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STEWARDSHIP OR CENSORSHIP?

BALANCING BIOSECURITY, THE PUBLIC'S HEALTH, AND THE BENEFITS OF SCIENTIFIC OPENNESS

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February 2006

A white paper commissioned by the Policy, Ethics and Law Core of the Southeast Regional Center of Excellence for Emerging Infections and Biodefense (SERCEB), NIH/NIAID grant #U54 AI 057157.

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March 2006

Dear Reader,

I am pleased to present this important new study, "Stewardship or Censorship: balancing biosecurity, the public's health, and the benefits of scientific openness," by Julie Fischer, Senior Associate at the Henry L. Stimson Center. Julie's book tackles the thorny issue of how several distinct communities – bioscience research, public health, and national security – relate to each other in the complicated post-September 11 legal and policy environment. While tensions between science and government have a long pedigree, this study brings the story up to date, and outlines some of the passionate disagreements that have arisen over new limitations and requirements imposed on scientific research in the biosciences since the anthrax scare and the enduring concern about terrorism and weapons of mass destruction.

We are grateful to Julie Fischer, a microbiologist turned policy analyst, for offering in such clear and illuminating ways the policy problems and possible solutions. Her study should serve to facilitate communication across these different professional communities, and to help concerned citizens understand better the difficult tradeoffs in trying to promote innovative research that could well help protect the public's health without encouraging dangerous or illicit use of that same research in ways that would threaten health and security more broadly.

This book was commissioned by the Southeast Regional Center of Excellence for Biodefense and Emerging Infections, consortium of researchers from six institutions based at Duke University. We are grateful for their support for this publication, and for their willingness to collaborate on its release and dissemination as part of the Stimson Center's book series.

Sincerely,

Ellen Laipson
President and CEO

— 1 —
INTRODUCTION

"Of the many institutions of American government that emerged in the course of the 20th century, none has received, in relation to its importance, so little attention as that of secrecy."

"The Science of Secrecy," Daniel Patrick Moynihan[1]

Frictions between the science and security communities long pre-date any conflicts arising from the Global War on Terror declared by the George W. Bush administration. Donald Kennedy (editor-in-chief of *Science*), commenting in 2000 on a debate over restrictions newly imposed upon basic space research, noted:

> It is difficult for some, both inside and outside the security community, to understand why science and secrecy find it so hard to get along. The reason is simple: Scientific culture is by nature oriented toward disclosure. Because the research venture grows by accumulation of information, it depends on the free availability of previous work through publication. Security requirements, on the other hand, often dictate concealment. Scientists tend to be exquisitely careful about data but more casual about office order or precise dates, whereas security processes emphasize compartmentalization and strict adherence to procedure. When the two cultures mix, the contrasts between them are dramatically enhanced, sometimes creating conflict.[2]

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[1] Moynihan, Daniel Patrick. AAAS/Massachusetts Institute of Technology *Colloquium on Secrecy in Science*, Cambridge, MA, March 29, 1999.

[2] Kennedy, Donald. "Science and Secrecy." Science 289.5480 (2000): 724.

Despite calls for strengthened ties between the research and security communities to explore and overcome such conflicts, relationships between the two remain frequently strained. For example, policies designed to diminish U.S. vulnerability to terrorism after the fall 2001 attacks, such as new visa requirements for foreign scientists and graduate students, directly affected research, teaching, and engineering as graduate student applications from abroad declined.[3] In a December 2002 statement, the presidents of the three branches of the National Academies voiced concerns that "ongoing research collaborations have been hampered; that outstanding young scientists, engineers, and health researchers have been prevented from or delayed in entering this country; that important international conferences have been canceled or negatively impacted; and that such conferences will be moved out of the United States in the future if the situation is not corrected."[4]

In the wake of the terrorist attacks and anthrax assaults of fall 2001, U.S. policymakers developed the nucleus of a new regulatory framework to address the suddenly evident threat of bioterrorism.

In the wake of the terrorist attacks and anthrax assaults of fall 2001, U.S. policymakers facing the suddenly evident threat of bioterrorism developed the nucleus of a new regulatory framework designed to control access to materials, skills, and knowledge equally fundamental to developing defenses against disease or producing a biological weapon. Many of these controls concentrate on a specific group of human and agricultural pathogens, classed as "select agents" and deemed to pose a high risk to public health or the economy if disseminated successfully. No objective metric has been developed to measure the long-term effectiveness of this regulatory framework in preventing the potential diversion of resources in U.S. academic, government, and industry

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[3] Arnone, Michael. "Security at Home Creates Insecurity Abroad." Chronicle of Higher Education 50.27 (2004): A21.

