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Regulating the Boundaries of Dual-Use Research

Mark S. Frankel

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understanding of the genetic evolution of influenza viruses should positively affect our ability to recognize and respond to influenza outbreaks.

However, whenever one deliberately manipulates a virus or a microbe, it is always possible, at least theoretically, that the research results could be used by bioterrorists to intentionally cause harm, or that an accidental release of a pathogen from a laboratory could inadvertently cause harm. Such research is referred to as "dual-use research," as the research potentially has both positive and negative applications. A particular subset of dual-use research is referred to as "dual-use research of concern" or DURC. DURC is defined as life sciences research that, on the basis of current understanding, can be reasonably anticipated to provide knowledge, information, products, or technologies that can be directly misapplied to pose a significant threat with broad potential consequences to public health and safety, agricultural crops and other plants, animals, the environment, materiel, or national security (*6*). If a particular experiment is identified as DURC, that designation does not inherently mean that such research should be prohibited or not widely published. However, it does call for us to balance carefully the benefit of the research to public health, the biosafety and biosecurity conditions under which the research is conducted, and the potential risk that the knowledge gained from such research may fall into the hands of individuals with ill intent. Research that could enhance the transmissibility of H5N1 viruses clearly is DURC.

In this regard, the question of whether to publish the two H5N1 studies in ferrets has been intensively discussed by an independent federal advisory committee known as the National Science Advisory Board for Biosecurity (NSABB) (*7*, *8*). On the basis of their recommendations and other evaluations, the U.S. government agreed that the research is important for the public health and should be published. However, important lessons were learned along the way and, appropriately, triggered an examination of our approach concerning the conduct, oversight, and communication of DURC. In this regard, the U.S. government announced on 29 March 2012 the U.S. Government Policy for Oversight of Life Sciences Dual Use Research of Concern (*6*). This policy document outlines, for federal departments and agencies that conduct or fund life sciences research, steps to determine whether projects fall under the definition of DURC, to assess the risks and benefits of these projects, to review them regularly, and to develop risk mitigation plans. In the process of weighing the potential risks and benefits of publishing these two manuscripts (*4*, *5*), it also became clear that, when possible, it is critical to identify research with DURC potential before the initiation of the project and, certainly, before the results are submitted for publication. Such monitoring in the case of NIH-funded research requires the concerted effort of all involved, including scientists applying for or in receipt of NIH funding and NIH program officials. Additional guidelines will be needed as well to assist biosafety committees in evaluating DURC at the institutions where the research is conducted.

Furthermore, as a result of the public discussion of these two manuscripts, major gaps in our knowledge of influenza became painfully obvious. For example, there was considerable scientific debate about how well data from the ferret model can be extrapolated to understand influenza virus transmission and pathogenesis in humans. An H5N1 virus strictly adapted for ferret transmissibility may not be entirely relevant to humans. Moreover, although it is likely that the officially reported 60% case-fatality rate for human H5N1 influenza is artificially high (because nonfatal cases are less likely to be reported), there are limited surveillance data on which to base a more accurate estimate. NIH has begun a dialogue with the influenza research community about addressing these and other questions and will initiate a more strategic approach to defining the research gaps that must be addressed in order to responsibly move the field forward. In addition to identifying research gaps, the discussion of these manuscripts underscores the important practical issues of implementing rapid turnaround time between virus isolation and sequencing to provide real-time surveillance.

Finally, despite the importance of performing influenza research that may have DURC potential, this recent experience has underscored the fact that civil society needs to be involved in the dialogue early on. Clearly, research should be conducted and published only if the potential benefits to society outweigh the risks to national security and the potential harm to society. The risk/benefit calculation for certain experiments and their communication is not always obvious, and the current experience reflected considerable disagreement even in the scientific community. The ultimate goal of the new U.S. government-wide DURC policy is to ensure that the conduct and communication of research in this area remain transparent and open and that the risk/benefit balance of such research clearly tips toward benefitting society. The public, which has a stake in the risks and the benefits of such research, deserves a rational and transparent explanation of how decisions are made. It is hoped that the upcoming dialogue related to the new DURC policy will be productive. A social contract among the scientific community, policy-makers, and the general public that builds trust is essential for success of this process.

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PERSPECTIVE

Regulating the Boundaries of Dual-Use Research

Mark S. Frankel

A new U.S. policy for dual-use life science research defines what is permissible by scientists and the government. However, further negotiations will be needed as governments realize the consequences of such boundaries for research and society.

The recent furor surrounding H5N1 influenza research and the intervention of national and international governmental bodies into the publication process (*1*) have brought to the fore a long-standing question regarding the relationship between science and society. That is, what is the proper role of government in regulating science? The science-society relationship has evolved from a time when science was seen as best left to the scientists to the current environment in which scientists are subject to competing claims from an expanding number of stakeholders who see the relevance

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of science to their core concerns—businesses seeking a profit, universities seeking federal and state funding, patients seeking cures, and politicians seeking votes, among others. As such, there has been an increasing demand for accountability on the part of the scientific community. Toward this end, what should governments do?

