafety plan, drawing on the biosafety and biosecurity standards for work with pathogens outlined in the CDC manual, *Biosafety in Microbiological and Biomedical Laboratories*.¹⁶

Since 1976, guidelines have been issued by the NIH Recombinant DNA Advisory Committee (RAC) to ensure the safety of research involving recombinant DNA molecules and organisms and viruses containing such molecules. The original NIH Guidelines prohibited six types of experiments. Over time, however, these prohibitions were replaced by a system of tiered oversight and review, in which Institutional Biosafety Committees (IBCs) and Institutional Review Boards (IRBs) at individual facilities displaced the RAC as the primary oversight authority for most categories of regulated research.¹⁷

Although the NIH Guidelines formally apply only to research conducted at institutes in the US and abroad that receive NIH funding for recombinant DNA

research, it is widely believed that many private companies and foreign researchers follow the Guidelines voluntarily.¹⁸ A 2004 study by the Sunshine Project of US-based IBCs, however, revealed that scores of US biotechnology companies, including some three dozen companies conducting biodefense research for the US government, had no IBC registered with NIH and many of the university and other IBCs that were registered either did not meet or issued blanket approvals rather than review each specific project.¹⁹ No comparable study has been done of US-based IRBs and none seems likely given privacy considerations. Nevertheless, federal regulations governing IRBs are far more elaborate than those that currently exist for IBCs, containing not only specific requirements for IRB approval of human subject research, including for assessing the risks and benefits of such research, but also for documenting the results of IRB deliberations.

Under the current NIH Guidelines, only two categories of laboratory research involving recombinant DNA technology require oversight by the NIH itself. The first, “Major Actions,” cannot be initiated without the submission of relevant information on the proposed experiment to the NIH Office of Biotechnology Activities (OBA) and require IBC approval, RAC review, and NIH Director approval prior to initiation. These include experiments that involve the “deliberate transfer of a drug resistance trait to microorganisms that are not known to acquire the trait naturally if such acquisition could compromise the use of the drug to control disease agents in humans, veterinary medicine, or agriculture.” The second class of experiments requiring IBC approval and NIH/OBA review prior to initiation involves the cloning of toxin molecules with LD₅₀ of less than 100 nanograms per kilogram body weight.²⁰ Under the new regulations to implement the May 2002 bioterrorism bill, the Secretary of HHS must also approve experiments that fall under these categories if they involve the use of agents or toxins on the select agent list, and the Administrator of USDA’s Animal and Plant Health Inspection Service must approve them if they involve agents or toxins on USDA’s control lists.²¹ Unlike the NIH Guidelines, however, these requirements are both legally binding and apply to all entities conducting the relevant research, not just to those receiving funding from NIH for recombinant DNA research.

Other types of research may soon be added to the NIH Guidelines and thus subject to IBC and, in some cases, possibly national-level review. In its October 2003 report, “Biotechnology Research in an Age of Terrorism,” an expert panel convened by the US National Academy of Sciences, under the chairmanship of MIT professor Gerald Fink, recommended giving IBCs responsibility for considering the security implications of seven categories of dual-use research.²² These “experiments of concern,” as the Fink Committee called them, included those that would:

- demonstrate how to render a vaccine ineffective;
- confer resistance to antibiotics 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 Fink Committee also recommended the development of education programs for scientists on the dual-use issue; pre-publication review of manuscripts by scientists and scientific journals; enhanced communication between the national security, law enforcement and life sciences community on threat assessment and countermeasures development; and international harmonization of efforts to manage the risks from dual-use research. To help guide these efforts, the Committee also called for the establishment of a National Science Advisory Board for Biodefense within HHS.

In March 2004, the Bush administration responded to the Fink Committee report, announcing the creation of a new government body to advise US government agencies on how to reduce the risk that legitimate research will be misused for hostile purposes.²³ The main functions of this new body, known as the National Science Advisory Board for Biosecurity (NSABB), include:

- developing criteria for identifying dual-use research and research results;
- developing guidelines for local (IBC) oversight of dual-use research, including the risk/benefit analysis of such research;
- advising on criteria and processes for referring research to the NSABB for additional guidance;
- responding to requests from institutions for advice on research that has been denied by an IBC;
- providing recommendations on the development of a code of conduct for scientists and laboratory workers;
- providing recommendations on the development of mandatory biosecurity education and training programs for scientists and laboratory workers at federally funded institutions;
- advising on national policies governing the dissemination of research results, including publication; and
- recommending strategies for coordinated international oversight of dual-use research.

At its first meeting, at the end of June 2005, the NSABB agreed to establish working groups in five initial areas: criteria for dual-use research; communication of research results; codes of conduct; international collaboration; and synthetic genomics. A sixth working group, on the critical issue of oversight of dual-use research, was not added until a year later. At the Board's July 2006 meeting, the NSABB also approved the initial work done by its criteria, communications, and codes working groups. In all three areas, however, the results were limited at best.²⁴ The criteria for identifying dual-use research of concern, for example, were largely a reformulation of the Fink Committee's experiments of concern. Like the Fink Committee approach, the NSABB criteria are too broad, and thus likely to capture a wide swath of research. The criteria also focus exclusively on research activities, rather than a combination of agents and activities, and fail to distinguish between levels of risk. Finally, the definition of dual-use research of concern that accompanies the criteria – “research that, based on current understanding, can be reasonably anticipated to provide knowledge, products or technologies that could be directly misapplied by others to pose a threat to public health, agriculture, plants, animals, the environment, or material” – both fails to consider the problem of inadvertence and requires a judgment about the likelihood that the research results could be misused. In short, the NSABB draft criteria are unlikely to

provide an adequate basis for identifying whether specific research projects pose potential dual-use concerns and thus should be subject to independent oversight.

At the Board's October 2006 meeting, the newly established oversight working group outlined its initial ideas.²⁵ Of particular interest were the key features identified by the working group for the oversight system. They include the following:

- institutional review of the scientific, ethical, and possible social consequences of dual-use research and research findings;
- the use of risk assessment and risk management principles in the review process, with the degree of institutional oversight linked to the assessed risk;
- a process for appealing the decisions of the institutional review body; and,
- the training of scientists, reviewers and others who are involved in dual-use research.

Unfortunately, at least in its initial formulation, the working group suggested that compliance with the oversight system should be mandatory for federally funded institutions but voluntary for others. Classified research already is exempt from the NSABB's purview by its charter. If research at private companies and other institutions that do not receive federal funding is also exempted from mandatory oversight, the system being proposed by the NSABB will have limited effect.

Development of Oversight Arrangements in the US

- 1976 NIH guidelines establish institutional biosafety committees (IBCs) to provide local oversight for recombinant DNA work. The Recombinant DNA Advisory Committee (RAC) at NIH reviews "Major Actions," including some transfers of drug resistance and the cloning of toxin molecules with an LD₅₀ of less than 100 ng/kg body weight.
- 1996 Registration requirement and notification to the CDC for any transfer of a human pathogen on the select agent list
- 2001 Legal prohibition on knowing possession of any biological agent, toxin or delivery system not reasonably justified for prophylactic, protective, bona fide research, or other peaceful purposes. Criminalizes possession and transfer of select agents by restricted persons, including illegal aliens and individuals from terrorist-list countries.
- 2002 Extension of the registration requirements to facilities that possess select agents. Government background checks required for anyone having access to select agents. HHS required to develop a national database of registered persons and select agents they possess. USDA required to keep similar registration, security, record keeping, and inspection measures for facilities that transfer or possess specific plant and animal pathogens. The Secretary, HHS and Administrator of APHIS (USDA) must approve certain experiments with agents or toxins on the select agent or control list, respectively.
- 2004 National Science Advisory Board for Biosecurity established to advise US government agencies on how to reduce the risk that legitimate research will be misused for hostile purposes.

In addition to the NIH Guidelines, there are also a number of other US government regulations concerning the handling or use of pathogens. Even those that govern research with pathogens, however, focus on their transfer or release rather than laboratory-based activities. For example, under USDA regulations, any person wishing to import, move, or release genetically engineered plant pests within the US must either submit a notification to or obtain a permit from USDA before proceeding with the proposed activity. A USDA permit also is required for the import of microorganisms that can cause infectious, contagious, or communicable diseases in poultry or livestock.²⁶ Under Environmental Protection Agency (EPA) regulations, small-scale tests of certain genetically modified microbial pesticides must be notified to, and receive approval from, EPA. An experimental release application must also be filed with EPA for certain research and development activities with microorganisms for commercial purposes.²⁷ EPA also administers the National Environmental Policy Act, under which federal agencies are required to prepare detailed environmental impact statements assessing both the risks of their proposed activities and efforts to mitigate risk through facility design and laboratory practices.²⁸ The US Army also regulates research and other activities with biological agents under the Biological Defense Program, requiring audit trails of all agent shipments and the use of simulants in all open-air tests unless the Secretary of Defense determines that testing with actual agents is necessary for national security reasons.²⁹

UK Controls

The United Kingdom has what may be the most robust oversight arrangements in place for research and other activities involving pathogens. Unlike the US, the UK government has direct legal authority over relevant research anywhere in the country, and does not have to rely on funding mechanisms to help bring scientists into their oversight systems.

Following the September 11 terrorist attacks, the UK enacted new anti-terrorism-related controls on pathogens similar to those adopted in the US. Under the Anti-Terrorism, Crime and Security Act passed in October 2001, facilities that possess or plan to possess specified human pathogens are required to notify the government and to comply with any reasonable security enhancements that may be imposed after an inspection of the site. The bill also requires facility personnel to comply with official requests for information about security measures at their facility and about persons who have or are proposed to have access to controlled pathogens. It also contains provisions for background checks and gives the government the authority to deny individuals access to controlled pathogens or the facilities in which they are held. The bill allows but does not require the same notification and other requirements to be extended to animal and plant pathogens and plant pests. The UK anti-terrorism legislation does not, however, require prior review of research projects involving these controlled pathogens.³⁰

Since the 1970s, the UK has also established a variety of controls on the handling and use of genetically modified organisms. As with the NIH Guidelines, the UK system was initially voluntary, with the categorization of experiments covered by the notification guidelines broadly similar to that in the

US.³¹ In 1992, a new Genetically Modified Organisms (Contained Use) Regulation was issued to implement the tighter controls on GMOs being developed in the European Union (EU). This regulation, as revised in 2000, requires a risk assessment prior to beginning any work with a genetically modified organism and prior notification to UK health authorities of plans to carry out genetic modification work in any facility for the first time.³² The regulation also requires prior-notification to local genetic modification safety committees of all but the lowest risk genetic modification work, with higher risk research requiring government consent. Prior to the 2001 terrorist attacks, all notifications were maintained in a register open to the public.³³ A separate regulation on the deliberate release of GMOs issued in 1992 and revised most recently in 2002 requires government consent before marketing a GMO or releasing such an organism into the environment. The application for consent must include an assessment of the environmental risk of the proposed activity as well as detailed information on the GMO itself, monitoring arrangements and, as appropriate, marketing or release plans.³⁴

Other regulations have been adopted in the UK to implement EU oversight requirements for human, plant and animal pathogens that could have an adverse impact on public health or the environment.³⁵ Under the 1994 Control of Substances Hazardous to Health Regulation, as amended most recently in 2002, employers must notify UK health authorities 30 days prior to storing or using certain human pathogens for research or other purposes for the first time. The notification must include an assessment of the risks to worker health and safety, information on the pathogen, and proposed measures to protect worker health and reduce the risk of exposure.³⁶ The 1993 Plant Health Order prohibits the import of infected plants or plant pests into the UK for research purposes without a license. The regulation also prohibits the import, movement, or keeping of genetically modified plant pests or genetic modification work with plant pests without a license.³⁷ Under the 1980 Importation of Animal Pathogens Order, a license is required to import an animal pathogen or carrier into the UK. The 1993 Specified Animal Pathogens Order, as amended in 1998, requires laboratories and scientific establishments that wish to hold or handle certain pathogens or nucleic acids capable of producing such pathogens to be licensed. The pathogens covered by this regulation are those that could potentially cause an epidemic among livestock.³⁸

The UK has even more extensive oversight arrangements for research activities involving animals. Under the 1986 Animals (Scientific Procedures) Act, a cost-benefit analysis, weighing the potential for animal suffering against the possible medical benefits, must be done before undertaking any research project involving animals. The Act provides for a triple licensing system of places, projects, and personnel. More specifically, it requires that animal research take place only at establishments that have appropriate animal accommodation and veterinary facilities, as part of an approved research or testing program, and by individuals with sufficient training, experience, and skills. Inspectors visit licensed research establishments, usually without warning, an average of eleven times a year. In 1998, the existing oversight arrangements were expanded to include a requirement for an ethical review process at all licensed establishments. This process, begun at the conceptual stage of new research projects, aims to provide support and independent ethical advice for licensees on potential issues concerning ethics and animal welfare. As of 1999, there were 13,700 active personal licenses and 296 facility licenses.³⁹

Development of Oversight Arrangements in the UK

- 1986 Triple licensing system established for places, projects, and personnel for animal research. Inspection of such licensed research establishments done an average of eleven times per year.
- 1993 Licensing requirement for the import of infected plants or plant pests into the UK for research purposes or for the import, movement, or keeping of genetically modified plant pests or genetic modification work with plant pests.
- 1998 Licensing requirement for laboratories and scientific establishments intending to hold or handle certain pathogens or nucleic acids capable of producing such pathogens.
- 2000 Requirement for a risk assessment prior to initiating work with a genetically modified organism and prior notification to UK health authorities of plans to carry out genetic modification work in any facility for the first time. Also a requirement for prior notification to local genetic modifications safety committees of all but the lowest risk genetic modification work, with higher risk requiring government consent.
- 2002 Requirement for employers to notify UK health authorities 30 days prior to storing or using certain human pathogens for research or other purposes for the first time.
- 2001 Notification and security enhancement requirements for facilities that possess or plan to possess specified human pathogens.

The UK Government has established several bodies to provide advice to UK health and safety agencies on these oversight arrangements.⁴⁰ GMO regulation and control are the focus of the Advisory Committee on Genetic Modification⁴¹ and the Advisory Committee on Releases to the Environment.⁴² The Advisory Committee on Dangerous Pathogens⁴³ assists the UK Government in protecting workers and others against the risks from exposure to human, plant and animal pathogens. All three advisory bodies are composed of employee and employer representatives, as well as experts from the scientific community, thus allowing the UK Government to ensure that any new controls and regulations are based on field experience and are effective.

As in the United States, the UK's leading scientific advisory body, the Royal Society has also considered the risks from dual-use research and recommended relying predominantly on scientists themselves to prevent hostile applications of their work. Like the Fink Committee, the Royal Society has proposed greater oversight of dual-use research by funding bodies and research institutes as part of their general peer review process and by research institutions during execution of the work. They have given particular emphasis to the role of scientific 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 education and training programs on both national laws and regulations and international treaty obligations. They have also called for the research community to retain responsibility for assessing potential risks associated with publication of their work and to help develop universal standards for the

conduct of dual-use research that could be incorporated into existing international treaties.⁴⁴

Smallpox Research

The World Health Organization (WHO) successfully led the global program to eradicate the smallpox virus from nature.⁴⁵ As a result of its prominent role, without which the virus could have continued killing millions in the 25 years since its eradication, WHO acquired the scientific and moral authority to set policies for the safe handling of the variola virus at the two authorized depositories, in the US and Russia. In 1999, the World Health Assembly (WHA) decided to delay destruction of all known viral stocks in favor of a limited research program with the virus that WHO was to oversee.⁴⁶

Although the Committee on Orthopoxvirus Infections set guidelines for work with the variola virus in 1994,⁴⁷ a new body, the Advisory Committee on Variola Virus Research, was later formed to implement the WHA's 1999 resolution. The Advisory Committee conforms to WHO rules regarding adequate regional representation while also including the necessary scientific expertise to ensure that the experimental design is safe and commensurate with the goals set by the WHA.⁴⁸

Under this international process, WHO has approved research with the live virus aimed at: determining the full or partial DNA sequences of isolates in the US and Russian collections; validating improved diagnostic tests; screening antiviral drugs to identify those suitable for treating smallpox; developing and producing monoclonal antibodies to treat the disease; developing a safer vaccine; and creating a model of smallpox in a non-human primate to facilitate testing of antiviral drugs, vaccines, and diagnostics.⁴⁹

In November 2004, the Advisory Committee recommended revisions to the 1994 guidelines to allow newer techniques to be used for more efficient drug screening, among other purposes.⁵⁰ While scientific consensus was reached within the committee, its recommendations caused some controversy at the WHA's annual meeting in May 2005, leading to a ban on proposed gene-transfer studies, while allowing other types of research to proceed with closer scrutiny.⁵¹

As currently structured, WHO's oversight process provides for international scientific review of all research with the variola virus, while also assuring states that the research will be performed in a safe manner and in accordance with WHA's agreed research agenda. That balance is now being put at risk by WHO member states wanting to have more direct authority over the research rather than allowing the scientific committee its own discretion to make those judgments. Research is now reviewed twice before commencing: by the Advisory Committee and by the WHA, both of which meet only once a year. This adds significant delays and uncertainties.