[4] Alberts, Bruce, Harold Fineburg, and William Wulf. "Statement on the Impact of Current U.S. Visa Restrictions on Science and Engineering." 2002. The National Academies. 12 Dec. 2004. <http://www4.nationalacademies.org/news.nsf/isbn/s12132002?OpenDocument>.

bioscience laboratories to terrorist uses – or in raising awareness and genuine concern about such diversions among the general bioscience community. In much the same way, a system for weighing the unintended consequences of biological security measures is also still lacking. Perhaps not surprisingly, the research and public health communities have yet to evolve a strong consensus about the need for or desirability of such measures.

Attempts to evaluate the impact of the new framework on research have been complicated by policies designed to expand available defenses against biological weapons. The crafting of new U.S. biosecurity laws, regulations, institutional rules, and self-imposed standards coincided with dramatically increased funding for biodefense research, exerting often-discordant pressures on a field in a state of flux. Between fiscal years 2001 and 2004, the budget for biodefense research and vaccine development at the National Institute of Allergy and Infectious Diseases (NIAID, part of the National Institutes of Health, or NIH) climbed from $53 million to more than $1. 6 billion.[5] The growing area of biodefense now encompasses not only select agent studies but myriad interdisciplinary approaches, in addition to overlapping with the traditionally highly collaborative and international field of infectious diseases research. Thus, any exodus of the most directly affected researchers (those engaged in studying select agents) to less stringently regulated fields, or any cumulative loss of productivity at the laboratory level, has been masked by the swelling ranks of those seeking biodefense funding for the first time. The rapid growth in resources for biodefense research has itself engendered controversy: might such investment skew investigation away from other epidemiologically significant diseases, expose inexperienced researchers and the public to deadly pathogens through laboratory accidents, or even foster a new biological arms race by tacitly acknowledging that the United States has assumed the inevitability of bioweapons proliferation?[6,7,8]

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[5] Schuler, Ari. "Billions for Biodefense: Federal Agency Biodefense Funding, FY2001-FY2005." Biosecurity and Bioterrorism 2.2 (2004): 86.

[6] Altman, Sidney et al. "An Open Letter to Elias Zerhouni." Science 307.5714 (2005): 1409.

[7] Shane, Scott. "Exposure at Germ Lab Reignites a Public Health Debate." New York Times 24 Jan. 2005: A13.

[8] Wheelis, Mark and Malcolm Dando. "Back to Bioweapons?" Bulletin of the Atomic Scientists 59.1 (2003): 40.

The post-9/11 colloquy on scientific openness and access in bioscience research has been marked by flashes of passionate discourse from two camps – academic researchers who fear that (potentially ineffective) measures to prevent malicious use of data may unnecessarily impair scientific progress, and their counterparts in security, defense, and law enforcement who see such views as dangerously naïve. The extreme partisans of each argument have reciprocally fanned frustrations. On one side, they ignore the fact that an individual who has thus far eluded public justice successfully released anthrax as a biological weapon, using a mechanism no more complex than a stamped envelope. On the other, proponents of the new security measures overlook the fact that pathogen control in the nuclear model neglects the biological reality that select agents may occur naturally, replicate, and still cause endemic diseases throughout the world. Cultural, technical, and political preconceptions inevitably pervade the discussions.

As used by the George W. Bush administration, the term 'biosecurity' refers to "processes and procedures that are designed to minimize the likelihood biological research will be misused for the production or enhancement of biological weapons."[9] So far, the security template for protecting potential bioweapons materials and knowledge has focused primarily on government regulations to limit access to specific pathogens, and self-regulation to prevent the inadvertent sharing of "cookbooks" for biological weapons through peer-reviewed publications. The debate about whether these controls go too far – or not far enough – has reached a critical juncture with the pending reauthorization of major legislation underlying the current biosecurity regulations as well as increasingly restrictive policies proposed by some government agencies. Decisions on openness in bioscience information made now will certainly affect more than a handful of select agent researchers. The bioscience community has an opportunity to inform the dialogue on security and scientific openness, but must first become conversant with the decades-old discussion on restricting access to products and knowledge of scientific research.