The responsibilities associated with being a scientist can be viewed as two basic types. One is internal to science, which addresses the responsibility to adhere to accepted standards of scientific practice when conducting and reporting research. The other goes beyond the responsibilities related to doing science, focusing more on the social consequences of applying research findings. The H5N1 case, in which two research papers (*2*–*4*) show that the virus can mutate into a form that might spread rapidly among humans, presents a very compelling challenge for scientists. The controversy over whether to publish the papers intersects with both types of responsibilities. For the first type, it raises questions about how much of a researcher's methods should be readily accessible for others to assess the integrity of the research and its relationship to the published findings, which go to the core of what the scientific community considers to be acceptable research practices. It also raises questions about the scope of scientists' social responsibilities when the research has dual-use implications—offering knowledge that could contribute to greater resilience in the face of a potential pandemic, as well as be intentionally misused or accidentally released with potentially catastrophic effects. The H5N1 case also illuminates scientists' responsibility to follow appropriate biosafety practices to safeguard fellow researchers, as well as the public. World-leading H5N1 researchers agreed to a voluntary, temporary moratorium on research to allow for international discussion (*5*).

For governments, the challenges of responding to the H5N1 controversy are also compelling. They must deal with increasing public calls for greater government oversight of research, while at the same time relying on scientists to help them prepare for a pandemic disaster. They must also avoid overregulation out of concern that their actions will impede discoveries and innovation. Determining the level of regulation that is "just right" is a balancing act among many competing interests. What the history of the science-society relationship reveals is that the result is an outcome of ongoing negotiations by a range of stakeholders to determine the authority, jurisdiction, and responsibilities—setting the boundaries—of what is or is not permissible action by scientists and the government (*6*).

The debate over the two research papers led to a resolution regarding their publication (*7*) in which one paper was published in May by *Nature* (*3*) while the other is published in this issue of *Science* (*4*), both in updated, uncensored forms. However, that does not end the negotiations. At a recent hearing before the United States Senate, called primarily in response to the H5N1 research, Senator Joseph Lieberman (I-CT) remarked that "Although this particular issue appears to have been resolved, it's going to recur and we can't just 'kick this can down the road' and deal with it on an ad hoc basis when it happens again" (*8*). This is a reminder that while the focus of attention has been on the two papers, there is a larger landscape for which boundaries have yet to be negotiated.

One attempt to draw those boundaries in the United States is the new U.S. Policy for Oversight of Life Sciences Dual Use Research of Concern, designed "to establish regular review of United States Government funded or conducted research with certain high-consequence pathogens and toxins for its potential to be dual use research of concern (DURC)" (*9*). The Policy lists as a principle that the "Government will facilitate the sharing of the results and products of life sciences research conducted or funded by United States Government agencies,…. In executing this Policy, the United States Government will abide by and enforce all relevant Presidential Directives and Executive Orders,…. (*9*). On the surface, that's good news for science, since current U.S. policy for "sharing of the results and products" of research relative to national security is governed by a Presidential National Security Decision Directive (NSDD-189) issued in 1985 that fundamental (i.e.,"basic") research will remain "unrestricted," or if national security concerns require control, the mechanism for doing so will be to classify the research (*10*). However, if one reads further in the new U.S. Policy, the boundaries are less clear. The Policy gives the federal government the responsibility to consider "risk mitigation measures," including the following: "Determining the venue and mode of communication (addressing content, timing, and possibly the extent of distribution of the information) to communicate the research responsibly." If such measures are not adequate, the government will determine whether to "classify the research" or "Not provide or terminate research funding." The possibility of having one's research classified or funding terminated after the research is underway is not conducive to good science and may well discourage some researchers from engaging in such work.

> "… while the focus of attention has been on the two papers, there is a larger landscape for which boundaries have yet to be negotiated."

The U.S. government's policy is a boundary-changing document in its relationship with U.S.-based researchers engaged in dual-use life sciences research, setting aside a previous approach that had essentially deferred to the research community (i.e., scientists, their institutions, and journal editors) to decide what, how, and when research is published. But what does this mean for international research?

The Policy does apply to U.S. scientists in research partnerships with non-U.S. scientists, which could put those collaborations under a cloud of considerable uncertainty, if not in jeopardy. It could also put U.S. science at a disadvantage in competing for international prominence. The Policy does acknowledge the need to pursue "engagement with our international partners" but offers no details. There will be much boundary negotiation, as governments jockey over how policy differences, where policies exist at all, will be reconciled. One troubling example from the H5N1 incident is that the Netherlands required the authors of one of the disputed papers (*4*) to apply for government permission to submit their paper for publication, claiming that the study falls "under regulations that control the export of weapons technology" (*11*). That view of the research would appear to be in conflict with the U.S. NSDD-189, as well as U.S. export control regulations, which exempt basic research. But, then, boundaries are often fuzzy and subject to interpretation, and which ones will prevail is often unpredictable. In this case, the Netherlands government viewed the H5N1 research as applied, not basic, and although the authors contested this view, they applied (and received) an export license (*12*).