Despite these many hurdles and restrictions, no US or Russian scientist is known to have violated the recommendations of the WHO committees on smallpox research since the agreed research program began in 1999. The US and Russian governments comply with the arrangement, including biosafety

inspections of their BL-4 labs, even though WHO resolutions are only politically binding. WHO's oversight process provides accountability and legitimacy to research with the variola virus and reassurance about the defensive intent of such research. This process is a potential precedent for how to conduct highly consequential research through a scientifically rigorous and politically inclusive system.

Existing Arrangements and the BRSS

It is clear from this review that a variety of oversight arrangements have been developed both internationally and nationally in response to concerns about the possible misuse of biology. Most focus narrowly on limiting or controlling access to potentially dangerous pathogens or on ensuring that such pathogens are handled safely, including minimizing any adverse impact from research involving their release into the environment. The few proposals aimed at addressing the risks posed by dual-use research apply to only a portion of the life sciences research community and are generally based on voluntary adherence to measures that are national in scope.

Despite these limitations, some of the key principles of a more advanced system for oversight of dual-use research can be found within these existing arrangements. As with WHO oversight of smallpox research, the system would be based upon rules and procedures that have been developed and agreed internationally, with a presumption of equitable treatment of all legitimate participants. It would establish legally binding obligations for the handling of dangerous pathogens as the BWC and the Biodiversity Convention do. It would apply to all relevant biotechnology research activities – academic, government and industry – as is the case with the UK regulations on GMOs. And like the NIH Guidelines, it would rely heavily on input from scientists themselves, whose judgments would be critical to any evaluation of the potential implications of a given research project.

Many of the specific elements that might be included in an advanced oversight system like the BRSS can also be found within these existing oversight arrangements. Several of the provisions of the US and UK anti-terrorism legislation, for example, including those requiring facility registration, information disclosure (on both researchers and pathogens), data management, background checks, and inspections, are directly relevant to strengthening oversight of biological research. The US NIH Guidelines and the UK regulations on GMOs take the oversight process one step further, requiring tiered oversight and prior approval of certain categories of research involving the construction of genetically modified organisms. Both the UNEP Technical Guidelines and current US regulations governing human subject research require a risk-benefit assessment of all proposed research projects and careful record keeping throughout the oversight process. Even more advanced still are the oversight

...some of the key principles of a more advanced system for oversight of dual-use research can be found within these existing arrangements.

arrangements in the UK for animal research, in which risk-benefit assessment is coupled with a triple licensing system — of places, people, and projects — in an effort to guard against inappropriate or dangerous experiments. All of these elements have a potential role to play in a Biological Research Security System.

..... Elements of a Prototype Oversight System

Individual scientists, institutions, and security officials must currently find their own balance between the norm against destructive applications of biology and the equally strong but sometimes contradictory scientific drive to answer interesting questions and find useful applications of fundamental research.⁵² They have little knowledge of the decision rules used by others, and often no independent external review. The Biological Research Security System would reflect a shared recognition that, for some types of research, either foregoing the work or proceeding with inadequate protections could have damaging consequences that extend far beyond the laboratory, firm, or country where the decision was made. For these consequential lines of research, the BRSS would provide common standards, peer review, and reassurance that the power of biology was being used appropriately.

The right balance between freedom of scientific investigation and protective oversight depends on the degree of risk involved. Therefore, the design of the Biological Research Security System must start by attempting to define the different levels of research activity of concern so that they can be matched with the appropriate oversight procedures. The next step is to address a set of architectural questions associated with the overall system design, such as principles and elements, information disclosure requirements, institutional structure, and verification and compliance management. The third requirement is to explain how the system might work in practice at each level of oversight. Each of these issues is addressed below.

Defining Research of Concern

The first and arguably most critical step in establishing a protective oversight arrangement is that of determining a reasonably clear, globally credible and judiciously limited scope of application. Legal obligations cannot be imposed unless they are precisely and legitimately defined. Obligations formally imposed will not be effectively implemented unless the burden entailed is credibly related to a justifying purpose. The determination of that purpose must be understood and accepted in the entire community affected.

In regulatory practice to date, the purpose of oversight has been more restricted but the scope of application often more expansive than the Biological Research Security System would presumably require. For almost three decades, pathogens have been graded into four categories of danger in order to set biosafety standards for preventing laboratory accidents. The more recent US select agent list and UK pathogen control lists were constructed by researchers and medical professionals taking into account the demonstrated effects of the

agents in question as well as their susceptibility to public health measures and medical treatment. The judgments made are plausible in each instance, but the security risks associated with the various listed agents differ considerably.

The threat posed by anthrax, for example, is quite severe – usually lethal – to those who inhale the bacterial spores without realizing they have done so. Since there is typically a two-day incubation period before the disease produces detectable symptoms, however, and since the toxin-producing spores are normally quite susceptible to antibiotic treatment, the severity of the threat depends a great deal on the stealth and efficiency of its original dissemination. A person afflicted with anthrax generally will not infect another individual. Smallpox, by comparison, is less likely to be lethal to a given individual but is nonetheless much more dangerous to society generally because the virus spreads from one individual to another. In some historical outbreaks of smallpox each infected individual has infected on average some two to three other individuals, a multiplication factor sufficient to generate a devastating epidemic, absent rapid intervention. The case fatality rate for smallpox epidemics has typically been around 30%. Most variants of the influenza virus are yet more contagious than smallpox but also much less lethal. Even so, the notorious 1918 H1N1 influenza strain killed somewhere between 20 and 40 million people worldwide in the course of a year, with a case fatality rate estimated to have been about 4%. The anthrax bacterium and the variola virus that causes smallpox are on the select agent list. Until October 2005, when H1N1 was added, the only influenza strain on the select agent list was avian influenza.

If one of the primary goals of the BRSS is to prevent both the inadvertent and the deliberate creation of biological agents that are yet more lethal or otherwise more destructively consequential than those presently known, then the current control lists are inherently inadequate. They do not include pathogens that have become conceivable but do not yet exist and are not officially named. Regarding those pathogens that do exist and provide the basis for the construction of more destructive variants, the lists are at once too inclusive and not inclusive enough. They designate agents such as anthrax that are notorious but do not pose a mass danger. But until recently, they omitted one of the most virulent strains of influenza, perhaps the most contagious known agent, despite the fact that it could be made more lethal. They do not address research techniques that might transform currently benign biological agents into massively destructive ones.

An initial approximation of the concept of intrinsic danger can be derived from basic epidemiology.

To address the priority concern effectively, an intrinsic definition of danger will not only have to be devised but also translated into a form that can be implemented successfully. Admittedly, these requirements are much easier to state than to accomplish. But an initial approximation of the concept of intrinsic danger can be derived from basic epidemiology. It is generally understood that the course of an infectious disease depends on two basic characteristics of the pathogen that causes it: the ability to transfer spontaneously from one host to another and the consequence for the host of the resulting infection. Using common sense terms, one can label the first property transmissibility and the

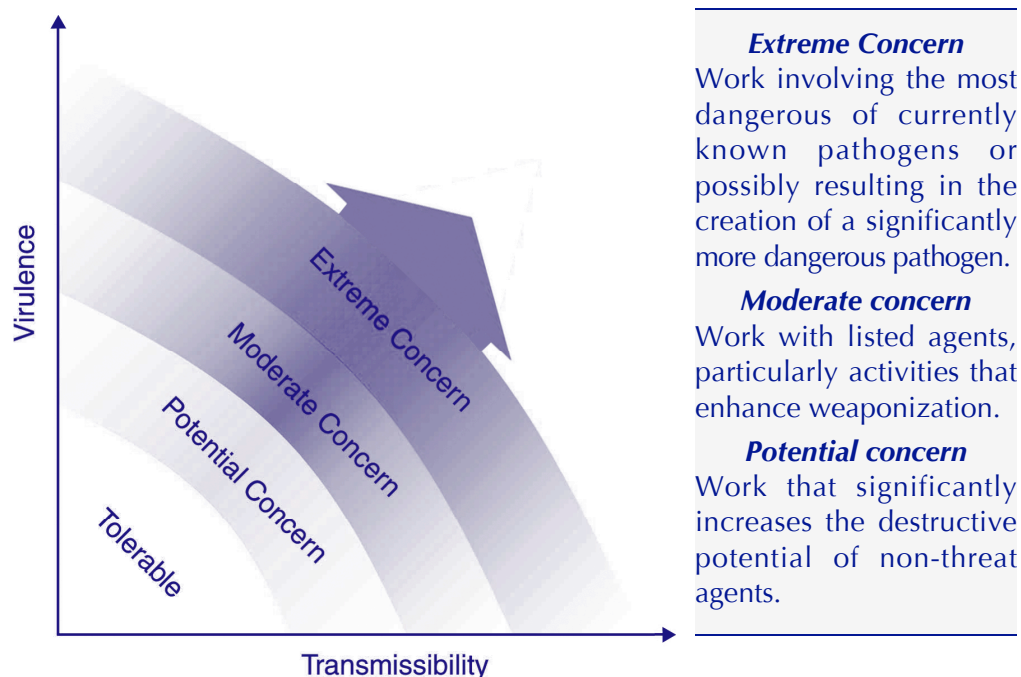
second virulence. Although any disease outbreak is also affected by environmental circumstances, public health measures, individual immune system reactions and therapeutic treatment, for a given set of such conditions pathogens clearly vary in terms of transmissibility and virulence. None of the currently known pathogens sets the highest standard for both properties, and there is some tradeoff between them. In particular a disease that is too rapidly lethal undermines its ability to propagate between hosts. There is no reason to believe, however, that either the intrinsic limits of these properties or the most destructive combination has yet been demonstrated in nature. As the dynamics of disease are understood in more detail, it has become evident that the natural process of evolution has been moderating rather than maximizing the overall lethality of human, plant, and animal pathogens. In principle, this moderating effect might be overturned by deliberate or accidental human intervention.

One can imagine a definition of intrinsic danger based on the combination of transmissibility and virulence of known pathogens as suggested in Figure 1. In principle these two properties might be measured in some standard manner and each known pathogen or agent located in the two dimensional space of the Figure. The space might then be segmented in terms of the degree of social danger posed as indicated by the bands. Research techniques can be conceived as vectors operating in this space – that is, as arrows indicating magnitude and direction. If a given technique is judged or shown to be capable of transforming a given agent so as to move it into a higher danger zone, then the oversight procedures associated with that zone would be applied as soon as the potential is recognized. This approach would consider the pathogens and the research techniques being applied to them, thus combining elements of the US select agent program, which focuses solely on agents, and the Fink Committee and NSABB approaches, which focus solely on research activities.

Under this conception, the highest demonstrated values for each of the dimensions would delineate the threshold of maximum concern, and the oversight process would attempt to keep the area beyond those thresholds unoccupied in nature even if it is explored in science. Work with a restricted set of pathogens whose performance defines the threshold area would be given special designation and subjected to the most active form of international oversight. Successively less intrusive and more permissive forms of oversight would be applied to the lower bands of concern.

Admittedly, it would be very difficult to establish broadly agreed measures of transmissibility and virulence for all known pathogens, let alone to predict how much change might result from a proposed research activity. Generally agreed specifications for even the most prominent pathogens cannot be extracted from existing literature,⁵³ and a systematic effort to undertake the measurements required could not be organized until the feasibility and importance of doing so was broadly established. One can nonetheless attempt to connect the basic conceptualization of danger represented in Figure 1 to an operational specification of differing risk levels that practicing scientists would recognize. A notional categorization scheme is outlined.

Figure 1: Conceptual Categorization of Danger



The category of extreme concern is limited largely to the relatively few activities that involve or could result in pathogens significantly more dangerous than those that currently exist. It also includes some work with agents classified as BSL-4/ABSL-4 in the United States or equivalent levels in other countries. The category of moderate concern encompasses a larger universe of activity involving biological agents already identified as posing a threat to public health, particularly activities that enhance the potential of such agents to be used as a weapon. The US select agent list is used for illustrative purposes, but it is recognized that an agreed list would have to be developed and maintained. Under an advanced oversight system, this would be done internationally, as discussed below. The category of potential concern focuses largely on activities that increase the destructive potential of biological agents that otherwise would not be considered a threat. The research activities covered by these categories are very similar to the experiments of concern outlined in the Fink Committee report, but have been calibrated to distinguish between different levels of concern.

In principle, the research activities listed in Table I could be used to determine oversight jurisdiction while the parameters of transmissibility and virulence in Figure I could be used as general guidelines for judgment within each of the oversight jurisdictions. But as discussed below, more specific criteria are also needed to assess the benefits and risks of proposed research projects and thus whether and under what circumstances they should proceed.

Table I: Illustrative Categories of Research Activities

Activities of Extreme Concern (AEC)
Work with eradicated agents*; work with an agent assigned as BL-4 / ABL-4; <i>de novo</i> synthesis of above; expanding the host range of an agent to a new host (in humans, other animals and plants) or changing the tissue range of a listed agent**; construction of antibiotic- or vaccine-resistant listed agent.
Activities of Moderate Concern (AMC)
Increasing virulence of listed agent or related agent; insertion of host genes into listed agent or related agent; increasing transmissibility or environmental stability of listed agent or related agent; powder or aerosol production of listed agent or related agent; powder or aerosol dispersal of listed agent or related agent; <i>de novo</i> synthesis of listed agent or related agent; construction of antibiotic- or vaccine-resistant related agent; genome transfer, genome replacement, or cellular reconstitution of listed agent or related agent.
Activities of Potential Concern (APC)
Work with listed agents – or exempt avirulent, attenuated, or vaccine strain of a listed agent – not covered by AEC/AMC; Increasing virulence of non-listed agent; increasing transmissibility or environmental stability of non-listed agent; powder or aerosol production of non-listed agent; powder or aerosol dispersal of non-listed agent; <i>de novo</i> synthesis of non-listed agent; genome transfer, genome replacement, or cellular reconstitution of non-listed agent.

* This would include, for example, activities with the 1918 influenza virus and chimeric influenza viruses with at least one gene from the 1918 influenza virus.

** This would include, for example, activities with chimeric influenza viruses with at least one gene from a human influenza virus and at least one gene from an avian influenza virus.

Table Definitions

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

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

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

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

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

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

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

Antibiotic: antibiotic of therapeutic utility against listed agent.

Vaccine: vaccine of therapeutic utility against listed agent.

This approach, which focuses on the impact of certain research activities on pathogens, will be criticized by those concerned with consequential applications of biotechnology that do not involve pathogens. The manipulation of the immune system, for example, using bioregulators delivered by non-microbial mechanisms such as immunotoxins or fusion proteins is a case in point.⁵⁴ But the most likely means of delivery for bioregulators, the ones that have been developed farthest up to now, are either aerosols or modified viruses or bacteria, both of which are covered by our oversight system. Moreover, if very large numbers of people — in the hundreds of millions or more — are to be exposed to a lethal or otherwise nefarious effect in a short period of time, at the moment that could only be accomplished by a highly transmissible and highly virulent pathogen. That fact provides an obvious rationale for devising an oversight arrangement whose initial scope of application is limited to the effects of certain research techniques on the inherent properties of pathogens.

The Fink Committee clearly believed that the experiments of concern that it proposed for oversight were a starting point for what ultimately would be an evolving system of review. “The Committee has initially limited its concerns to cover those possibilities that represent a plausible danger,” the report declared.

“Over time, however, the Committee believes it will be necessary to expand the experiments of concern to cover a significantly wider range of potential threats.”⁵⁵ So too is it with our approach. Extensive additional discussions within the many relevant professional communities will be required to work out which research activities should fall under the different oversight levels in our system and, ultimately, to extend the oversight process to include other, non-pathogen-related concerns. One cannot be confident in advance that workable consensus could be achieved. It seems evident, however, that an organized effort of this sort should be attempted. If it did succeed, it would provide the clarity of definition that is essential for a protective oversight arrangement. If it did not succeed, presumably the effort would be instructive.

System Architecture

Since there appears to be no valid categorical distinction that can be made between potentially beneficial and potentially destructive lines of fundamental research, there is a natural presumption that protective oversight must be performed by scientific peers able to understand the technical details of each individual project and to discern the probable implications. But there is also a presumption that protective oversight would have to include people whose experience and training would prepare them to judge social consequence — a significant extension of the established practice of scientific peer review. Because both the scientific and the social judgments made would have very broad consequence and would be potentially controversial, one would want them to emerge from a collaborative effort involving the relevant professional communities and government authorities, rather than simply being imposed by a government bureaucracy alone. At the same time, one needs the legal authority, financial resources, and the clarity of obligations that come from formal intergovernmental agreement on oversight standards and practices.

For maximum effectiveness, an oversight system would have to be:

- globally implemented;
- applied without exception to all scientists engaged in relevant research;
- adequately financed;
- efficiently organized;
- backed by appropriate legal authority; and
- accompanied by credible provisions to prevent misuse of its authority.