This document attempts to present the mechanisms, historical and current, that have been used to restrict scientific communication in the name of national security, and to consider the bioscience community's possible strategies to strengthen public trust, understand the real and perceived risks of "dangerous research," and contribute to a meaningful

[9] Department of Health and Human Services. National Science Advisory Board for Biosecurity. "Frequently Asked Questions: What is the Administration's policy on Biosecurity in Life Sciences Research?" Department of Health and Human Services. 1 Mar. 2005. <http://www.biosecurityboard.gov/faq.asp>.

national dialogue on the costs and benefits of various regulatory regimes. After a brief description of standards for sharing data and materials in the tradition of peer-reviewed publication (obvious, perhaps, to those steeped in laboratory culture, but a far from transparent process to many policymakers), the report outlines the body of laws and regulations that govern information exchange for "dual-use technologies." The discussion then focuses particularly on how the regulatory framework has grown to embrace the biosciences – arguably the most inherently dual-use of all research disciplines. Together, the lessons of this history and the still unanswered questions from the current debate can help inform new approaches to determining whether and how certain classes of biological experiments should be governed, and how the scientific community does and should protect the safety of researchers and the public when studying infectious diseases.

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THE OPEN EXCHANGE OF IDEA(L)S: SHARING INFORMATION AND DATA IN THE BIOSCIENCES

Biological and biomedical research has become a global enterprise. Rapid technological advances have lowered barriers to the dissemination of basic research capabilities, while the potential for rapid spread of pathogens through travel has expanded the need for international scientific partnerships during and between public health crises. Nearly ubiquitous Internet access extends the capability of researchers in developing nations to both submit and access scientific publications, and to communicate less formally with partners in the United States, Japan, and Europe. As an example of the increasingly international scope of large-scale biology, the Human Genome Project united 20 research centers in six countries.

Bioscience research not only tends to idealize openness and collaboration among colleagues but often depends upon it. In fields such as epidemiology and infectious diseases, work can rely on the ability to pool data from multiple populations to increase statistical significance, or on specimens collected from specific geographic regions, fostering community standards for sharing reagents, samples, techniques, and credit. Mechanisms for sharing scientific information include presentations at conferences (frequently sponsored by professional societies) or visits to other research institutions; research collaborations that involve the exchange of materials, ideas, or analyses; visits of collaborating scientists between laboratories to learn demanding techniques or to make use of specific tools; and – most importantly – publication in peer-reviewed journals. Here again the Human Genome Project aptly illustrates the prevalence and power of the collaborative system. The commitment of government-funded researchers on the project played a significant role in the curious blend of collaboration and

competition that spurred the race between public and private sectors to an early finish.[10]

PEER-REVIEWED PUBLICATIONS.

The system of peer-reviewed, open publication of research findings constitutes the backbone of contemporary biosciences research. Standard practices have evolved for publishing results in the biosciences: Researchers compose and edit a manuscript that presents their hypotheses, experimental methods, findings, and conclusions, and submit this to a scientific journal. Journal editors ask other scientists with relevant expertise to evaluate the validity of the findings, and to determine whether they merit publication as submitted, only after meeting specific conditions suggested during the editing process (such as additional experiments or changes in the presentation of the data), or not at all. Most scientific journals have recast traditionally tacit agreements for authors as requirements, explicitly demanding that authors present materials and methods in sufficient detail to "allow a qualified reader to replicate all experimental procedures."[11] Authors are also expected to share, within reason, any unique materials described in the published manuscript that would be required to validate, refute, or build upon their findings.

A 2002 economic analysis estimated that science, technology, and medical journals constitute a $7 billion global industry.[12] Collectively, commercial publishers, university presses, and professional societies publish about 1.2 million articles a year in about 16,000 periodical journals.[13] Many of the professional societies that publish scientific journals enjoy international memberships ranging from hundreds to the

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[10] Collins, F. S., M. Morgan, and A. Patrinos, "The Human Genome Project: Lessons from Large-Scale Biology." Science 300 (2003): 286-290.

[11] Committee on Responsibilities of Authorship in the Biological Sciences. Sharing Publication-Related Data and Materials: Responsibilities of Authorship in the Life Sciences. Washington, DC: The National Academies Press, 2003.

