CONTROLLING DANGEROUS PATHOGENS: A PROPOSED INTERNATIONAL BIOSECURITY OVERSIGHT SYSTEM[8]

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Dual-use biotechnology research poses global challenges that cannot be managed effectively either by traditional arms control or by voluntary self-governance alone. Legitimate science can create new dangers if a cutting-edge experiment has unanticipated results, if findings from research done for benign purposes are misused by someone else, or if the line between defensive and offensive biological weapon research becomes blurred in practice or perception. Moreover, the relevant pathogens, equipment, and knowledge are widely distributed in research institutions around the globe (http://cissm.umd.edu/projects/pathogens.php). Efforts to prevent biotechnology from leading to destructive consequences while, at the same time, not hampering beneficial research will require new approaches developed cooperatively by a broad range of stakeholders. One such approach has emerged from the Controlling Dangerous Pathogens Project at the Center for International and Security Studies at Maryland (CISSM).

[8] Portions of this chapter are drawn from Harris, E. D., "Dual-use Biotechnology Research: The Case for Protective Oversight", in Brian Rappert and Caitriona McLeish, eds., *A Web of Prevention: Biological Weapons, Life Sciences and the Governance of Research*, October 2007; Steinbruner, J. D, Harris, E. D

Published in Uganda National Academy of Sciences, Promoting Biosafety and Biosecurity Within the Life Sciences: An International Workshop for East Africa, UNAS Press, 2008.

A New Approach

Although dual-use technology has been discussed by arms control and non-proliferation experts for many years, the concern about dual-use biotechnology research is a more recent phenomenon. In February 2001, Australian researchers reported in the *Journal of Virology* that they had inserted an interleukin-4 gene into the mouse pox virus and created a pathogen that was lethal even to some mice that had been vaccinated against the disease.(Jackson et. al., 2001) While the original research had been trying to develop a means of controlling rodent populations, this project and others that followed raised concerns about whether the introduction of IL-4 into other orthopox viruses such as smallpox would have similarly lethal effects.

In the aftermath of the mousepox experiment and amidst controversy over other innovative work, (Harris, 2007) CISSM launched a multi-year effort aimed at trying to address two key questions: What types of dual-use biotechnology research pose the greatest potential danger? How can we manage the risks from such research without impeding scientific progress?

To help answer these questions, CISSM has held numerous workshops in the United States with leading experts from the scientific community, academia, public health and industry. It also has sought to raise awareness on the dual-use issue and to obtain feedback on its ideas through a series of regional workshops that have been held in Hungary for experts from Western and Eastern Europe, in Brazil for experts from Latin American and the Caribbean, in Singapore for experts from the Pacific region, and in Thailand for experts from South Asia and Southeast Asia.

Out of this effort has emerged a detailed proposal for protective oversight of dual-use research that would apply comprehensively to all research institutions conducting relevant research, whether government,

Published in Uganda National Academy of Sciences, Promoting Biosafety and Biosecurity Within the Life Sciences: An International Workshop for East Africa, UNAS Press, 2008.

academic or private sector, would rely on mandatory requirements rather than self-governance, and would be global in scope.[9]

This prototype or model oversight arrangement includes two key elements. The first is national licensing or registration of relevant personnel and research facilities.[10] The requirement for some type of personnel licensing or registration would apply to all scientists, students and technical staff proposing to conduct research covered by the oversight system. The purpose would be to ensure that the affected individuals are technically qualified, 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 serious biosafety violation) that would make it inappropriate for them to carry out consequential research. The requirement for facility licensing or registration 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.

Similar processes are already being used in advanced biology to ensure that certain individuals and facilities meet specified security and safety requirements. For example, under bioterrorism legislation and regulations adopted in the US, background checks are required on any individual having access to certain dangerous pathogens and toxins (designated as 'select agents'), and relevant facilities must be registered. [11]

[9] Successive versions of the study have been posted on the CISSM website since 2003. This chapter draws from the March 2007 version cited in note 1 above.

[10] The licensing process and requirements are discussed in more detail in Steinbruner et al, 2007. While the CISSM study focuses on licensing, the author has framed the proposal more broadly to include both licensing and registration.

Published in Uganda National Academy of Sciences, Promoting Biosafety and Biosecurity Within the Life Sciences: An International Workshop for East Africa, UNAS Press, 2008.

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 – such as doctors, or laboratories that work with radioactive materials. A national licensing or registration requirement for individuals and facilities involved in consequential dual-use research would thus be consistent with and build upon these existing requirements.