In meeting those requirements the oversight process would have to establish and preserve some important balances. Comprehensive jurisdiction over all relevant research would have to be qualified by judicious limitation of the oversight mandate to those areas of research that validly pose the possibility of broad social danger – hence the importance of identifying the determinants of social as distinct from individual danger. Within that limited mandate, oversight judgments would have to assess the balance of benefit and risk and recommend, whenever possible, ways to achieve the beneficial objectives while minimizing potential danger.

Full realization of all of those provisions would clearly be a major feat of institutional innovation. Many would argue it is an improbable accomplishment and some would consider it intrinsically undesirable because of its inherent intrusiveness. The underlying problem is certainly serious enough to induce innovation of some sort, however, and those who pose categorical objections are obliged to offer an equally effective scheme. Meanwhile the idea of an advanced oversight arrangement is a useful reference both for assessing potential alternatives and for considering other measures that could lay the foundation for a more advanced oversight system and that could more readily be achieved.

Principles and Elements

The basic standard on which any oversight arrangement would be based is the principle that biology should not be used to do deliberate harm under any circumstance for any reason. That is the core principle of the Hippocratic Oath that has been recognized since ancient times. It is also the core principle that underlies the prohibition on the use of biological weapons promulgated in the 1925 Geneva Protocol and on the possession of biological weapons embodied in the Biological Weapons Convention. Although neither of those accords enjoys universal legal adherence, no country currently proclaims the right or the intention to deploy biological weapons. The basic standard is already in practice a universal norm, and it could be substantially strengthened with a dedicated effort to do so. Indeed, a central purpose of an oversight process would be to assure consciousness of the basic standard by those undertaking work that could pose a meaningful violation and to provide reasonable reassurance of their compliance calibrated to the degree of danger entailed in the work they are doing.

The oversight process would include two key elements. The first, *national licensing*, would be used to identify relevant individuals and research facilities and formalize their adherence to the basic norm. Similar processes are already being used in advanced biology to ensure that certain individuals and facilities meet specified security and safety requirements. For example, both the May 2002 bioterrorism bill and the select agent regulations in the US require

background checks on any individual having access to select agents and registration of relevant facilities. Various regulations in the US and other countries also require licensing of facilities that produce drugs and other products derived from biotechnology to ensure their safety and efficacy. Outside of biology, there are other examples of licensing requirements for individuals and facilities engaged in activities that could affect substantial numbers of people — doctors, for example, and laboratories that work with radioactive materials.

The personnel licensing requirement would extend to all scientists, students and technical staff proposing to conduct research covered by the oversight system. The purpose of the licensing would be to ensure that the affected individuals are technically qualified (either by virtue of an academic degree or on the job experience), have undertaken biosecurity training (and thus have been sensitized to the dual-use potential of their work and educated about both national and international oversight rules), and have nothing in their background (such as a past biosafety violation) that would make it inappropriate for them to conduct consequential research. Receipt of a personnel license would be viewed as an acknowledgment of the individual's special status within his or her broader professional community. The facility licensing requirement would extend to all facilities where relevant research takes place, and would be designed to ensure that such facilities meet existing safety and security standards.

In addition to personnel and facility licensing, there would also be a *vetting* requirement for other students, secretaries, janitors and individuals working in licensed facilities but who are not themselves conducting research that is subject to oversight under the system. The purpose of this vetting process would be to ensure that there is nothing in the individual's background that would make it inappropriate for them to have access to areas where controlled pathogens are stored. In implementing both this vetting requirement and the personnel licensing system, it will be important to ensure that individuals are not arbitrarily disapproved for political or other reasons unrelated to their qualifications to carry out the relevant work.

The second element is independent *peer review* of relevant projects prior to their initiation. Any individual interested in conducting research covered by the oversight system would be required to provide information about their proposed project to the appropriate oversight body for review and approval. To ensure equitable treatment of all proposed research projects both within and between the different oversight levels, common criteria would be needed by the relevant review bodies for use in assessing the potential benefits of the work as well as the possible risks. Such a risk-benefit assessment process would be similar to that which is currently required in the US for IRB approval of human subject research. Like the IRB review process, the risk-benefit assessment of dual-use biological research would apply to all relevant research, irrespective of whether it is to be carried out in a government, industry or academic laboratory. In addition, the relevant review body would be required to consider certain specified issue areas as part of its deliberations and to document the discussion of these issues as well as its overall risk-benefit assessment in its meeting minutes. A record of the review judgments would be preserved at all levels and under the most advanced arrangement the international review body would periodically organize efforts to harmonize the judgments made by separate

national and local review bodies using project case histories as the basis for discussion.

Ten issue areas and nearly two dozen suggested questions are listed on the IRB review protocol.⁵⁶ Based on a peer review simulation exercise of five hypothetical projects,⁵⁷ we have developed a comparable set of issues and questions that could be used to assess the risks and benefits of proposed dual-use research projects. The first two issue areas, which focus on biosafety and the details of the proposed research plan, concern the conduct of the work. The remaining four issue areas relate to the justification for the work, and cover public health, biodefense, current necessity and potential impact. Similar issue areas and questions have been suggested by the British Royal Society for assessing dual-use research.⁵⁸ Our notional risk-benefit assessment criteria are listed in Table II.

Information Disclosure

As the criteria outlined above show, meaningful peer review would require disclosure to the appropriate review body of detailed information necessary to weigh the risks and benefits of a proposed experiment. In an advanced arrangement, the international review body would have primary right to information directly relevant to projects falling under its jurisdiction. In particular, information demonstrating extreme risk to the human species as a whole would have to be disclosed, as would information relating to the defining determinants of risk. Within a strict definition of direct relevance, these requirements would override considerations based on proprietary interest or national security. National and local review bodies would also need sufficient information to be able to assess projects and, assuming that the overall judgment was positive, to make recommendations about ways to maximize benefit while minimizing risk.

In rare cases, the relevant review body might decide to approve a proposed project but to restrict the dissemination of information about the project or its results. That would require agreed guidelines for determining whether and under what circumstances information might have to be restricted or classified. It would also require an agreed process for determining who could be given access to controlled information, based on professional qualification and documented responsibility rather than on national identity or organizational affiliation. At the moment there are no such provisions, and practical discussions generally debate the merits of open publication as compared to propriety or national security classification.

One possible approach would be to build upon the ideas outlined in 1982 by a National Academy of Sciences panel on scientific communication and national security chaired by former Cornell University President Dale Corson. The Corson Report, as it is known, concluded that the national welfare, including national security, is best served by allowing the free flow of all scientific and technical information “not directly and significantly connected with technology critical to national security.” The report recommended that most fundamental research at universities should be unclassified; that a limited amount might require classification; and that a small grey area could require limited restrictions short of classification. Criteria for making these classification decisions were also included, which, with some modification, could serve as a model for similar decisions concerning sensitive life sciences research today.⁵⁹

**Table II: Notional Criteria for
Risk-Benefit Assessment of Dual-Use Research**

Biosafety Issues

- (1) Does the proposed research plan contain appropriate protections to minimize risk to the public or environment?
- *Proposals receiving a “no” answer would have a low biosafety rating*

Evaluation of Research Plan

- (1) Are the proposed research plan and stated rationale for the work consistent with one another?
- (2) Are the risks posed by the agent (either from the perspective of public health or bioterrorism) and the stated rationale for the work consistent with one another?
- (3) Is the proposed research plan logically sequenced?
- (4) Are there scientific reasons why the same outcome cannot be pursued through alternate means? For example, could other methods or materials be used?
- *Proposals receiving two or more “no” answers would have a low research plan evaluation rating*

Public Health Considerations

- (1) Do agents to be constructed currently exist in nature?
- (2) If not, are said agents expected to be generated by natural processes?
- (3) Will the research advance our understanding of disease-causing properties of currently existing agents?
- *Proposals receiving “no” answers either to questions (1) and (2) or to question (3) would have low public health rationale*

Biodefense Considerations

- (1) Do agents to be constructed currently exist in nature?
- (2) If not, is the work being done in response to a “validated threat” (i.e. one for which there is credible information) or “theoretical threat” (i.e. one that is possible but for which there is no credible information)?
- (3) Will the countermeasures that are expected to result from the work significantly reduce the threat posed by the agent?
- *Proposals receiving two or more “no” answers would have low biodefense rationale*

Current Necessity

- (1) Are countermeasures against agents to be constructed currently unavailable?
- (2) Are there scientific reasons why countermeasures cannot be developed without access to such agents?
- *Proposals receiving one or more “no” answers would be of limited current necessity*

Potential Impact

- (1) Will the proposed research contribute to new knowledge (e.g., by furthering our understanding of basic life processes or pathogenesis) rather than primarily confirm work already done?
- (2) Are the research results likely to be definitive enough to inform policy decisions (e.g., vaccination strategies)?
- (3) Are there significant obstacles to using the research results to develop a more dangerous pathogen or to overcome current countermeasures?
- *Proposals with two or more “no” answers would have limited positive impact*

Admittedly, the context in which the Corson panel put forward its recommendations is very different than the one the world currently faces. The 1982 Report was a response to concerns that the Soviet Union was benefiting militarily from access to US scientific and technical information, especially in computer science and other areas of the physical sciences. Today, the dominant concern is about a much more diffuse set of national and possibly subnational actors misusing advances in the life sciences for hostile purposes. But no rogue nation much less any terrorist group that currently exists is better capable than the Soviet Union was of adapting fundamental research results for destructive purposes. If these criteria were deemed appropriate to deal with the Soviet military threat, they should be at least as effective against the much less sophisticated threats the world now faces.

Drawing on the Corson Report, one could require that no restrictions should be placed on basic or applied research or research results at university, industry or government laboratories unless the following criteria are met:

- the technology is developing rapidly and time from basic science to application is short;
- the technology has identifiable direct military applications or is dual-use and involves process or production-related technologies;
- the transfer of technology would give a BW proliferator (e.g., national level or subnational) a significant near-term capability;
- there are no other sources of information about the technology, or all those that could also be the source have effective systems for securing the information; and,
- the duration and nature of the proposed restrictions would not seriously compromise the work of those directly responsible for public health.

The requirement to take account of the public health implications of any proposed restrictions was not, of course, part of the original Corson panel approach. But precisely because legitimate applications of life sciences research can have a profoundly positive impact on public health, considering only the security implications of such research is not sufficient.

In situations where certain research results might need to be restricted, it would be important to ensure that anyone with a legitimate need to know for the purposes of research, public health or medical practice would have access to the relevant information, and that such access is documented and the individual is held accountable to rules about the use and further dissemination of the information. A relevant process was used by the US NAS to handle the dissemination of sensitive portions of its 2002 study on agricultural bioterrorism. In response to security concerns from the US Department of Agriculture, which funded the study, NAS officials developed guidelines for the types of individuals who could be given access to the controlled information. Anyone interested had to submit a written request and be interviewed by NAS staff before being provided a copy of the controlled information.⁶⁰

Arguably, arrangements such as this for the disclosure and use of scientific information might be more readily accepted in the public health community and academia than in industry or in the many national security establishments that conduct biological research programs. The operating principles of most public

health practitioners and academics are generally aligned with the rules of transparency and independent peer review even if they do not as yet implement them to the extent that an advanced oversight arrangement would require. In contrast, proprietary and national security organizations generally reserve the right to restrict outside access to their research activities and consider that practice to be justified by their respective missions. At the present time, prevailing definitions of legitimate interest are not refined or robust enough to provide a widely agreed basis for subordinating these organizations to an advanced oversight process. The authoritative delineation of legitimate interest therefore would be one of the first and fundamental requirements for implementing such an oversight arrangement.

Advanced information technology would be used at each level of the oversight system to help protect against the unauthorized release of sensitive information and to facilitate reporting by affected researchers and to speed the peer review process. To illustrate how this might be done, we built a prototype data management system using open source software and financial-grade security standards. The system we have developed has a tree-like structure, with each oversight node (i.e. local institutions, national authorities, and the international body) operating its own secure server for storing information under its jurisdiction. Information required for licensing and peer review would be collected using questionnaires that meet BRSS reporting requirements as well as other national or local reporting requirements. Information would be sent securely from one node to another – such as when a proposed project meets the requirements for higher-level review – but higher-level nodes would not be able to access information from lower nodes without the lower node’s permission. The data management system makes it easy to add new questionnaires or revise existing ones and automatically propagate these changes throughout the system to keep pace with advances in science and technology. The use of open-source software decreases expense and allays concerns about hidden features while still including multiple levels of security. Details about the prototype data management system are in Appendix C.

Institutional Arrangements

Decisions concerning the institutional entities necessary to implement the oversight system would naturally be a product of the process that created them. For purposes of immediate discussion, we use the term Biological Research Security System to describe the overall arrangement. The term International Pathogens Research Authority (IPRA) refers to the body that would fulfill the international functions of the BRSS. National Pathogens Research Authority (NPRA) refers to the governmental bodies exercising national oversight, while Local Pathogens Research Committee (LPRC) refers to the review bodies that would exercise oversight within individual institutions or regionally.

WHO has some of the relevant expertise and mission that would be relevant to a fully developed IPRA, given its work in recent years helping develop national preparedness and response capabilities, international disease surveillance systems, and laboratory biosafety and biosecurity guidelines for handling pathogens. But neither it nor any other existing international organization currently has either the specific mandate or the full range of scientific, security, legal, and other expertise necessary to implement an advanced oversight arrangement. Moreover, since plant and animal pathogens would also be within

its scope of concern, the IPRA would have to have a close functional relationship with the Food and Agricultural Organization (FAO) and the World Organization for Animal Health, known as the OIE. Thus, although it might ultimately be desirable to bring some or all of the global-level functions of the IPRA into a WHO with more reliable finances and more authority, for now it makes sense to conceptualize the international part of the system without being constrained by the limitations of any existing international organization.

The International Pathogens Research Authority need not be a large organization, but it will require an administrative structure that reflects its mixed character as a security, scientific, and public health organization. The IPRA should be established with the legal authority to perform some functions itself (a direct system of regulation) and to set requirements for the performance of other functions by its States Parties (an indirect system of regulation). Like most international organizations, it should include a governing body comprised of all member states that would meet annually to set guiding principles and priorities, approve budgets, and make other authoritative policy decisions. It would also need a smaller executive body to oversee implementation of the system, the seats on which would be allocated both to ensure geographic representation and to reflect the global distribution of relevant industries and scientific expertise. The IPRA would also need a technical secretariat, as well as several standing committees that include policy representatives from national delegations, specialists from the technical secretariat, and non-governmental experts as needed. It would also have special committees of internationally respected scientists and security experts who would be responsible for peer reviewing research of extreme concern and for helping define the research activities that would be subject to oversight at each level of the system.⁶¹

To achieve the requirements of an advanced oversight arrangement, the BRSS would have to be established by treaty or an equivalent legal instrument and adherence to the instrument would have to be made such an insistent obligation that all countries would be under enormous pressure to ratify it. The IPRA would have to be provided with an assured budget tailored to its responsibilities.

Under an advanced conception, the IPRA would have the following functions:

1. It would define the categories of research activities subject to oversight and establish standards for review, with updates as required to keep pace with scientific advancement.
2. It would conduct the oversight process for all projects involving activities of extreme concern, including initial approval of the individuals, research facilities and projects; implementation of the approved research plan; and dissemination of the results.
3. It would determine the criteria for identifying research that is of unusual importance for reasons of global protection and would actively encourage and fund high priority projects meeting those criteria, whether identified by the organization or outside researchers.
4. It would establish reporting requirements, rules for access to sensitive information, and protections against the misuse of disclosed information.

5. It would provide software and technical support for a secure data management system to be used at each oversight level and would maintain a database of information, including strain variations, on all projects reviewed under international authority.
6. It would provide scientific, legal, and technical assistance upon request to help member states, local review committees, and individual scientists meet their national- and local-level oversight obligations.
7. It would assess the case judgments being made on a national basis for research meeting the criteria for activities of moderate concern and potential concern.
8. It would conduct periodic conferences designed to encourage harmonization of national standards and case judgments, and identify any major discrepancies that appear to be of legitimate international concern.

In order to perform these functions in a world of irretrievably divided legal and political jurisdiction, the IPRA would have to be constituted in a manner that is globally representative and explicitly dedicated to providing an equitable distribution of burden and benefit. It would also have to specify procedures that assure compliance with its requirements but also protect against misuse of its authority. In general, it must be given the mandate to be equitable and sufficient capacity to be effective but not the ability to be abusive.

Of these underlying requirements, the incentive to be equitable should be the least controversial. Concern about the misuse of advances in biology is currently highest in more economically advanced countries, with poorer countries focused on infectious diseases such as malaria, tuberculosis and HIV/AIDS, which kill millions of people each year. The poor provide a reservoir for emergent diseases that also pose an incipient threat to more affluent populations, but lack the money and expertise to handle the problem on their own. Although participation in the BRSS is likely to impose few burdens on such countries, governments already stretched thin might be more willing to participate if the oversight system also funded research on some of the human, plant or animal pathogens that pose a clear threat to their own country's security and well-being. Scientists and public health officials in the developed world might also have a stronger incentive to participate in the oversight system if it also included a positive mission aimed at contributing to the global fight against infectious disease. Recent international cooperation on SARs and on avian influenza demonstrates the importance both of international scientific collaboration and of ensuring that those who conduct consequential research adhere to common procedures and rules.