[12] Morgan Stanley Media Report. Scientific Publishing: Knowledge Is Power. New York: Morgan Stanley, 2002. 1 Feb. 2005. <http://www.econ.ucsb.edu/~tedb/Journals/morganstanley.pdf>.

[13] "Scientific Publishing: Access All Areas." 5 Aug. 2004. The Economist. 1 Feb. 2005. <http://www.economist.com/science/displayStory.cfm?story_id=3061258>.

tens of thousands. For example, the American Society for Microbiology (ASM) – the largest and oldest life sciences membership organization in the world – has a membership of more than 42,000 and publishes 11 internationally distributed journals, while *Science*, a weekly general science journal published by the American Association for the Advancement of Science (AAAS), reaches an estimated total readership of one million worldwide.[14,15] Several developments may change the face of scientific publishing in the next decades, with general opinion inclined toward broader distribution of information. The increasing ease of electronic communications has prompted political dialogue in the United States and Europe on whether and how scientific publications describing research funded by the government should be made "open access," or available to the public without subscription.[16] In response to such pressures, the NIH recently announced that, as of May 2005, a new policy will create a "stable archive" of NIH-supported research papers made freely available within six months of initial publication.[17]

The ideal of openness embodied in peer-reviewed publishing, however, is not without blemishes. Although the culture of contemporary scientific publishing dates to the seventeenth century British *Philosophical Transactions of the Royal Society*, traditions remain shallowly rooted in some newer disciplines within the life sciences, evoking concerns that some researchers play more fairly than others.[18] A National Research Council committee on the responsibilities of authors and journal editors in the life sciences, prompted by these concerns to

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[14] "About ASM." The American Society for Microbiology. 1 Feb. 2005. <http://www.asm.org/general.asp?bid=14772>.

[15] "About AAAS." The American Association for the Advancement of Science. 1 Feb. 2005. <http://www.aaas.org/aboutaaas/>.

[16] "Scientific Publishing: Access All Areas." 5 Aug. 2004. The Economist. 1 Feb. 2005. <http://www.economist.com/science/displayStory.cfm?story_id=3061258>.

[17] Department of Health and Human Services. National Institutes of Health. Policy on Enhancing Public Access to Archived Publications Resulting from NIH-Funded Research. Notice NOT-OD-05-022. Bethesda, MD: Department of Health and Human Services, 2005. 1 Mar. 2005. <http://grants.nih.gov/grants/guide/notice-files/NOT-OD-05-022.html>.

[18] Sharing Publication-Related Data and Materials: Responsibilities of Authorship in the Life Sciences, 27.

evaluate whether the community requires formal standards to maintain the tradition of open sharing of data and materials, observed:

> While largely unwritten, the community's expectations of authors are a reflection of the value of the publication process to the life-sciences community. The central role of publication in science also explains its value to scientists who want to publish their findings. For individual investigators, publication is a way of receiving intellectual credit and recognition from one's peers (and perhaps the broader public) for the genesis of new knowledge and the prospect of its conversion into beneficial goods and services. Publication also enhances a researcher's job prospects, ability to be promoted or gain tenure, and prospects for research support….Ultimately, this system benefits all members of the scientific community and promotes the progress of science. Although society encourages innovation in other ways (for example, through the patent system), the sharing of scientific findings, data, and materials through publication is at the heart of scientific advancement. A robust and high-quality publication process is, therefore, in the public interest.[19]

[19] Sharing Publication-Related Data and Materials: Responsibilities of Authorship in the Life Sciences, 3.

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THE PRE-9/11 REGULATORY FRAMEWORK IN THE BIOSCIENCES

Prior to the regulations developed after the fall 2001 terrorist attacks, two major systems governed access to materials and information in the biosciences. The first encompasses behaviors and guidelines that comprise biosafety (controlling exposures to potentially hazardous materials). The second includes codes that protect potential proprietary interests in commercial or academic-corporate hybrid endeavors (governing unrestricted release of information to preserve financial incentives for private investment in research and development).

BIOSAFETY: CONTAINING THE HAZARDS OF RESEARCH.