The second element is independent peer review of relevant research activities 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 an independent oversight body for review and approval (Steinbruner et al., 2007).
This is consistent with a recommendation from a US National Academy of Sciences expert group, known as the Fink Committee, which in 2003 called for using local institutional biosafety committees (IBCs) for the initial review of what it deemed dual-use "experiments of concern" (NRC, 2003).

As with national licensing or registration, precedents for independent peer review of consequential research can also be found. Within the US and many other countries, review bodies already exist at the local level for research involving recombinant DNA techniques, human subjects and animals. National- level oversight bodies – such as the Recombinant DNA Advisory Committee (RAC) in the US and the National Biosafety Committee (NBC) in Uganda — also already exist. Internationally, a special committee of the World Health Organization has been given responsibility for reviewing and approving smallpox research at the two designated repositories for the smallpox virus in the US and Russia. A requirement for independent peer review of certain types of dual-use research could be undertaken by similar bodies, thus adding the biosecurity mission to existing biosafety and ethical review processes.

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Clearly, any proposals aimed at addressing the threat from dual-use research must balance a number of critical interests. They must protect both the right of scientific investigation *and* the norm against destructive applications of biology. They must provide reassurance both to scientists that they will not be subject to excessive regulation *and* to society that the power of biology is being used appropriately.

To that end, the prototype oversight system developed by CISSM has a number of important features. First, it is narrowly focused in that only the most consequential types of dual-use research are included. Most biomedical and agricultural research would be outside the oversight requirements. Second, it can be readily implemented in that the types of research that must be peer reviewed are clearly defined and presented. Researchers would be able to determine easily whether and, if so, where their proposed work falls within the oversight system and therefore what steps they must take to meet their peer review obligations. This is critical for any oversight system that is mandatory. Third, it is responsive to the threat in that it covers not just specific pathogens, but also the research techniques applied to those pathogens. In so doing, the proposal combines the best of the agent-based controls enacted by the US in 2002 and of the activity-based approach reflected in the Fink Committee's proposed "experiments of concern". Finally, it is based on a tiered design in that the level of risk determines the level of oversight. As discussed below, most research would be reviewed locally at the institutional level, with only a small subset of research considered at a higher level.

At the top of the proposed oversight system there would be a global standard-setting and review body (Steinbruner et al., 2007).This body would be responsible for overseeing and approving activities of extreme concern – research with the most dangerous pathogens or that could result in pathogens significantly more dangerous than those which

[11] Select agents refer to specific human, plant and animal pathogens whose possession and transfer is regulated by the US government because they can be used for destructive purposes. The law establishing this requirement and associated regulations are Public Law 107–188, 12 June 2002, 42 Code of Federal Regulations 73, 7 Code of Federal Regulations 331, and 9 Code of Federal Regulations 121.

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currently exist. This would include work with an eradicated agent such as smallpox or the construction of an antibiotic- or vaccine-resistant controlled agent, as was done during the Soviet offensive biological weapons programme.

In addition to overseeing research activities of extreme concern, the global body would also be responsible for defining the research activities subject to oversight under the different categories and establishing standards for review and reporting. It would also develop rules to protect against the misuse of information reported as part of the oversight process. The global body would also help national governments and local review bodies to meet their oversight obligations by, for example, providing software and technical support for a secure data management system and by assisting in achieving international standards for good laboratory practices. This will be particularly important for developing countries, many of which have neither the biosafety rules nor the institutional mechanisms that could provide the basis for dual-use oversight efforts. No existing organization currently fulfils all of these functions. The closest model is WHO, which not only oversees one specific type of highly consequential research, but also has developed international guidelines for laboratory biosafety and biosecurity.

At the next level of the CISSM model there would be a national review body. This body would be analogous to the RAC in the US or the NBC in Uganda. It would be responsible for overseeing activities of moderate concern – research that involves pathogens or toxins already identified as public health threats, especially research that increases the weaponization potential of such agents. This would include research that increases the transmissibility or environmental stability of a controlled agent or that involves production of such an agent in powder or aerosol form, which are the most common means of disseminating biological warfare agents. The national body would also be responsible for overseeing the work of local review bodies, including licensing or registering qualified researchers and facilities, and for interacting with the global body.

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At the foundation of the proposed CISSM oversight system there would be a local review body. This committee would be analogous to the review bodies at universities and elsewhere that currently oversee recombinant DNA, human and animal research. It would be responsible for overseeing activities of potential concern – research that increases the potential for otherwise benign pathogens to be used as a weapon or that demonstrates techniques that could have destructive applications. This would include research that increases the virulence of a pathogen or that involves the *de novo* synthesis of a pathogen, as was done in the poliovirus experiment. The vast majority of microbiological research would either fall into this category or not be affected at all.