Of course, the financial costs of the IPRA would need to be shared equitably as well. If the IPRA's responsibilities were narrowly restricted to the mission of research oversight, an appropriate level of operations might fall in the range of hundreds of millions of dollars per year. A more advanced arrangement that included the mandate to address the most destructive of the current infectious diseases might well require billions of dollars per year or more. Those would be large increments to current international public health expenditures but comparable to the additional amounts the US has explicitly directed to bioterrorism research in the aftermath of the 2001 anthrax letters.

Compliance and Verification

The question of compliance, a term that involves the perennially contentious issue of verification, is likely to be a controversial issue in the development of any oversight system. Some will argue that the threat of malicious intent is virtually the entire problem and that those dedicated to destructive applications of biology will readily evade any oversight arrangements acceptable to everyone else. When applied in extreme form against nation states, that argument makes any preventive effort intractable in principle and leaves military force against those with evil intent as the only supposedly realistic option. Even in more moderate form, the argument seeks to impose a heavy burden of proof on the expectation of compliance and the feasibility of verification. Although tolerably robust compliance provisions have been demonstrated in what would appear to be roughly comparable situations – financial accounting, for example – in its formative stages an advanced oversight arrangement for biotechnology would undoubtedly have to labor against categorical doubts about compliance that would be very assertively expressed.

The constructive case for the feasibility of compliance rests on a number of arguments. The first holds that there is a problem of innocent misjudgment serious enough to justify the establishment of a system of independent peer review of relevant research. Most practicing scientists strongly believe in their own good intentions, but most can also be readily induced to recognize the possibility of unpleasant surprise. Many also are distinctly less confident of their colleagues collectively than they are of themselves. If misjudgment is accepted as the occupational hazard it certainly appears to be and not as a character flaw, then it is reasonable to expect that compliance with a carefully designed oversight process can be established as a professional standard endorsed, practiced and enforced by virtually all practicing researchers as protection against social backlash triggered by inadvertent error. That can in principle be made an integral part of the social contract and a routine feature of professional practice. That would not preclude willful violation but it would make it unambiguously illegitimate and much riskier as a practical matter than it currently is. Detection of violation is more likely to occur against a background of routine disclosure and peer review, and detected violations are more likely to be prosecuted if clear standards of compliance are set. In general, consensual information disclosure ubiquitously practiced offers far more consequential protection than adversarial forms of verification evoked only in instances of alleged violation.

Officials at all levels of the oversight system are likely to rely heavily on information gathering and analysis mechanisms to assist them in assessing compliance.⁶² This includes reviewing project reports for internal consistency, cross-checking information provided by one lab with submissions from others with which it interacted, or comparing research project records with findings published in academic journals and patent applications for bio-medical products. To supplement the data reported formally under the system, information could also be obtained from unofficial sources such as non-governmental organizations. Additional information could come from periodic visits or inspections, which many laboratories already are subject to on a national basis for reasons other than suspicion of wrongdoing.

BRSS member states can also enhance confidence in compliance by being responsive to questions from other countries about their implementation of their oversight obligations. This could be done at the annual meetings of the IPRA where, in addition to approving budgets and making other policy decisions, governments could answer questions from other participating states. They could also consult directly with other member states if they had a question or concern, following established consultation and clarification procedures.

The IPRA could also require additional protective measures that are feasible and prudent for projects undertaken at its level. This includes, for example, allowing activities of extreme concern only to be carried out at a limited number of designated sites that would have access controls to laboratory work areas as well as to the containers in which dangerous pathogens are stored. That would create a detailed record of access and enable the imposition of multiple person rules analogous to those applied to nuclear weapons-related work. There also could be continuous video monitoring of the work areas and electronic monitoring of the equipment to assure a detailed record of research activity as well as basic access. Rules and procedures of this sort are provisionally being developed in some places but not yet comprehensively applied and managed. If they were, the standard of protection would clearly be much higher than it currently is.

Despite these mechanisms, one can still imagine that a rogue state might evade the oversight system by exempting its national and local review bodies from the agreed requirements or by refusing to establish a national oversight system at all. If all major countries endorsed and implemented the system, however, it would be much harder for a rogue state to defy it. With virtually the entire international community adhering to the system, the UN Security Council might more readily develop a supplementary verification process capable of imposing adversarial inspections on suspect facilities believed to be engaged in activities that threaten international peace and security, including international public health. Sustained and unresolved issues of compliance arising within the oversight system's more cooperative processes could be made the trigger of assertive verification. Many of the standard enforcement provisions, ranging from sanctions to, in extreme cases, the use of military force, could be credibly brought to bear if basic rules of behavior were set and broadly practiced. It can reasonably be argued that an advanced oversight system would substantially enhance the prospects of disciplining a tempted rogue. That supposition is at least as plausible as the contrary assertion that rogues are inevitable and unpreventable.

In fact, despite predictable disputes over probable levels of compliance, assuring appropriate restraint in an advanced oversight process is probably the more demanding problem over the longer term. As discussion proceeds and the basic features of the situation are absorbed, most people are likely to recognize the potential power of systematic information disclosure and mandatory peer review and are likely to be insistently interested in effective protection against misuse of that power both as a basic legal right and as a matter of administrative procedure.

Since the functions of the IPRA, in particular, are essentially unprecedented, it seems evident that substantial legal innovation is likely to be required to establish appropriate safeguards. Rules regulating access to information

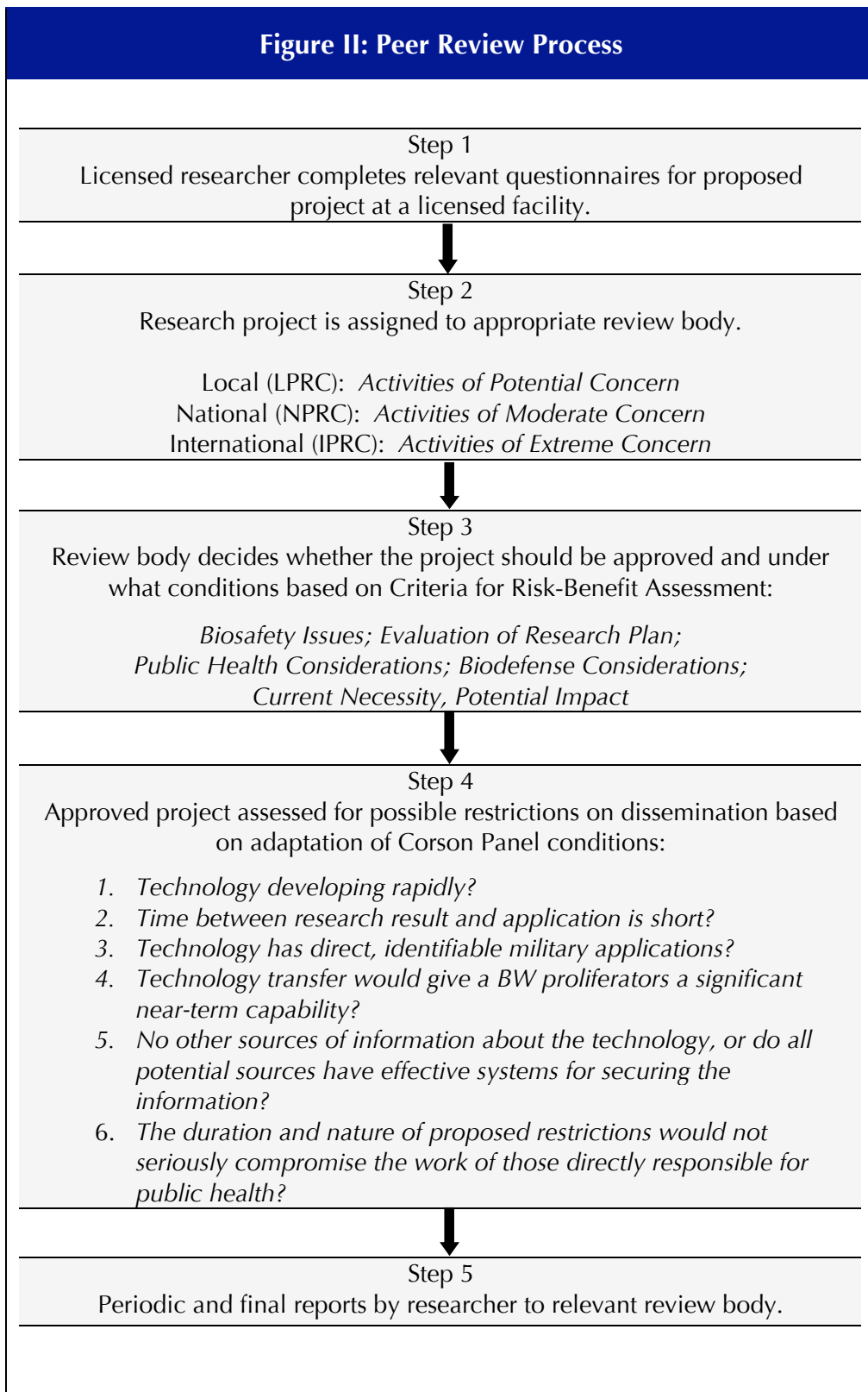
disclosed under the oversight system, specifying both legitimate uses and prohibited application, would be needed. Civil remedies and possibly criminal sanctions would have to be allowed in national jurisdictions for unauthorized disclosures. Within the United States, and probably within many other countries as well, a decision by the international review body to deny approval of a proposed project in the category of extreme concern would have to be subject to appeal in the courts as a matter of constitutional right. An international ruling that was contested and not upheld in a national court system could create an operational problem for the oversight system as a whole. So would civil suits against the international body for any inadvertent or willful mismanagement of the information it gathers. Presumably national courts would be reluctant to contest international rulings on scientific grounds, but they would appropriately demand procedural safeguards protecting the rights and interests of those subjected to oversight. Concerns about due process would be minimized to the extent that oversight procedures and rules have been harmonized both among countries and between the national and the international level, and involve similar licensing and peer review requirements.

The System in Practice

In envisaging how the oversight process might work in practice, it is helpful to begin with the licensing provisions for scientists and facilities. We then consider the project peer review process starting from the lowest level, both because this is the part of the system, if any, that would directly affect most scientists, and because this is the point at which all projects subject to oversight would initially enter the system. A diagram of the key steps in the peer review process is in Figure II below.

Any scientist wishing to carry out a research project subject to oversight under the BRSS would have to be licensed as would the facility where the proposed work would take place. In order to obtain a personnel license, the researcher would complete a new user questionnaire. This form would require information on the individual's academic credentials and employment history, including current employer. In order to obtain a facility license, the institution housing the laboratory where BRSS-covered research is to take place would complete both a new institution questionnaire and a new laboratory questionnaire. The former would require general information about the institution (name, address), the activities of its biosafety and other review bodies (e.g., IBC, IRB) and its laboratory inspection and hazardous materials handling procedures. The new laboratory questionnaire would require information specific to the laboratory where the BRSS research would take place, including the agents which are used in the laboratory and the individual responsible for coordinating agent research. Completion of the new laboratory questionnaire would also trigger a separate questionnaire on security measures, which would require detailed information on measures in place at the lab for preventing unauthorized access to dangerous pathogens. Once a project that was subject to BRSS oversight was proposed, all relevant licensing forms would be provided to the appropriate peer review body for use in its risk-benefit assessment. A complete set of prototype licensing questionnaires is at Appendix D.

Figure II: Peer Review Process



Institutional Review – Activities of Potential Concern

Proposed research activity in this category would be subject to institutional review and approval by a Local Pathogens Research Committee. The LPRC would be similar in some ways to the Institutional Biosafety Committees that currently exercise local oversight of much recombinant DNA research, but would need to meet more frequently and be provided with more resources, including compensation for the committee members' time and administrative support. It would also need to have more formalized procedures for conducting risk-benefit assessments and for documenting its deliberations and resulting decisions. The LPRC would consist of no fewer than five voting members who collectively have expertise both in the research areas subject to oversight at this level and if possible on security matters. At least one member would be required to be a public representative. Advisors to the committee could be appointed on an ad hoc basis if additional expertise was required to review a particular project.

A licensed scientist who wanted to initiate a project involving activities of potential concern at a licensed facility would start by logging into the data management system and completing a new project questionnaire. The questionnaire would require a description of the proposed project (both general and technical) and its purpose, as well as information on the agent or sequence involved, prior relevant work, techniques to be employed (including human or animal experiments, recombinant DNA work or aerosol studies), expected benefits, potential risks (including impact on virulence, environmental stability or host-range), biosafety level, and whether there are alternative means of obtaining the same information. It would also require a certification from the researcher that the proposed project does not raise BWC compliance concerns. Completion of the new project questionnaire would trigger a separate personnel security questionnaire identifying the scientists participating in the project as well as other laboratory personnel and a laboratory biosafety questionnaire containing questions on biosafety-related equipment and procedures in the lab. Other questionnaires would have to be completed if the work involved the use of recombinant materials or pathogenic microorganisms. If the data management system was being used to meet other regulatory requirements, such as those related to human subject or animal research, questionnaires pertaining to those issues would be completed as well. A complete set of prototype project questionnaires is at Appendix E.

The institutional biosafety officer would be responsible for ensuring that the proposal received all appropriate reviews before work began. He or she would confirm that the necessary questionnaires had been completed by the researcher and, together with the chairperson of the Local Pathogens Research Committee, that the necessary expertise was available on the Committee to peer review the proposed project for its dual-use implications. The biosafety officer also would act as a liaison with the other local review committees, such as those governing human subject or animal research, in an attempt to promote expeditious and efficient consideration of the proposed project by those bodies. This would be facilitated by the data management system, which in our prototype includes not

only the questions required to meet BRSS obligations but also some of those necessary to meet other regulatory requirements.

When deciding whether to approve a project, the LPRC would consider the experience of the principal investigator but the most important factor would be the results of its risk-benefit assessment of the proposed work. A standardized protocol, along the lines of the one described earlier, would be used to guide the Committee's deliberations and inform its decision. The LPRC could approve a proposal as submitted, require that the research activities be redesigned to reduce risks, recommend that the research be reviewed and conducted at a different facility with additional biosafety and security features, or elevate the proposal to the National Pathogens Research Authority for review. As part of its peer review of the project, the Committee would also consider the possible need for restrictions on the dissemination of information about the research or research results, based on standardized criteria like those discussed above, although such restrictions generally would not be expected at this level. If, however, a project produced unexpected results that met the criteria for research activities of moderate or extreme concern, then the scientist would be required to work with the national or international oversight body as appropriate on a plan for handling any sensitive materials or information that had been developed. The LPRC would be required to reach a decision on the project within 45 days of receiving a completed application package.

Researchers would not be required to be present at the LPRC meeting when their project is discussed although they would be encouraged to do so in order to answer any questions the Committee might have. Minutes of the LPRC meetings would be kept confidential but would be made available to the NPRA upon request. These minutes would need to include the meeting participants, decisions reached (including the number voting for, against or abstaining), the basis for any required changes in or disapproval of the research, and a summary of the discussion.

At the discretion of the chairperson of the LPRC, an expedited review process could be followed, in which the chairperson, a subset of the Committee or the entire Committee would review the proposed project electronically rather than during a formal meeting. Such a process would only be used in cases involving new proposals believed to pose minimal risk or minor changes to previously approved proposals. A written record of the risk-benefit assessment and the decision would be prepared and circulated to other LPRC members for any project given expedited review.

Upon completion of the project, the principal investigator would be required to submit a brief report on the research results. This report would be included in the institution's database along with other information submitted as part of the project application. Select information from the local level would be sent to the national review body, which in turn would forward information of broader international relevance in an annual report to the international organization.

National Review – Activities of Moderate Concern

Research activities in this category would require oversight and approval by the National Pathogens Research Authority. The NPRA would also periodically

review the work of the Local Pathogen Research Committees and provide guidance on how to handle research of potential concern that produced unexpected results that, if misapplied, could have serious public health consequences.

The National Pathogens Research Authority would be a government body with direct authority to regulate scientists and facilities within its jurisdiction. It could be established within an existing agency such as the National Institutes of Health in the US, or it could be a separate government agency, perhaps including personnel drawn from different government departments. The NPRA would include one or more review committees of up to 20 members with expertise on both the scientific issues subject to oversight at this level and on security issues. Review committee members would be highly respected leaders in their respective professional communities willing to devote a portion of their time to reviewing proposals and making policy recommendations. Review committees would also include individuals who are neither scientists nor security experts but who have other relevant forms of expertise (e.g. ethics) or whose interests would be affected by their recommendations. The specific form of this input could vary by country.