Biosafety practices control access to materials, rather than information, and aim to reduce or eliminate accidental exposures of laboratory workers, the public, and the environment to biological materials that could pose a risk to human health. Past accidents offer horrifying lessons: in 1978, a photographer who worked in a darkroom above a British university laboratory died of smallpox, the last known victim of a disease that had been eliminated as a natural threat.[20] U.S. biosafety controls evolved specifically to address experiments involving recombinant DNA technology (based on uncertainties during the field's nascency), and have broadened to include the study of infectious diseases more generally. Biosafety can be defined as the collection of containment practices that protect researchers and the public from the risks inherent in studying infectious agents, whether genetically modified or isolated from natural sources. These include training in and adherence to standard microbiological techniques, use of protective equipment and clothing, use of prophylactic vaccines where available, and facility

[20] H. Pennington, "Smallpox Scares." London Review of Books. 5 Sept. 2002, Vol. 24, No. 17.

design and operational practices that provide a secondary barrier between the laboratory and the outside world.

[Editor's note: The term "biosafety" is also used, especially in international treaty contexts, to refer to efforts to protect biological diversity from risks theoretically posed by the deliberate or accidental introduction of genetically modified organisms into the environment.[21] In the context of this document, biosafety is used solely in the context of laboratory practices to prevent accidental release or exposures of any biological hazard.]

Scientists seeking a better understanding of particular diseases may require highly purified, and sometimes highly infectious, pathogen cultures for their studies.

Although no exact incidence has been defined, descriptive historical evidence suggests that occupational infections among laboratory workers handling pathogens occur in small numbers but with predictable regularity.[22] As noted in the fourth edition of *Biosafety in Microbiology and Biomedical Laboratories* (BMBL), a set of guidelines issued jointly by the NIH and the Centers for Disease Control and Prevention (CDC) and updated regularly since 1984, "(m)icrobiological laboratories are special, often unique, work environments that may pose identifiable infectious disease risks to persons in or near them."[23] Over time, incorporating experiences that include several decades of exposures in U.S. government laboratories studying biowarfare agents, best practices for avoiding unintentional exposures have emerged.[24]

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[21] "About the Protocol." Cartagena Protocol on Biosafety. 1 Feb. 2005. <http://www.biodiv.org/biosafety/background2.aspx>.

[22] Commission on Physical Sciences. Mathematics, and Applications. Biosafety in the Laboratory: Prudent Practices for Handling and Disposal of Infectious Materials. Washington, DC: The National Academies Press, 1989.

[23] Department of Health and Human Services. Centers for Disease Control and Prevention and National Institutes of Health. Biosafety in Microbiology and Biomedical Laboratories, Fourth Edition. Washington, DC: United States Government Printing Office, 1999. 1 Mar. 2005. <http://www.cdc.gov/od/ohs/biosfty/bmbl4/bmbl4toc.htm>.

[24] Biosafety in Microbiology and Biomedical Laboratories, 13-33.

Scientists seeking a better understanding of particular diseases may require highly purified, and sometimes highly infectious, pathogen cultures for their studies. Accordingly, the BMBL describes four "biosafety levels…which consist of combinations of laboratory practices and techniques, safety equipment, and laboratory facilities."[25] Each biosafety level describes the elements of a containment system appropriate to the health risk posed by various biological agents. These range from Biosafety Level 1 for working with microorganisms not known to cause disease in healthy adults (relying only on standard microbiological practices and hand-washing, and thus suitable for most educational laboratories), to Biosafety Level 4 for "agents that pose a high individual risk of life-threatening disease, which may be transmitted via the aerosol route and for which there is no available vaccine or therapy."[26] Biosafety Level 4 work demands complex ventilation, and barrier protections for workers and laboratory facilities to prevent any biohazards from reaching the former, or leaving the latter. Biosafety Levels 2 and 3 focus on moderate-risk pathogens with escalating potential to be transmitted and cause disease, and prescribe correspondingly stringent levels of personal protective equipment and secondary barriers, such as the use of biological safety cabinets, air filters, and decontamination techniques for potentially hazardous waste. Other secondary barriers include mechanisms, ranging from warnings to locked doors, designed to restrict laboratory access to qualified personnel only as appropriate to each biosafety level. The BMBL also lists infectious agents commonly studied in the laboratory and recommends appropriate precautions for handling each.