To ensure equitable treatment of all proposed research projects across countries, common criteria would be needed for the relevant review bodies to use in assessing the potential risks of the work, as well as the possible benefits (Steinbruner et.al., 2007). A comparable risk-benefit assessment process is currently used in the US for reviewing human subject research. As in this review process, the risk-benefit assessment of dual-use biological research should apply to all relevant research, irrespective of whether it is carried out in a government, private sector or academic lab. In addition, the relevant review body should be required to consider certain issues as part of its deliberations and to document the discussion of those issues as well as its overall risk-benefit assessment in its meeting minutes.

Based on a peer review simulation exercise of five hypothetical research projects[12], CISSM has developed a set of proposed dual-use risk-benefit assessment criteria analogous to those used for human subject research. 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, biodefence, current necessity and potential impact.

[12]The projects that were peer reviewed are 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.

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Similar issues and questions have been suggested by the British Royal Society for assessing dual-use research (Royal Society, 2005).

Conclusion

Scientists, understandably, are concerned about the potential impact of any measures aimed at addressing the dual-use issue. To help respond to this concern, CISSM undertook a survey of scientific journal articles published in the US between 2000 and mid 2005 , to try to determine how much research would have been covered if its proposed oversight system had been in place[13] (Kuhn, 2005). The survey indicated that less than 1 per cent of US publications concerning bacteria, viruses or prions involved research that would have been subject to oversight had an oversight system like CISSM's been in effect. Overall, based on their publications, some 310 US facilities and 2574 US scientists engaged in research activities that fell within the system. Among those that would have been affected, only 12 of the facilities and 185 of the individuals would have been subject to international oversight – a tiny fraction of the American biotechnology research community. Fourteen facilities and 133 individuals would have been subject to national oversight; and 231 facilities involving 2119 individuals would have been subject to local oversight. Fifty-three facilities and 137 individuals would have encountered multiple oversight levels. Those numbers suggest that an oversight system like that developed by CISSM would impinge upon only a very narrow swath of biotechnology research in the US. The impact in other countries would be even more limited.

Until an oversight arrangement like the model developed by CISSM is achieved, other measures of a more limited nature can and should be pursued (Steinbruner et al. 2007). For example, considerable attention has been given by individual scientists and professional scientific

[13] As the working paper makes clear, these are rough estimates only: 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 more recent version of CISSM's 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 100 or more.

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organizations to the role of scientific codes (Rappert B. 2004). Much of this discussion has focused on ethical codes, which describe personal and professional standards, or codes of conduct that provide guidelines on appropriate behaviour. Serious attention should also be given to codes of practice, which outline enforceable procedures and rules.

But it is not enough to simply have scientific codes, whatever the type. Both students and established scientists should be educated about the details of such codes and the potential for misuse of their work. They should also be informed about relevant laws and regulations governing the conduct of dual-use research and be provided with training to enable them to meet the oversight requirements that are in place. These initiatives could be significantly reinforced if scientific funding agencies and journals required all of those with whom they interact on a professional basis to explicitly consider the dual-use implications of their work, and if all research institutions made this a condition of employment.

Other interim steps could be taken by national governments that would more directly strengthen oversight of dual-use research. The US and other countries that have oversight processes for recombinant DNA research could include specified dual-use research activities in their national regulations and require mandatory adherence by all facilities undertaking such work. These national standards and regulations could then be harmonized among like-minded countries, perhaps on a regional basis. Efforts such as this could be facilitated by the WHO, which has a long history of providing technical information, guidance and assistance to the public, healthcare professionals and policy-makers on the control of dangerous pathogens (www.who.int/csr/delibepidemics/en). In addition to raising awareness about the opportunities and risks of dual-use research, the WHO could take the lead in bringing together the various stakeholder communities to develop technical guidelines for oversight of dual-use research for use by member states.[14]

[14] The development of guidelines for oversight of dual-use research was one of the priority areas identified by a scientific working group convened by the WHO in October 2006. See, World Health Organization, "Scientific Working Group on Life Science Research and Global Health Security, Report of the First Meeting," WHO/CDS/EPR/2007.4, 2007.

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There are thus a number of incremental steps that can be pursued by scientists, national governments and international organizations to help prevent biotechnology research from leading either inadvertently or deliberately to the creation of new, more destructive, pathogens. None is sufficient; but all of them can help to lay the foundation for the type of comprehensive, mandatory, internationally harmonized oversight system outlined by CISSM.

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