One of the toughest challenges for the NPRA will be to maintain domestic and international confidence in its oversight without compromising confidential business or national security information. To this end, the NPRA should be transparent about its processes, should conduct public forums to promote broad debate on contentious policy questions, and should publish an annual report summarizing the significance of research proposals approved, modified, or rejected. If necessary to protect sensitive information, the report should include a special annex that was only available to cleared individuals with a “need to know.” All NPRA staff and review committee members and anyone else who had access to sensitive commercial and national security information through the NPRA would be vetted and required to sign strict confidentiality agreements. Review committee meetings would not be conducted publicly nor would meeting minutes be available to the public. As with the LPRC, however, detailed meeting records would be kept.

The National Pathogens Research Authority would maintain a comprehensive picture of high-consequence research within its jurisdiction by licensing all scientists, technical support staff, and facilities engaged in research covered by the Biological Research Security System. The NPRA would work with other appropriate government agencies to conduct background checks on researchers and other personnel who work with or have access to dangerous pathogens and to conduct inspections of relevant facilities. Once approved, a personnel license would remain valid for up to five years, as long as annual activity reports were submitted and there was no evidence of violations of other relevant regulations. Facility licenses would be valid for up to 10 years but would have to be renewed in the case of any major structural changes.

Scientists who wished to pursue research activities of moderate concern would be required to submit a project application through their local review body to the NPRA for consideration. Applications for research at this level would require a signature from a senior official at the institution where the research was to take place indicating institutional support for the proposed project. Researchers would be required to present their proposed project to the NPRA

review committee. The committee would have to reach a decision on the project within sixty days of receiving a complete application package. If the results of the research might be subject to dissemination restrictions, the NPRA would advise the principal investigator at the time the project is approved. The NPRA could also determine that the proposed work meets the definition of research of extreme concern and therefore should be submitted for international review by the IPRA.

Once the project was approved, the principal investigator would receive a project permit to conduct only the activities authorized. Although minor modifications to the project could be handled through an expedited process, significant changes would have to be considered under the regular review procedures. Upon completion of the project, a detailed report would be submitted to the NPRA. This report would be included in the national database along with other information submitted as part of the project application.

As discussed above, the NPRA could use a wide range of information gathering and analysis techniques to ensure the accuracy and completeness of information that has been disclosed and to confirm compliance with other BRSS obligations. The NPRA could also request help from other national regulatory bodies and law enforcement agencies as well as from the IPRA to assist it in meeting its oversight requirements.

The NPRA would report annually to the IPRA about its implementation of BRSS obligations. This would include a basic description of completed research projects and any results with protective implications for the broader international community. This would facilitate IPRA efforts to promote international harmonization of national implementation activities. The NPRA would also report on national compliance issues and steps taken to redress them.

International Review – Activities of Extreme Concern

The IPRA would perform many of the same functions that the National Pathogens Research Authority performs for research activities under its control. Thus, it would have one or more review committees of up to 15 scientists and security experts who would be responsible for conducting risk-benefit assessments of projects under the IPRA's jurisdiction. Other IPRA advisory committees would provide advice on the types of high priority research the IPRA should support and help define and update the categories of research activities subject to oversight at each level of the system. The IPRA would have the discretion to select additional members on an ad hoc basis to complement the expertise on these standing panels.

Scientists from member states who wished to pursue research activities of extreme concern would submit a project application through their local and national review bodies to the IPRA for consideration. In addition to the relevant questionnaires, proposals for research at this level would also require a statement of support from the relevant national review body. All senior scientists involved in the proposed project would have to be present during the IPRA review committee's consideration of the proposal. As the volume of research proposals would be much lower than at the other levels of the BRSS, the review committee would be expected to reach a decision on the project within 45 days of receiving a complete application package. If a proposed

project raised important new policy questions, however, the committee's recommendation on the conduct of the research and the handling of the results would have to be approved by the executive body of the international organization.

Because research projects at this level generally would be expected to be important to global health, all project decisions by the International Pathogens Research Authority would be reported to member states. The results of all research approved by the IPRA also generally would be disseminated to all members. Whenever possible, the IPRA would follow the model of openness set by WHO in reviewing proposed research projects with smallpox, the most dangerous existing pathogen. WHO meetings to review proposed projects are open to observers from WHO member states, with detailed meeting notes available on the WHO website. The results of all WHO-approved projects are also publicly available, although there can be a delay between submission to WHO and publication. As noted above, however, in rare circumstances the IPRA might conclude, on the basis of standardized criteria like those used at other levels of the system, that the global interest was best served by restricting access to the details of a research project under its jurisdiction or the subsequent results.

Researchers carrying out projects involving activities of extreme concern would be required to submit biannual reports to IPRA, outlining proposed changes in personnel; detailed experimental results and plans for further research; proposed changes in protocols; the status of agent stocks; safety violations or security breaches; and licensing changes. As at other levels of the oversight system, minor changes could be approved by an expedited process but significant changes would have to go through the regular review procedures. Upon completion of the project, the principal investigator would submit a final report to the IPRA on the research results, the disposition of any recombinant materials (accounting both for the agents consumed in experiments and destruction of excess materials), and publication plans.

IPRA-approved research facilities would be monitored to ensure that the work was done in accordance with protocols authorized by the IPRA. This could include the review of laboratory notebooks, interviews, and sampling. Any irregularities would be promptly reported and scientists who strayed substantially from their proposed work would be subject to penalties and possibly suspension or loss of their right to participate in IPRA-level projects.

In rare circumstances the IPRA might conclude, on the basis of standardized criteria like those used at other levels of the system, that the global interest was best served by restricting access to the details of a research project under its jurisdiction or the subsequent results.

In addition to its work directly overseeing projects involving activities of extreme concern, the International Pathogens Research Authority would also establish and maintain a database of information on such projects, the researchers involved, and all relevant pathogen strains. The database would include strong firewalls to prevent unauthorized access and a sophisticated system for storing, retrieving, translating and cross-referencing data. Access would be limited to specified employees of the IPRA. Confidentiality agreements would be in place and information that was accessed could only be used for approved purposes.

The IPRA would also engage in a variety of activities aimed at assisting participating countries in developing the capacity to meet the peer review and oversight requirements at the heart of the system. Such capacity building measures could include the development of detailed guidelines outlining best-practices; programs to train national officials on what is required to comply with the oversight system; formal processes for sharing information, including lessons learned; and specific assistance on national implementation, including regulatory requirements. It would also assess the judgments being made on a national basis on research of potential and moderate concern and hold periodic conferences aimed at promoting harmonization of national implementation activities.

..... The Way Forward

The advanced oversight system that has been outlined would involve three major innovations over existing oversight arrangements: it would subject the most consequential areas of research to international jurisdiction; it would apply oversight comprehensively within all jurisdictions; and it would make the oversight process a legal obligation. Those provisions are suggested in order to assure effective protection. It is doubtful that exclusive national jurisdiction can achieve a globally harmonized system. It is similarly doubtful that adequate protection could be achieved in any jurisdiction if oversight is partial and optional. It is uncomfortably probable that secretive national threat assessment programs exempted from independent oversight will ultimately generate hostile emulation. Those are serious considerations that can be said to reflect the imperatives of emerging circumstance. They do clearly defy, however, the dominant inclination of institutional tradition and political sentiment.

Legal authority and political affiliation are both vested primarily in national governments throughout the world, and those governments will predictably be the preferred venue for exploiting the benefits and managing the dangers of advances in biology. Moreover, the momentum of scientific discovery that is the source of benefit and danger is based on freedom of inquiry, and the autonomy of the fundamental research process will predictably be defended against fears of perverse regulatory intrusion. The practical question is whether acceptable incremental measures can be devised that would mitigate these objections and provide meaningful benefit without compromising the ultimate achievement of an advanced oversight system.

In principle that is clearly possible. The BRSS would be based on national and local oversight and would subject only a limited set of especially dangerous activities to direct global jurisdiction. A survey of journal articles published in the US from 2000 to mid-2005 indicates that some 310 US facilities and 2,574 US researchers would have been subject to the suggested BRSS oversight procedures had they been in effect.⁶³ Less than 1% of US research publications involving bacteria, viruses or prions would have been affected in any way. Among those that would have been affected, only 12 of the facilities and 185 of the individuals

A survey of journal articles published in the US from 2000 to mid-2005 indicated that some 310 US facilities and 2,574 US researchers would have been subject to the suggested BRSS oversight procedures had they been in effect.

would have been assigned to international jurisdiction — a tiny fraction of the American biomedical research community. Fourteen facilities and 133 individuals would have been assigned to national jurisdiction; and 231 facilities involving 2119 individuals would have fallen under local jurisdiction. Fifty-three facilities and 137 individuals would have encountered multiple jurisdictions. Those numbers suggest that independent development of national and local oversight provisions would cover most of what an advanced system would eventually involve and would lay the foundation for such a system as long as the national and local provisions are based on globally compatible principles.

In practice, relevant initiatives already are being undertaken. With encouragement from the US National Academy of Sciences and the British Royal Society, for example, individual scientists and professional scientific organizations are discussing applicable scientific codes.⁶⁴ Much of this discussion is focused on ethical codes, which describe personal and professional standards or codes of conduct, which provide guidelines on appropriate behavior. Virtually no attention is being given to codes of practice, which outline enforceable procedures and rules. Thus, in September 2001, the World Medical Association issued a declaration on biological weapons which, among other things, called on “all who participate in biomedical research to consider the implications and possible applications of their work and to weigh carefully in the balance the pursuit of scientific knowledge with their ethical responsibilities to society.”⁶⁵ In June 2004, guidelines to prevent the malevolent use of biomedical research were adopted by the American Medical Association and incorporated in the AMA’s Code of Medical Ethics.⁶⁶ Other codes of conduct related to life sciences research have been put forward by the International Committee of the Red Cross⁶⁷ and by Canadian bioethicist Margaret Somerville and former ASM president Ronald Atlas.⁶⁸ In December 2005, the Inter-Academy Panel, an association of over 80 national academies of science, released a set of general principles to guide the development of codes of conduct by individual scientists and local scientific communities.⁶⁹ As noted earlier, work also is being done by the NSABB in the United States on the issue of codes of conduct for scientists and laboratory workers.

It is not enough, of course, to simply have scientific codes, whatever the type. Scientists must be educated about the details of such codes and the potential for misuse of their work. They also must be informed about relevant laws and regulations governing the conduct of dual-use research and provided training to enable them to meet the oversight requirements that are in place. Such education and training programs will be important not only for students at the beginning of their academic studies but also for established researchers who before now have considered the potential benefits but not the potential risks of their work. A prototype biosecurity course for students has been posted on the website of the US journal, *Politics and the Life Sciences*. Additional biosecurity educational modules are being developed by the Federation of American Scientists and other organizations.⁷⁰

These initiatives could be significantly reinforced by scientific funding agencies, research institutions and journals if they required all those with whom they interact on a professional basis to adhere to relevant scientific codes, laws and regulations. In September 2005, the UK’s three leading bioresearch funding agencies, the Medical Research Council, the Wellcome Trust, and the

Biotechnology and Biological Sciences Research Council, announced that they would now require grant applicants, reviewers and funding agency board members to all consider whether the proposed research could be misused for harmful purposes.⁷¹ Research institutions, especially those in industry or government that might initially be outside the scope of a formal oversight arrangement, could impose a similar requirement for individual researchers and the heads of the laboratories in which they work to explicitly consider the dual-use implications of research they conduct as a condition of employment. For their part, scientific journals could refuse to publish manuscripts submitted by researchers who did not follow such rules.

In addition to these measures, other interim steps could be taken by national governments that could more directly strengthen oversight of dual-use research. In the United States, this would include adding the categories of dual-use research and the risk-benefit assessment criteria developed by the NSABB to the NIH Guidelines, consistent with the Fink Committee recommendation. It would also include extending the scope of the *NIH Guidelines* to apply to all relevant research facilities, irrespective of whether they are receiving recombinant DNA funding from NIH,⁷² and converting the Guidelines from a voluntary commitment to a legally binding requirement. As discussed above, the US has already taken a step in this direction by requiring government approval of two particular classes of recombinant DNA experiments if they involve work with pathogens on the select agent list. New legal authority as well as additional funding would be required to revamp the IBC system to take on these added responsibilities and to give NIH the capacity to more effectively monitor, through IBC reporting and periodic inspections, compliance with its rules. IBC as well as NIH oversight would also be enhanced by the adoption of an electronic data management system like the prototype we have developed, which not only consolidates various biosecurity, biosafety and other reporting requirements but also facilitates the transfer of relevant information to the necessary oversight body.⁷³

Outside of the US, other countries that follow the *NIH Guidelines* or that have similar oversight processes for recombinant DNA research could also be encouraged to include specified dual-use research activities in their national regulations and to require adherence by all facilities undertaking such work, on a mandatory basis. These national standards and regulations could then be harmonized among like-minded countries, perhaps beginning with the 30 nations (plus the European Union) that comprise the Organization for Economic Cooperation and Development (OECD). This would be consistent with the OECD's efforts since 2001 to develop a harmonized approach to the management and security of culture collections and other biological resources⁷⁴ as well as its more recent interest, coming out of the September 2004 Frascati conference, in promoting responsible stewardship in the biological sciences and preventing abuse of research.⁷⁵ The OECD could develop a uniform list of dual-use research activities to be subject to oversight as well as standardized criteria for assessing the risks and benefits of such research. It could also establish a process for periodic reporting on national implementation of these measures by OECD member states.

Efforts such as this by the OECD or other like-minded countries could be facilitated by WHO, which has a long history of providing technical information, guidance and assistance to the public, healthcare professionals and

policymakers on the control of dangerous pathogens.⁷⁶ WHO's *Laboratory Biosafety Manual*, first published in 1983, has provided practical guidance on biosafety techniques for use in laboratories around the world. Since the 2001 anthrax letter incidents in the US, WHO has also been developing guidelines for enhancing the security of dangerous pathogens in laboratory environments. And it has been helping to strengthen global public health preparedness and response capabilities for natural, accidental or deliberate releases of biological and other agents that affect public health by developing networks of laboratories and experts on biological agents, providing guidelines for assessing national capabilities, and disseminating technical information on specific agents that pose a threat to public health. In mid-2004 WHO initiated an exploratory project on the governance of life sciences research and its implications for public health.⁷⁷ Many of the issues that were highlighted in this exploratory work are now being considered in a new WHO project aimed at examining the implications of life sciences research for global health security. In addition to raising awareness about the opportunities and risks of life sciences research, this project could also lay the foundation for the development by WHO, in partnership with FAO and OIE, of technical guidelines for overseeing dual-use research.⁷⁸

There are thus a variety of incremental measures that can be pursued by scientists, national governments and international organizations that can help prevent life sciences research from being used, either deliberately or inadvertently, for destructive purposes. Some of these measures, such as ethical codes and codes of conduct, are likely to have a very limited impact unless scientists are educated about the potential risks of their work and their responsibilities to society and funders, employers and publishers formally require them to comply with existing rules, whatever their form. Others, such as national oversight systems and internationally developed technical guidelines, can clearly have a more direct and positive impact on efforts to manage dual-use research. None is sufficient but all of them can help lay the foundation for the more advanced oversight system outlined above.

..... Concluding Observations

Both the arguments underlying our approach to the dual-use problem and the specific proposals we have put forward in this monograph and in other publications seem distinctly less radical today than when we first began this project in 2001. This is especially true in the United States, where attitudes among the scientific elite and among policy experts have undergone a significant change. This is perhaps best exemplified by the work of the Fink Committee, which in its initial meetings appeared confident that the existing process for overseeing recombinant DNA research was more than capable of handling any residual concerns about biotechnology. In its final report, however, the Committee painted a much starker picture of the potential threat posed by dual-use research and underscored the absence of national and international oversight mechanisms to address the problem. It also challenged the conventional wisdom that dangerous research could not be defined and explicitly endorsed the adoption of a tiered peer review process to assess such research. And it made clear that any serious attempt to reduce the risks associated with biotechnology must ultimately be international in scope.

Since the Fink Committee report in 2003, other leading scientists have acknowledged the weaknesses of the existing IBC system,⁷⁹ as documented by the Sunshine Project, with some recommending that the NIH Guidelines on which it is based be replaced by a more comprehensive, legally binding requirement.⁸⁰ Support has also come from a number of different quarters for licensing not only facilities doing work with dangerous pathogens⁸¹ but also biologists themselves.⁸² And former senior officials from both US political parties have recently called for the development of international guidelines for reviewing, approving and monitoring dual-use research, and urged that WHO and other international scientific organizations play a role in this effort.⁸³

At the moment we know that the pace of scientific discovery is rapid and that the accomplishments are truly extraordinary. We do not know what the ultimate consequences will be or the amount of time over which they will emerge. We also do not know how much of a managerial burden will be imposed, but there is good reason to assume that it will eventually be substantial enough to change even deeply entrenched habits and practices. As we evolve carefully, therefore, and do what is immediately acceptable, we should strain to think broadly and boldly. And the appropriate we in this situation is the human species as a whole. If our survival is not literally at stake, then our prosperity very likely is and our common interest much stronger than we have yet appreciated. If so, then we will eventually need more advanced forms of protective organization, and we had best start discussing the detailed implications.