What dual-use life sciences research will look like in the U.S. and whether, how, and when it might be disseminated are still open to boundary

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definition. Toward that end, governments should agree on a core set of principles that reflect a global consensus on fostering international cooperation, followed by efforts to harmonize policies and practices, including those pertaining to the dissemination of dual-use research, to mitigate the potential for malevolent uses of dual-use research. The scientific community cannot afford to be bystanders in these efforts. This is not merely a matter of self-interest. Scientists have a social responsibility to inform the scientific community, the public, and policy-makers of the potential dangers of their work, as well as of the risks and lost opportunities associated with restricting the flow of scientific information. There may be good reasons for governments to control dissemination, but they should understand what the consequences may be for science and policy.

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POLICY FORUM

Implementing the New U.S. Dual-Use Policy

Carrie D. Wolinetz

After a decade of intensive policy discussions on the topic of dual-use research of concern (DURC) in the life sciences, there has been a lack of consensus on how to practically define DURC; whether it is feasible to identify and regulate DURC experiments; how to address the risks associated with DURC; and how to balance this risk with the necessity of fostering life sciences research for public health and biodefense. The publication of two avian influenza studies has brought the DURC issue back into sharp focus and has resulted in a new set of federal guidelines. However, the new DURC policy raises questions regarding whether this is the best policy solution to a complicated biosecurity concern.

Since the publication of a 2001 experiment synthesizing polio virus de novo received national attention, the research community has been engaged in a philosophical and policy debate over how to deal with the challenge of dual-use life science research. Dual-use research of concern (DURC) is roughly defined as research that is intended for legitimate, beneficial purposes but also carries a risk of being misused for malicious purposes. The ability to define DURC in a way that facilitates its identification and regulation has been an issue that the biosecurity community has struggled with for nearly a decade (*1*). Mitigating the risks associated with biological DURC has been the subject of two National Academies reports and major international fora, including meetings hosted by the InterAcademy Panel and associated with the Biological Weapons and Toxins Convention (BWTC). These led to the formation of the National Science Advisory Board for Biosecurity (NSABB), a U.S. federal government advisory committee that has produced multiple reports and workshops in the 8 years since its inception (*1*). However, there is still no consensus on how to practically define DURC; whether it is feasible to identify and regulate DURC experiments; how to address risks associated with DURC; and how to balance this risk with the necessity of fostering life sciences research for public health and biodefense.

Recent public attention on the publication of two avian (H5N1) influenza studies has brought the dual-use issue into sharp focus and has resulted in a swift response from the U.S. government in the form of the "United States Government Policy for Oversight of Life Sciences Dual Use Research of Concern" (*2*). The policy calls on federal agencies to review research involving 15 agents from the select agent list, determine whether they meet the definition of DURC, conduct a risk assessment, and then mitigate risks in collaboration with the institution and scientist conducting the research. It was issued in unusual fashion by posting on the National Institutes of Health (NIH) Office of Biotechnology Activities' Web site on 29 March 2012 and has raised questions in the research community about whether it is the best policy solution to a complicated biosecurity concern.

Does the Policy Fully Address Dual Use?

The DURC policy is limited to experiments involving 15 agents that are already on the select agent list (which includes roughly 80 agents). This list was initially generated as part of the federal Select Agent Program established under the Public Health Security and Bioterrorism Preparedness and Response Act of 2002.

This raises a number of questions about the redundancy of the policy. Experiments involving select agents are already stringently regulated by a system that includes background checks on all personnel involved and licensing of the facilities (*3*). In addition, the Select Agent Rule is currently under review (*4*), and the proposed changes to the regulations add even more controls to the agents addressed by the DURC policy. Many institutions that conduct a substantial amount of research involving select agents have incorporated this research into biosafety review systems that take place at the local level through Institutional Biosafety Committees (IBCs).

Moreover, many well-documented case studies of DURC that have been cited by the NSABB and many other organizations as evidence for the need for additional DURC guidance or regulation would not be covered by this policy. The de novo synthesis of polio virus, the Australian mousepox experiment, and the Penn State aerosolization study (*5*)—none of these notorious DURC cases would have been regulated under the new policy.

To the U.S. government's credit, this policy clearly tries to limit the scope to prevent the over-identification of legitimate research that does not pose much of a risk and to limit the associated burden on research institutions. However, the redundancy with the Select Agent Program and its inherent failure to capture experiments that are commonly agreed to be DURC raises the question of whether it addresses the DURC issue at all. This is the very quandary identified in a 2007 Congressional Research Service report that explored the challenges of defining DURC for the purposes of oversight (*6*).

Is the DURC Policy Feasible?

The recent review and re-review of the H5N1 avian influenza publications by the NSABB illustrates the difficulty in making decisions about

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