Appendix A

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Appendix C

Prototype Data Management System: Overview

The proposed Biological Research Security System for protective oversight of research with dangerous pathogens rests on two information-intensive elements: personnel and facility licensing and independent peer review. Individual researchers and academic, corporate, or government administrators will only make sensitive information available to outside scrutiny if they believe that the benefits of disclosure will outweigh the inconvenience, expense, and potential for misuse. The BRSS has been designed to match the disclosure requirements with the degree of risk involved in a particular line of research. Thus, one necessary component for the success of the overall BRSS is a multi-level, access-controlled data management system that is easy to use, relatively inexpensive, highly reliable, and extremely secure.

No such data system for tracking research with dangerous pathogens currently exists, and the more limited systems that are available have been criticized on grounds of usability, security, and privacy. For example, U.S. legislation passed in May 2002 requires all facilities that possess certain human, plant or animal pathogens to register with the Centers for Disease Control and Prevention or the Animal and Plant Health Inspection Service. It also directs the Departments of Health and Human Services and Agriculture to develop a national database of registered persons and the controlled agents they possess, including strain and other characterizing information if available. Scientists and administrators have reacted to this limited data collection effort with complaints about the cumbersome reporting process, questions about the security value of some required information, and uncertainty about who could access the reported information and how it might be used. Clearly, both the currently mandated data collection effort and our more ambitious proposal to collect information about research activities as well as pathogen holdings would benefit from a more systematic effort to think through the data management questions from the perspectives of the scientists, administrators, and technical support staff whose cooperation is essential.

Prototype Data Management System¹

The BRSS is essentially a set of rules about what types of information must be disclosed by whom, to whom, when, for what purposes, and with what protections. Accordingly, we have approached the BRSS's prototype data

¹ Jason Harenski developed the functional specification and Gordon McMillan built the prototype system, with assistance from Tim Gulden. The questionnaires were developed by Jessica Mann McCormick.

management software as a workflow system. A workflow system passes information and tasks from user to user according to clearly defined internal rules. Such a system must be dynamic, with defined procedures for updating and disseminating its internal rule sets when, for example, a BRSS policy decision is made to add new research activities to existing oversight procedures or to require additional information about research activities at an existing oversight level.

Our prototype data management system is distributed in a tree-shaped structure, with each locus of oversight having the ability to operate its own server so that it can add customized questions and retain direct control over its data. While we have conceptualized this as a three level structure with local, national, and international level nodes, the software is capable of supporting an arbitrary number of levels. Every end user (researcher, administrator, or technical support staff) is a “client” who communicates exclusively with a server that contains the relevant rule sets and retains physical control over records associated with its clients. The data management system could operate with only one functioning server (the root node at the international level), but typically the servers associated with the broader oversight bodies will act as parent nodes for child nodes that possess more detailed information about a geographically smaller set of less dangerous activities. This structure provides tremendous flexibility and scalability. For example, it means that if a decision was made to start the BRSS with a small number of like-minded countries and then to expand it over time, the data system could be fully functional at the outset and grow with the oversight system. It also means that different countries can organize the nodes under their jurisdiction into different patterns depending on their own national regulatory structure, economic and technological circumstances, and amount of research with dangerous pathogens.

We have built the prototype data management system using open-source software, including some pre-existing packages that have been integrated with custom-written code. This design strategy has made it possible to satisfy our stringent requirements without paying for unnecessary and expensive features. The data management system has been designed so that no license fee needs to be paid by individual users or server nodes. Thus, decisions about participation and node operation can be made on the merits alone. Using open-source software is also consistent with the BRSS philosophy of transparency, reliability, and integrity. Before entrusting sensitive information to the system, any potential user can check the complete code to make sure that the software will do what it is supposed to do and nothing more.

System Description

The prototype BRSS data management system is designed to demonstrate the key features of such a system and to provide a concrete example on which a discussion of a full-blown system can be based. These features include the ability to:

- establish client/server and parent-node/child-node relationships;
- present users with user-friendly questionnaires at appropriate times;
- collect, store, manage, and transmit information between databases according to existing internal rules;

- change internal rules and disseminate modified questionnaires to reflect new BRSS policy decisions or additional requirements established by national or local oversight officials;
- flag situations in which existing rules are not followed or new rules are rejected, so that the situation can receive appropriate follow-up at the appropriate oversight level; and,
- provide financial-industry-grade access controls and information security at all times.

In the interest of security and deployment simplicity, we have chosen a “thin client” framework where all processing and storage is conducted on server nodes that users access via a web browser client. This avoids the need for individual users to install custom software and allows client-server security protocols to be handled in an industry standard way.

The prototype system uses questionnaires reflecting BRSS policies as a basis for the oversight of institutions, laboratories, users, and projects. When a new institution, laboratory, user, or project is created in the system, the user associated with this newly created entity is prompted (via email) to log into the system and respond to a set of questions regarding the new entity (a new project, for example). This opening questionnaire gathers basic information about the new project and then asks a series of questions designed to determine the need for further questions. If, for example, the project involves the use of recombinant DNA technology, the user is queued a follow-up questionnaire about how the technology will be used, what the researcher hopes to accomplish through its use, etc. Answers to these questions may, in turn, trigger additional questionnaires.

Working in conjunction with biosafety officers and bench scientists in the area of pathogen research, we have developed eleven prototype questionnaires with a cascading design to minimize irrelevant questions. Although the system contains many questions overall, most users will need to address relatively few of them for any given project.

Assigning administrative responsibilities by institution, laboratory, user, and project also allows us to avoid redundant questions. Questions pertaining to an institution (e.g. whether it has an institutional biosafety committee) need be answered only once, by the administrator (most likely, the biosafety officer) of that institution. The system will prompt this administrator to update these answers periodically, so individual researchers need not be burdened with them for each new project they undertake. Similarly, a laboratory administrator (which may or may not be the same person as the principle investigator on projects in that laboratory) will answer and update questions pertaining to his or her laboratory, but will not need to answer them again for each new project. Each user will answer and update questions about their own training, status, activities, etc. This means that a project administrator (usually the principle investigator for that project) need not track down all of the relevant information for each researcher on a project. Instead, the system will make it clear to the project administrator whether the researchers involved with the project meet existing BRSS requirements.

Questionnaires propagate automatically down the tree hierarchy so that questions which are approved by the international governing body can be entered into the

data system at the international node and automatically copied to all of the national and local nodes. This allows the system to ensure that the questions required for international review are asked in a uniform manner. This also provides a mechanism for harmonizing review guidelines among nations for projects that will not be subject to international review. Where there is international agreement on questions that should be asked of all projects undergoing national- or local-level review, they can be asked in a uniform fashion. It is also possible for national (or lower) level nodes to add questions of their own that would apply only to nodes under their supervision. One objective of the prototype is to demonstrate that a single software approach can support a range of decisions in this area.

Answers to questions about a proposed project are sent to a review committee comprised of scientists, security and public health experts. These reviewers are initially anonymous relative to the investigator but are known to one another. As the questionnaires are completed, the reviewers are prompted (by email) to log into the system and review them. If the proposal has been determined by the relevant review committee chairperson to pose minimal risk or to involve minor changes to a previously approved project the reviewers can approve the project electronically. Otherwise the proposal would be reviewed in a formal meeting, which the senior scientists involved in the project generally would attend. The reviewers can approve, disapprove, or elevate the project to a higher oversight level. Decision making in this prototype is by consensus, with approval required from all reviewers before a project can proceed. A procedure roughly analogous to this project review procedure is used for licensing institutions, laboratories, and users.

If the reviewers choose to elevate the project, the questionnaires and related documents pertaining to the project are shared with the parent node. For example, if reviewers at a university determine that a project falls into the category of “moderate concern” and thus requires national oversight, they can elevate the project for review by the national node. Review at the national node proceeds as it did at the local level. If, in turn, these reviewers find that the project fits the criteria for activities of “extreme concern,” they can further elevate it for review at the international level.

If at any point in the process a node would like outside input – either from an expert at a peer institution or from someone at one of the higher (or lower) level nodes, the system allows an outside expert who meets BRSS obligations to “visit” another node at the invitation of the host node. This provides a mechanism by which institutions can supplement their internal expertise while retaining control over projects which do not require elevation to a higher review level. This mechanism also provides limited support for collaborative projects which involve researchers from several institutions, though a full-scale system might need more elaborate mechanisms in this area.

The system uses multiple levels of encryption to ensure secure handling of data. All user interactions with the system are conducted using the HTTPS protocol, which is the industry standard means of transmitting sensitive financial information to and from web browsers. The server nodes use state of the art, open-source security standards which provide a unique balance of security on the one hand, and transparency in the means of achieving that security on the

other. Finally, stored data is encrypted, ensuring that even if an intruder were to breach the system security, he could not retrieve any meaningful information.

By providing a secure and systematic framework to facilitate the development, distribution, and review of questionnaires relating to the institutions, laboratories, persons and projects involved with high consequence pathogens research, this prototype provides a concrete example of how the information flow associated with a full-scale BRSS might work. While the prototype does not address every concern that a full-blown system might raise, we believe that it is a valuable platform for demonstrating the information management techniques that would be needed for a real system and for advancing discussion from abstract issues toward concrete policies.

Appendix D

Prototype Licensing Questionnaire

New User

- | | | | |
|--|-------------|---|------------------------|
| 1. What is your name? | <i>Text</i> | 6. What is your current address? | <i>Long Text</i> |
| 2. Please enter your Social Security Number. If you do not have one, list your visa information. | <i>Text</i> | 7. What is your current phone number? | <i>Text</i> |
| 3. What is the highest academic degree you have obtained?
<i>Bachelors degree (BA,BS, etc.)
Masters degree (MA, MS, etc.)
PhD MD
No post secondary school</i> | | 8. Please enter your work contact information. | <i>Long Text</i> |
| 4. From what institution did you obtain this degree? | <i>Text</i> | 9. Please upload the most recent copy of your Curriculum Vitae. | <i>Upload Document</i> |
| 5. What is the name of your current employer? | <i>Text</i> | 10. For which role are you applying?
<i>Investigator Reviewer Compliance Officer Site Administrator Lab Manager Technician Other</i> | |

New Institution

- | | | | |
|--|-------------|--|---------------|
| 1. Is this application:
<i>A new institution
A renewal of an existing license
An amendment to an existing license</i> | | 8. Current CDC registration number, issue date, and expiration date (if applicable): | <i>Text</i> |
| 2. Institution name: | <i>Text</i> | 9. Current APHIS registration number, issue date, and expiration date (if applicable): | <i>Text</i> |
| 3. Address of institution: | <i>Text</i> | 10. Responsible Official: | <i>Text</i> |
| 4. City: | <i>Text</i> | 11. Name of Alternate Responsible Official: | <i>Text</i> |
| 5. State: | <i>Text</i> | 12. Does your institution have an Institutional Biosafety Committee? | <i>Yes No</i> |
| 6. Zip code: | <i>Text</i> | | |
| 7. Type of Institution:
<i>Academic Government Commercial Private Other</i> | | | |

13. Please list the name and title of the Chairperson of the IBC: *Text*
14. How often does your IBC meet? *Text*
15. How is the procedure conducted for the review of protocols? *Long Text*
16. Please upload all approved and pending IBC applications for infectious materials and rDNA for the past 12 months: *Upload Document*
17. Does your institution have an Institutional Animal Care and Use Committee (IACUC)? *Yes No*
18. Please list the name and title of the Chairperson of the IACUC: *Text*
19. How often does the IACUC meet? *Text*
20. Please attach all approved and pending applications pertaining to animal research for the past 12 months: *Upload Document*
21. Which department in your institution is responsible for biosafety and chemical hygiene? *Text*
22. Are routine lab inspections performed? *Yes No*
23. How are records of these inspections maintained? How frequent are the inspections? *Long Text*
24. Attach a copy of the inspection checklist: *Upload Document*
25. Does your institution have a chemical hygiene plan? *Yes No*
26. Does your institution have a standard procedure for handling hazardous materials? *Yes No*
27. Does your institution have an Institutional Review Board (IRB)? *Yes No*
28. Please list the name and title of the Chairperson of the IRB: *Text*
29. How often does your IRB meet? *Text*
30. Please attach the applications and consent form templates used by your IRB: *Upload Document*

New Laboratory

1. Is this application:
*A new laboratory |
 A renewal of an existing license |
 An amendment to an existing license*
2. Laboratory Name: *Text*
3. Address of laboratory: *Text*
4. City: *Text*
5. State: *Text*
6. Zip code: *Text*
7. Type of laboratory:
*Academic | Government |
 Commercial | Private | Other*
8. If "other" please explain:
Long Text
9. Which listed agents are used in your laboratory?
*Dropdown list of listed agents
 (see attached)*

10. Is there a coordinator of all listed agent related research in your laboratory? *Yes No*
11. If yes to question 10, please list the name and title of the person coordinating this research.
Dropdown list of individuals at this institution
12. Upload a copy of the laboratory floorplan. *Upload Document*
13. Please choose all from the following list that describe your HVAC system.
Single-pass | Re-circulated | Dedicated exhaust | Shared exhaust | Constant air volume | Variable air volume | Redundant exhaust fans | Emergency Power Backup
14. Which class of Bio-Safety Cabinet is being used in this laboratory?
I | II, Type A1 | II, Type A2 | II, Type B1 | II, Type B2 | III
15. How is the Bio-Safety Cabinet connected to the HVAC System?
Duct | Thimble | Re-circulating | none of the above
16. How often is the Bio-Safety Cabinet Certified?
Six months | one year
17. Upload a description of the alarms and other monitors in your laboratory that are connected to the HVAC system. Explain each alarm and what it signals, as well as the repair efforts for each alarm type.
Upload Document
18. Does laboratory have eyewash? *Yes No*
19. How often is the eyewash tested?
Weekly | every two weeks | every three weeks | once per month
20. Does this laboratory have a bio-safety manual? *Yes No*
21. MSDS forms available for workers? *Yes No*
22. Upload a copy of your Emergency Response Plans.
Upload Document
- 23 Please upload a copy of all first responder assurance forms.
Upload Document
- 24 Please summarize training methods for the Emergency Response Plan. *Long Text*
- 25 Have employees been provided with Bloodborne Pathogens Training in the past year? *Yes No*

Security Measures

1. Which of the following barriers are present at your laboratory?
Card Swipe | Pin Numbers | Locks on doors | Locks on incubators, refrigerators, etc. | Video cameras/Motion sensors | Other
2. Are security guards present at the entrance to the building in which your laboratory is located? *Yes No*
3. Is there a sign in/out book? *Yes No*
4. Explain how stored pathogens are coded (if at all): *Long Text*
5. Do you maintain inventories on all agents contained in your laboratory? *Yes No*

6. How are the inventory records for listed agents maintained? *Long Text*

7. How is loss/theft of agents detected? *Long Text*

8 How many people have access to the agents? *Text*

9 Please explain the steps that persons wanting access to select agents must complete as well as measures in place to protect the select agents from theft. *Long Text*

10 Upload the current security plan for your laboratory: *Upload Document*

11 Summarize training plans for your security plan: *Long Text*

12 Has your laboratory undergone a threat/vulnerability assessment?
Yes No

13 Which agencies have performed threat/vulnerability assessments for your laboratory? *Long Text*

Appendix E

PROTOTYPE PROJECT QUESTIONNAIRES

New Project

1. Please describe the purpose and provide background information as to the reason for this project. *Long Text*
2. Explain your project in lay terms. *Long Text*
3. Please explain your project in detail in scientific terms. *Long Text*
4. What is your hypothesis? *Long Text*
5. Where will this project be conducted?
Dropdown list of laboratories at the institution
6. Please explain why you are qualified to perform this research. *Long Text*
7. Will research on listed agents be included in this project? *Yes No*
8. Select organism(s) you will be working with:
Dropdown list of select organisms (see attached)
9. Will you be working with an agent related to a listed agent? *Yes No*
10. If yes to question 9, please list the agent name (genus and species). *Text*
11. Will you be working with a non-listed agent? *Yes No*
12. If yes to question 11, please list the agent name (genus, species). *Text*
13. Does the agent(s) used in this project have any recognized or anticipated pathogenic, toxigenic or virulence potential for humans, plants or animals? *Yes No*
14. If yes to question 13, please explain in detail. *Long Text*
15. What Bio-Safety Level will be used? *BSL1 | BSL2 | BSL3 | BSL4*
16. Could these experiments increase virulence or environmental stability? *Yes No*
17. Could the host range be expanded as a result of these experiments? *Yes No*
18. Could the host range of the agents used in this project be expanded due to natural processes? *Yes No*
19. Will these experiments be performed in animal models? *Yes No*
20. Will you be utilizing human subjects? *Yes No*
21. Will aerosol studies be conducted? *Yes No*
22. Will work on recombinant materials (prions, DNA, replicating RNA, etc) be conducted? *Yes No*

23. Will genome transfer, genome replacement, de novo synthesis, or cellular reconstitution of an agent be performed? *Yes No*

24. Please upload a detailed description as to the possible risks of this research as well as the possible benefits. In the discussion include a risk versus benefit comparison.

Upload Document

25. Is an alternative method for conducting this experiment available that would achieve the same results? If so, would the alternative approach be safer? *Long Text*

26. Will this project be conducted at

multiple institutions? *Yes No*

27. If yes to question 26, please list the other participating institutions.

Long Text

28. Are projects similar to the one proposed being conducted at other institutions? *Yes No*

29. The Biological Weapons Convention (BWC) prohibits developing, producing, stockpiling of biological agents and toxins of types and in quantities that have no justification for prophylactic, protective or other peaceful purposes. I certify that I am in compliance with this international treaty. *Yes No*

Pathogenic Organisms

1. What is the name and strain designation of the pathogenic organism to be used in this project? If it is not the wildtype strain, please explain how it differs from the wild type. *Long Text*

2. Does this pathogen infect:
Humans | Animals | Plants

3. Is the organism attenuated? *Yes No*

4. If the organism is not attenuated and is a listed agent, why must it used in the virulent form? *Long Text*

5. Is a toxin produced? *Yes No*

6. If a toxin will be produced, will the project work with the toxin? *Yes No*

7. Is drug resistance expressed?

8. Is the organism inactivated prior to

use? *Yes No*

9. If yes to question 8, by what method? *Text*

10. Do you concentrate the organism in your protocol? *Yes No*

11. If yes to question 10, what concentration will be used (in cfu/ml or pfu/ml) in experiment. *Text*

12. Method of concentration:
centrifugation | precipitation | filtration | other | not applicable

13. Source of organism: *Long Text*

14. Amount of acquisition: *Text*

15. CDC permit # for acquisition, if applicable. *Text*

16. APHIS permit # for acquisition, if applicable. *Text*

17. Will this organism require human blood, human or primate cells for growth? *Yes No*
18. If yes to question 17, list the cell line used in this project, when pertaining to this organism. *Long Text*
19. Are cultures, stocks, and items decontaminated prior to disposal? *Yes No*
20. If yes to question 19, by what method?
autoclave | chemical disinfectant | other | not applicable
21. If other, specify method: *Text*
22. Will the organism be aerosolized? *Yes No*
23. If the organism will be aerosolized, please upload detailed protocols to ensure personnel safety as well as experimental protocols for the production of aerosolized particles. *Upload Document*
24. Will these experiments increase the environmental stability or virulence of the organism? *Yes No*
25. If yes to question 24, please explain how. *Long Text*
26. Is this strain resistant to any antibiotics? *Yes No*
27. If yes to question 26, list. *Long Text*
28. Will strains be constructed to be antibiotic resistant? *Yes No*
29. If yes to question 28, please explain which antibiotic resistance gene(s) will be added. *Long Text*
30. Please list the antibiotics that are able to be used to treat possible infections with this pathogenic organism. *Long Text*
31. Is there a vaccine available against this agent? *Yes No*
32. If yes to question 31, please list recommended vaccines. *Long Text*
33. If no to question 31, is a vaccine currently being developed? *Yes No*
34. Will the strains be vaccine resistant? *Yes No*
35. Is medical surveillance necessary when working with this organism? *Yes No*
36. Have all potentially exposed employees received the Hepatitis B vaccine or proven immunity? *Yes No*
37. Is there an additional recommended vaccination for workers when handling this organism? *Yes No*
38. What other means will be taken to monitor workers health when handling this organism? (i.e. serum banking, tuberculin skin testing, temperature taking) *Long Text*
39. If an accidental release of this organism were to occur, either from a theft or a breach in engineering controls, please explain possible consequences to public health. Please also describe possible economic impacts including those on agriculture and livestock. *Long Text*

Recombinant Materials

1. Provide a brief description of the proposed recombinant research. This should include any parts of the project in which recombinant materials enable the propagation of phenotypes as well as parts involving DNA, replicating RNA, and prions.
Long Text
2. Specify the source and nature of the DNA sequence(s) to be inserted (genus, species, gene name): *Long Text*
3. Will the inserted gene be expressed? *Yes No*
4. If yes to question 3, what are the gene product effects? (specifically, its toxicity, physiological activity, allergenicity, oncogenic potential or ability to alter cell cycle.) *Long Text*
5. Describe the virus, phage and/or plasmid used for constructing your recombinants(prokaryotic, eukaryotic)
Long Text
6. Identify host cell(s) or packaging cell line in which recombinant vector will be amplified: *Long Text*
7. Is the vector replication competent? *Yes No*
8. Are any viral components/sequences present? *Yes No*
9. Specify the function and nature of any viral components specified in question 8: *Long Text*
10. Does the insert contain more than 2/3 of a eukaryotic viral genome?
YES NO
11. Is a helper virus used? *Yes No*
12. If yes to question 11, please specify its type: *Text*
13. Is it a retrovirus? *Yes No*
14. Describe the cell line or species that will be exposed to the recombinant? *Long Text*
15. Will animals be exposed to rDNA? *Yes No*
16. If yes to question 15, please specify animal: *Text*
17. Will the work involve transgenic animals? *Yes No*
18. Will human subjects be exposed to rDNA? *Yes No*
19. Does the donor rDNA, RNA, cDNA source or its vector have any recognized or anticipated pathogenic, toxigenic or virulence potential for animals, plants, or humans?
Yes No
20. If yes to question 19, please explain: *Long Text*
21. What quantity of material will be used? *< 1 Liter | 1-10 Liters | > 10 Liters*

Human Subjects

1. Select all categories of subjects you will be using for this research.
Minors | Non-English Speaking | Minorities | Females | Genetic Materials | Pregnant Females | Fetuses | Abortuses | Healthy Volunteers | Students or Employees | Psychiatrically impaired | Cognitively impaired | Prisoners | Other
2. Number of subjects to be enrolled at this site *Text*
3. Is this a multicenter study? *Yes No*
4. If this is a multicenter study, please enter the names of all sites. *Long Text*
5. If this is a multi-center study, please list the total number of human subjects for the project, encompassing all sites. *Text*
6. Is there a Clinical Trial Agreement or Letter of Indemnification? *Yes No*
7. If yes to question 6, upload a copy of the Clinical Trial Agreement or Letter of Indemnification and a budget. *Upload Document*
8. Please upload a copy of the Human Subjects Protection Training and Examination certificate for all those listed as PIs, co-Investigators, study coordinators or other personnel on this project *Upload Document*
9. What procedures and/or processes will be used during this project that affect the subject? Examples: phlebotomy, amount of blood drawn, bone marrow aspiration, exact procedure used and how much sample is taken. *Long Text*
10. Please give an outline of the proposed study, including plans for analysis and inclusion/exclusion criteria. *Long Text*
11. What are the potential benefits to subjects or others? *Long Text*
12. What are the potential risks to subjects and the incidence of these risks? *Long Text*
13. What are the alternative treatments? *Long Text*
14. Will you recruit your own patients for this study? *Yes No*
15. Please outline the recruitment process. *Long Text*
16. If using a flier or email text to recruit subjects, please upload a copy here. *Upload Document*
17. If non-English speaking subjects are being recruited, has the consent form been translated? *Yes No*
18. If the consent form was not translated please provide the rationale. *Long Text*
19. During the consent process, at what times will the subjects be asked if they have questions?
before | during | after signing | before procedure
20. Will subjects receive a copy of the signed consent form? *Yes No*
21. How will the consent process be documented? *Long Text*

22. Upload a copy of the current consent form. *Upload Document*
23. Please explain where the signed consent forms will be kept as well as efforts to maintain subject confidentiality. *Long Text*
24. Who will obtain consent?
PI | co-PI | Co-Inv | Study Coordinator | Other
25. Please list the names of all those who will be charged with obtaining consent. *Long Text*
26. Is there a data safety monitoring board for this project? *Yes No*
27. Describe what educational activities or scientific knowledge, if any, will be furthered by this study. *Long Text*
- 28 Will patient charts or medical records be reviewed? *Yes No*
29. If personal medical history will be obtained from the subjects, please upload the blank medical history sheet. *Upload Document*
30. If questionnaires will be used, please upload them. *Upload Document*
31. Will specimens be stored for future use? *Yes No*
32. If yes to question 31, please list the specimens stored, and how confidentiality will be protected. *Long Text*
33. Will the storage of specimens serve as a database or repository? *Yes No*
34. Will an investigational drug be administered? *Yes No*
35. If yes to question 34, please list the IND# for the drug being administered. *Text*
36. Will an investigational device be used in this study? *Yes No*
37. If yes to question 36, please supply the IDE# for the device. *Text*
38. Is this a clinical trial? If yes, please choose the type of trial:
Phase 1 | Phase 2 | Phase 3 | Phase 4 Post Marketing
39. What is the status of this project with your institution's IRB:
Denied | Submitted via this form

Animal Use

1. Will materials be administered to animals? *Yes No*
2. If yes to question 1, please list the animal species: *Text*
3. What kind of material will be administered to the animal? *Text*
4. Is the material an animal pathogen? *Yes No*
5. Is the material a human pathogen? *Yes No*
6. Is it possible for the agent to be transmitted from animals to humans in the laboratory environment? *Yes No*

7. Will the material or organism be inactivated prior to use in animals?
Yes No
8. By what route will the material be administered? Text
9. In what volume will it be administered? Text
10. At what titer will it be administered? Text
11. Please explain this choice of route, volume and titer: Long Text
12. Will microisolator cages be used?
Yes No
13. Will barrier housing be used?
Yes No
14. What special procedures will be used for containment? Long Text
15. Will work be done in a biosafety cabinet?
Yes No
16. What disinfectant will be used? Text
17. Describe your procedure for changing bedding and papers. How will these be disposed? Long Text
18. Describe disposal method for animal carcasses: Long Text
19. Describe routine cleaning/decontamination of animal cages: Long Text
20. What Animal Biosafety level has been requested? Text
21. What is the status of this project with your institution's IACUC:
Denied | Submitted via this form
22. Please provide IACUC number, IACUC approval date, and IACUC approval expiration date. (specify if pending) Long Text

Laboratory Biosafety & Engineering Controls

1. Please list the building/room in which experiments will be performed. Text
(e.g. centrifugation, vortexing, sonification, egg harvesting):
Class I Biological Safety Cabinet (BSC) |
Class II BSC | Centrifuge safety cups |
Containment Suite | Other
2. Please list the building/room location in which the bacteria/viruses will be stored. Text
3. At what biosafety level will the work be done? (Reference CDC/NIH BMBL4th Edition. www.cdc.gov 1 | 2 | 3 | 4)
4. What engineering controls are available to control significant aerosol generating steps for work requiring BL-2 containment or higher
5. If other, please describe: Long Text
6. Will sharps (syringes, scalpels, glass) be used? Yes No
7. Has the research protocol been reviewed to minimize the use of sharps where possible? Yes No
8. Will sharps with integrated safety devices be used? Yes No

9. If yes to question 8, please describe these devices (type, model, brand): *Long Text*

10. What personal protective equipment is recommended and available for this work (select all that apply):

Lab Coat | Nitrile Gloves | Non-powdered Latex Gloves | Vinyl Gloves | Safety Glasses w/side shields | Respiratory Protection | Other

11. What disinfectant(s) will be used to for routine cleanup?

1/10 bleach | 70% ethanol | povidone-iodine | phenolic product

chlorine dioxide product | quaternary ammonium product | other

12. What disinfection method(s) will be used for solid waste?

1/10 bleach | 70% ethanol | povidone-iodine | phenolic product | chlorine dioxide product | quaternary ammonium product | other

13. What disinfection method will be used for liquid waste?

1/10 bleach | 70% ethanol | povidone-iodine | phenolic product | chlorine dioxide product | quaternary ammonium product | other

Personnel Security

1. Please select the approved individuals who will be involved with this project.

Dropdown list of licensed individuals at this institution

2. Are there any individuals in your laboratory currently awaiting approval? *Yes No*

3. If yes to question 2, please list the name and social security and/or DOJ number for each person awaiting approval. *Long Text*

4. Has anyone in your laboratory been denied approval? *Yes No*

5. If yes to question 4, please list the name, social security number and/or DOJ number, and the reason given for denial for each person who has been denied approval. *Long Text*

6. Is anyone awaiting approval or who has been denied approval currently working on a different aspect of this project? *Yes No*

7. If yes to question 6, please explain. *Long Text*

End Notes

- ¹ See, for example, 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* (February 2001): 1205-1210 and Jeronimo Cello et al., “Chemical Synthesis of Poliovirus cDNA: Generation of Infectious Virus in the Absence of Natural Template,” *Scienceexpress* (July 11, 2002), available at www.sciencemag.org/cgi/content/abstract/1072266v1.
- ² National Research Council, “Biotechnology Research in an Age of Terrorism,” (Washington, DC: National Academies Press, 2003), available at <http://www.nap.edu/books/0309089778/html/>; and, Royal Society, “Do no harm: reducing the potential for the misuse of life sciences research,” RS policy document 29/04, October 2004.
- ³ In addition to basic research, these figures also cover construction of new biosafety laboratories and development of medical countermeasures. Department of Health and Human Services, “Budget in Brief, Fiscal Year 2007,” available at www.hhs.gov/budget/07budget/2007/BudgetInBrief.pdf.
- ⁴ US Department of Homeland Security and US Army Garrison, “Final Environmental Impact Statement: Construction and Operation of the National Biodefense Analysis and Countermeasures Center (NBACC) Facility by the Department of Homeland Security at Fort Detrick, MD,” December 23, 2004. For a critical analysis of the BTCC’s potential role, see Milton Leitenberg, James Leonard, Richard Spertzel, “Biodefense crossing the line,” *Politics and the Life Sciences* 22, no. 2 (May 17, 2004).
- ⁵ US Department of Homeland Security and US Army Garrison, “Final Environmental Impact Statements” (23 December 2004).
- ⁶ The final document from the Sixth Review Conference is available at [www.unog.ch/80256EDD006B8954/\(httpAssets\)/ICEE7A27069559C5C125723E00647FBF/\\$file/BWC+CON.F.VI+CRP.4-altered+as+ammended.pdf](http://www.unog.ch/80256EDD006B8954/(httpAssets)/ICEE7A27069559C5C125723E00647FBF/$file/BWC+CON.F.VI+CRP.4-altered+as+ammended.pdf).
- ⁷ This discussion draws on Graham S. Pearson and Malcolm R. Dando, “Strengthening the Biological Weapons Convention, Briefing Paper No 6: Article X: Some Building Blocks,” March 1998, available at www.brad.ac.uk/acad/sbtwc. See also the University of Bradford Genomics Gateway website, available at www.brad.ac.uk/acad/sbtwc/gateway/.
- ⁸ For a copy of the Code, see http://binas.unido.org/binas/regulations/unido_codes.pdf
- ⁹ The Convention uses the term “living modified organisms.” For the text, see <http://www.biodiv.org>.
- ¹⁰ The UNEP Guidelines are available at <http://www.unep.org/unep/program/natres/biodiv/irb/unepegds.htm>.
- ¹¹ World Health Organization. *Laboratory Biosafety Manual, Third Edition* (Geneva: World Health Organization, 2004).
- ¹² NSDM 35, November 25, 1969; and U.S. Department of Defense, Office of the Special Assistant for Gulf War Illnesses, Medical Readiness, and Military Deployments, “Nuclear, Biological and Chemical Warfare Defense,” January 8, 2002, available at http://deploymentlink.osd.mil/faq/faq_nbc.shtml.
- ¹³ P.L. 104-132, April 24, 1996, Section 511.
- ¹⁴ P.L. 107-56, October 26, 2001, Section 817.
- ¹⁵ P.L. 107-188, June 12, 2002.
- ¹⁶ For the final regulations, see 42 CFR 73.12 and 9 CFR 121.12; for the BMBL, see US Department of Health and Human Services, “Biosafety in Microbiological and Biomedical Laboratories, Fourth Edition,” (Washington, DC: USGPO, 1999).
- ¹⁷ IBCs are responsible for ensuring the safety of recombinant DNA research, while IRBs focus on the safety of research involving human subjects.
- ¹⁸ See, for example, Ronald M. Atlas, “Applicability of the NIH Recombinant DNA Advisory Committee Paradigm for Reducing the Threat of Bioterrorism,” April 2002.

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- ¹⁹ Sunshine Project, “Mandate for Failure: The State of Institutional Biosafety Committees in an Age of Biological Weapons Research, October 2004, available at <http://www.sunshine-project.org/biodefense/ibcreport.html>.
- ²⁰ NIH Guidelines, April 2002, available at <http://www4.od.nih.gov/oba/rac/guidelines/guidelines.html>.
- ²¹ 42 CFR 73.13 and 9 CFR 121.13.
- ²² National Research Council, “Biotechnology Research in an Age of Terrorism,” (Washington, DC: National Academies Press), October 2003, available at <http://www.nap.edu/books/0309089778/html/>
- ²³ Information on the NSABB, including copies of presentations given at its public meetings, are available at <http://www.biosecurityboard.gov/>
- ²⁴ The draft guidance documents from the three NSABB working groups are available at www.biosecurityboard.gov.
- ²⁵ See, “Conceptualizing an Oversight Framework for Dual-Use Research,” October 25, 2006, available at www.biosecurityboard.gov.
- ²⁶ 7 CFR 340.3; 7 CFR 340.4; and 9 CFR 122.2.
- ²⁷ 40 CFR 172.45; 40 CFR 725.255; 40 CFR 725.234; and 40 CFR 725.238.
- ²⁸ Information on NEPA is available at <http://www.epa.gov/compliance/nepa/>
- ²⁹ Army Regulation 385-69, Biological Defense Safety Program; and 32 CFR 627.
- ³⁰ Statutory Instrument 2001 (No. 4019) The Anti-terrorism, Crime and Security Act 2001 (Commencement No. 1 and Consequential Provisions), available at <http://www.opbw.org/>.
- ³¹ Donald Fredrickson, *The Recombinant DNA Controversy, A Memoir: Science, Politics, and the Public Interest, 1974-1981* (Washington DC: ASM Press, 2001), 40-41, 101.
- ³² Statutory Instrument 2000 (No 2831) The Genetically Modified Organisms (Contained Use) Regulations, available at <http://www.opbw.org/>.
- ³³ An amendment to the 2000 regulation allows information provided in notifications or otherwise part of the public register to be kept confidential for national security reasons. Statutory 2002 (No. 63) The Genetically Modified Organisms (Contained Use) (Amendment) Regulations, available at <http://www.opbw.org/>.
- ³⁴ Statutory Instrument 1992 (No. 3280) The Genetically Modified Organisms (Deliberate Release) Regulations; Statutory Instrument 2002 (No. 2443) The Genetically Modified Organisms (Deliberate Release) Regulations, available at <http://www.opbw.org/>.
- ³⁵ These are discussed in more detail in Graham S. Pearson and Malcolm R. Dando, “Strengthening the Biological Weapons Convention, Briefing Paper No 7: Article X: Further Building Blocks,” March 1998, available at www.brad.ac.uk/acad/sbtwc.
- ³⁶ Statutory Instrument 2002 (No.2677) The Control of Substances Hazardous to Health Regulations, available at <http://www.opbw.org/>.
- ³⁷ This is discussed in Pearson and Dando, “Briefing Paper No 7,” pp. 6-7.
- ³⁸ The 1980 regulation is discussed in Pearson and Dando, “Briefing Paper No. 7,” pp. 4-5; Statutory Instrument 1998 (No. 463) The Specified Animal Pathogens Order, available at <http://www.opbw.org/>.
- ³⁹ See Parliamentary Office of Science and Technology, “GM Animals,” Postnote, Number 157, June 2001 available at <http://www.parliament.uk/post/pn157.pdf>. The Act is available at <http://www.homeoffice.gov.uk/animalsinsp/reference/legislation/index.htm>. Information on local review is available at http://www.homeoffice.gov.uk/animalsinsp/reference/erp/erp_statement.htm.
- ⁴⁰ This discussion of advisory committees draws from Graham S. Pearson and Malcolm R. Dando, “Strengthening the Biological Weapons Convention, Briefing Paper No 4: National Implementation Measures,” January 1998, available at www.brad.ac.uk/acad/sbtwc.
- ⁴¹ Information available at <http://www.hse.gov.uk/aboutus/hsc/iacs/acgm>.
- ⁴² Information available at <http://www.defra.gov.uk/environment/acre>.
- ⁴³ Information available at <http://www.doh.gov.uk/acdp>.
- ⁴⁴ See, for example, Royal Society, “Paper for UN Foundation meeting on the individual and collective role scientists can play in strengthening international treaties,” RS policy document 05/04, April 2004; Royal Society, “Do no harm: reducing the potential for the misuse of life sciences research,” RS policy document 29/04, October 2004; and Royal Society, “The role of scientific codes in preventing the misuse of scientific research,” RS policy document 03/05, May 2005.

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- ⁴⁵ This discussion draws on Jonathan Tucker and Stacy Okutani, "Global Governance of 'Contentious' Science: The Case of the World Health Organization's Oversight of Smallpox Virus Research." The Weapons of Mass Destruction Commission (December 2004), Paper #18.
- ⁴⁶ World Health Organization, "Smallpox eradication: destruction of variola virus stocks," Ninth Plenary Meeting, WHA52.10., 24 May 1999.
- ⁴⁷ WHO, "Report of the meeting of the Ad Hoc Committee on Orthopoxvirus Infections," (Geneva, Switzerland: WHO, 9 September 1994).
- ⁴⁸ A scientific subcommittee reviews all research proposals. Okutani interview with Dr. Riccardo Wittek, Lausanne, Switzerland (May 2004).
- ⁴⁹ World Health Organization, WHO Advisory Committee on Variola Virus Research, "Report of a WHO Meeting," Geneva: 6-9 December, 1999, WHO/CDS/CSR/2000.1
- ⁵⁰ World Health Organization, WHO Advisory Committee on Variola Virus Research, "Report of the Sixth Meeting," Geneva (4-5 November 2004), WHO/CDS/CSR/ARO/2005.4
- ⁵¹ Martin Enserink, "WHA Gives Yellow Light for Variola Studies," *Science* 308 (May 27, 2005): 1235.
- ⁵² Robert H. Sprinkle, "The Biosecurity Trust," *BioScience* 53, no. 3 (March 2003).
- ⁵³ This issue is explored in Alex Greninger, "The Definition and Measurement of Dangerous Research," July 2004, available at <http://www.cissm.umd.edu/documents/Greninger%20Paper%202007-16-04.pdf>.
- ⁵⁴ This is discussed in more detail in Kathryn Nixdorff, Neil Davison, Piers Millet, and Simon Whitby, "Technology and Biological Weapons: Future Threats," available at http://www.brad.ac.uk/acad/sbtwc/ST_Reports/ST_Report_No_2.pdf
- ⁵⁵ National Research Council, "Biotechnology Research in an Age of Terrorism," p. 5.
- ⁵⁶ This can be found at <http://ohsr.od.nih.gov/irb/protocol.html>
- ⁵⁷ The following projects were peer reviewed by some twenty scientists and security experts: Cloning of MHC I Immunomodulators into Vaccinia Virus; Enhancement of Virulence and Transmissibility of Influenza Virus; Immunosuppression and Immuno-Transition in Plague-Mouse Model; Manipulation of Temperate Sensitivity in Pospiviroidae; and, Exploring New Non-Lethal Incapacitation Options.
- ⁵⁸ See Royal Society, "The role of scientific codes in preventing the misuse of scientific research," RS policy document 03/05, May 2005.
- ⁵⁹ US National Academies of Science, "Scientific Communication and National Security," (Washington, DC: National Academy Press), 1982, available at <http://www.nap.edu/books/0309033322/html/>
- ⁶⁰ Martin Enserink, "Entering the Twilight Zone of What Material to Censor," *Science*, November 22, 2002.
- ⁶¹ The IAEA's Standing Advisory Group on Safeguards Implementation, which provides impartial advice on the efficacy of safeguards, might be a useful model for this latter group.
- ⁶² This is discussed in Barry Kellman, "Mechanisms for Impelling Compliance with the BRSS," March 2005.
- ⁶³ As the working paper makes clear, these are rough estimates only, as the author did not screen for all of the categories of research involving non-listed agents because of the overall number of papers and the absence of a suitable search strategy. The figures also do not reflect the broader definition of *de novo* synthesis used in the final version of the Research Categories Table. At the same time, the author almost certainly included some scientists and facilities that were part of research projects outside of the US, simply because they were American or affiliated with an American research facility. Although it is difficult to estimate, these factors could well increase the number of projects subject to local oversight, in particular, by a hundred or more. See Jens H. Kuhn, "Qualitative and Quantitative Assessment of the 'Dangerous Activities' Categories defined by the CISSM Controlling Dangerous Pathogens Project," CISSM Working Paper, December 2005.
- ⁶⁴ See Brian Rappert, "Towards a Life Sciences Code: Countering the Threat from Biological Weapons," Bradford Briefing Paper (2nd series) No. 13, 2004, available at http://www.brad.ac.uk/acad/sbtwc/briefing/BP_13_2ndseries.pdf; and Royal Society, "The role of scientific codes in preventing the misuse of scientific research," RS policy document 03/05, May 2005.
- ⁶⁵ World Medical Association, "Declaration of Washington on Biological Weapons," Document 17.400, September 2001, available at <http://www.wma.net/e/policy/b1.htm>
- ⁶⁶ American Medical Association, "Opinion of the Council on Ethical and Judicial Affairs: Guidelines to Prevent Malevolent Use of Biomedical Research," CEJA Opinion 1-I-04, available at <http://www.ama-assn.org/ama1/pub/upload/mm/465/cejo1i04.doc>

⁶⁷ International Committee of the Red Cross, “Principles of Practice,” in “Preventing Hostile Use of the Life Sciences: From ethics and law to best practice,” November 11, 2004.

⁶⁸ Margaret A. Somerville and Ronald M. Atlas, “Ethics: A Weapon to Counter Bioterrorism,” *Science*, vol. 307, March 25, 2005, available at http://www.sciencemag.org/cgi/content/full/307/5717/1881?maxtoshow=&HITS=10&hits=10&RESULTFOR MAT=&fulltext=atlas%2Band%2Bsomerville&searchid=1120837341834_5746&stored_search=&FIRSTIND EX=0#ref6

⁶⁹ InterAcademy Panel, “IAP Statement on Biosecurity,” November 7, 2005, available at [http://www4.nationalacademies.org/iap/iaphome.nsf/weblinks/WWW-6JPTY/\\$file/IAP_Biosecurity.pdf?OpenElement](http://www4.nationalacademies.org/iap/iaphome.nsf/weblinks/WWW-6JPTY/$file/IAP_Biosecurity.pdf?OpenElement)

⁷⁰ The *Politics and Life Sciences* course is available at http://www.politicsandthelivesciences.org/Biosecurity_course.html; Information on the FAS modules is available at <http://www.fas.org/main/content.jsp?formAction=297&contentId=150>

⁷¹ Medical Research Council, “Organizations address biomedical research misuse threat,” Media Release, September 8, 2005, available at http://www.mrc.ac.uk/prn/public-press_08_sept_2005 The Medical Research Council appears to be using the Fink Committee’s seven experiments of concern to define the types of research that should be reviewed for dual-use risks, but it is unclear whether the other UK funding agencies are taking a similar approach. The MRC statement is available at http://www.mrc.ac.uk/doc-bioterrorism_biomedical_research.doc

⁷² Harvard Professor Matthew Meselson has made a similar proposal, suggesting that local oversight bodies be established at all institutions conducting consequential life sciences research.

⁷³ We intend to work with various institutions to test our data management software in the hope that their adoption of our prototype will help lay the groundwork for the type of comprehensive oversight arrangement outlined in this monograph.

⁷⁴ For a brief discussion of OECD activities in this area, see Jonathan Tucker, “Biosecurity: Limiting Terrorist Access to Deadly Pathogens,” US Institute of Peace, November 2003.

⁷⁵ A summary of the discussion at the Frascati meeting can be found at <http://www.oecd.org/dataoecd/30/56/33855561.pdf>; the organization’s biosecurity website is at <http://www.biosecuritycodes.org>

⁷⁶ For information on WHO’s activities on the health aspects of biological weapons, see <http://www.who.int/csr/delibepidemics/en/>

⁷⁷ See World Health Organization, “Life sciences research: opportunities and risks for public health,” WHO/CDS/CSR/LYO/2005.20, 2005 available at http://www.who.int/csr/resources/publications/deliberate/WHO_CDS_CSR_LYO_2005_20.pdf

⁷⁸ This was also one of the priority areas identified by a scientific working group convened by WHO in October 2006. See, World Health Organization, “Summary Report from the Scientific Working Group Meeting on Life Sciences Research and Global Health Security (Draft).” December 2006.

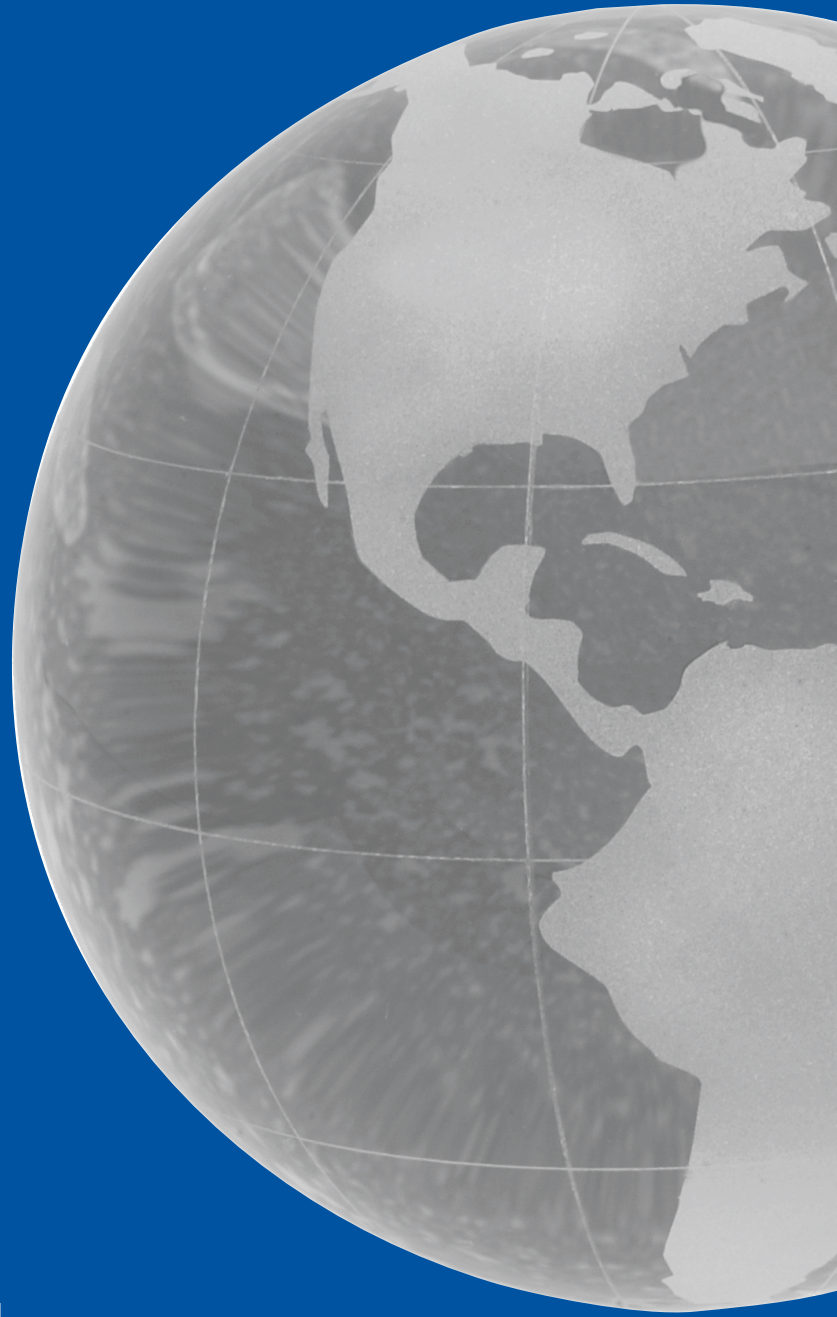
⁷⁹ See “Issues in Biosecurity and Biosafety,” *Science* 308, no. 5730, June 24, 2005 for a letter signed by eleven scientists.

⁸⁰ Philip Chandler, the chair of the Medical College of Georgia IBC, has been quoted as saying that the NIH Guidelines give institutions too much “poetic license” and replacing them with a law would “remove the inconsistencies” and more effectively discourage people from flouting the rules. Kelly Field, “Biosafety Committees Come Under Scrutiny,” *Chronicle of Higher Education* 51, Issue 34, April 29, 2005.

⁸¹ Jonathan Tucker has endorsed facility licensing as part of his proposal for strengthening controls on access to dangerous pathogens. See, Jonathan Tucker, “Biosecurity: Limiting Terrorist Access to Deadly Pathogens,” US Institute of Peace, November 2003.

⁸² Gigi Kwik Gronvall of the UPMC Center for Biosecurity has endorsed licensing biologists in a number of public appearances in recent years. Outside of the US, the British Medical Association called for licensing biologists in a presentation in Geneva in June 2005 as did the journal *Nature* in an editorial the following month. See “Rules of Engagement,” *Nature* 436, No 7047, July 7, 2005.

⁸³ See, United States Institute of Peace, “American Interests and UN Reform: Report of the Task Force on the United Nations,” Washington, DC, 2005, available at http://www.usip.org/un/report/usip_un_report.pdf The Task Force, which was chaired by former Speaker of the House Newt Gingrich and former Senator George Mitchell, recommended doing this under the auspices of a new UN organization for biological weapons issues.



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