As facility in manipulating genetic materials began to grow in the early 1970s, fears that recombinant DNA experiments might transform benign microorganisms into new and insidiously deadly pathogens began to escalate concomitantly among scientists as well as policymakers.[27] The bioscience community agreed to assume a voluntary moratorium on such research until a group of scientists – convened at Asilomar Conference Center in 1975 with the assistance of the National Academy of Sciences and covered widely in the news media – could develop a system for matching the hypothetical risk of different classes of experiments to

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[25] Biosafety in Microbiology and Biomedical Laboratories, 11.

[26] Biosafety in Microbiology and Biomedical Laboratories, 13-14.

[27] Berg, Paul. "Asilomar and Recombinant DNA." Nobelprize.org. 1 Feb. 2005. <http://nobelprize.org/medicine/articles/berg/>.

appropriate containment levels.[28,29] The recommendations made at Asilomar informed a set of guidelines developed by the NIH Recombinant DNA Advisory Committee (RAC) intended to "prevent unintended release or inadvertent exposure to either genetically modified organisms or recombinant DNA."[30]

The NIH *Guidelines for Research Involving Recombinant DNA* describe experiments that must be approved prior to initiation, with increasingly stringent requirements for review and approval based on the source of the DNA, the nature of the DNA sequences, the types of host and vector into which the DNA would be transferred, and whether a foreign gene would be expressed in the host or vector.[31] (For example, more scrutiny would be required for experiments involving DNA from a highly virulent virus, creating DNA constructs complete enough to code for virulent viruses, or transferring novel genes into a pathogenic bacterial strain or into an animal, plant, or human.) Appendix B of the NIH *Guidelines for Research Involving Recombinant DNA* also classifies commonly studied human pathogens according to risk, and Appendix G offers guidance on physical containment practices, recapitulating the BMBL.

The regulatory framework for biosafety in the United States relies largely on legally voluntary compliance and local oversight, reinforced with funding and accreditation pressures. Oversight begins with the review of proposed research at the institutional level. According to the NIH guidelines, researchers planning any experiments involving recombinant DNA (except those explicitly classed as safe by the NIH Guidelines) must submit a proposal to the Institutional Biosafety Committee (IBC), a board composed of at least five institutional representatives or outside

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[28] Berg. "Asilomar and Recombinant DNA."

[29] Berg, Paul et al. "Summary Statement of the Asilomar Conference on Recombinant DNA Molecules." Proceedings of the National Academy of Sciences of the United States of America 72.6 (1975): 1981-1984.

[30] National Institutes of Health. Recombinant DNA Advisory Committee. "About RAC." Bethesda: NIH, 2004. 1 Feb. 2005. <http://www4.od.nih.gov/oba/rac/aboutrdagt.htm>.

[31] National Institutes of Health. Guidelines for Research Involving Recombinant DNA Molecules. Bethesda: NIH, 2002. 1 Mar. 2005. <http://www4.od.nih.gov/oba/rac/guidelines_02/NIH_Guidelines_Apr_02.htm#_Toc7261601>.

consultants with relevant expertise.[32] (Although most of the approximately 400 IBCs registered with the NIH Office of Biotechnology Activities are found in academia, several federal agencies and commercial research companies maintain their own IBCs, either because they receive NIH funding or because they have voluntarily adopted the NIH guidelines as the "gold standard" for biosafety.[33]) The IBC evaluates whether the experiments pose any apparent risk to health or the environment, and if proposed containment procedures appear appropriate.[34] The IBC then approves or denies the proposal, and determines what oversight will be required. Only human gene transfer trials, or those that raise scientific, legal, ethical, social, or safety issues at initial screening, require in-depth discussion at a public RAC review, the federal oversight level.[35] Other primary roles of the RAC include setting policy on classes of experiments and advising NIH and HHS policymakers on biotechnology. As the use of recombinant DNA has become both ubiquitous and unremarkable in the last 20 years, many IBCs have also assumed responsibility for review and oversight of other classes of potentially hazardous research, including proposals involving highly pathogenic organisms.

Enforcement of biosafety codes lies in the threat of endangered funding rather than criminal penalties. Institutions that receive any NIH funding for recombinant DNA research must ensure that every single experiment, even if privately funded, complies with the NIH guidelines, or risk the loss or suspension of all relevant NIH grants.[36] Corporations and individuals not covered under these provisions are encouraged to comply voluntarily. The recommendations within the BMBL are also "intended

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[32] "Frequently Asked Questions of Interest to IBCs." 2005. National Institutes of Health. Office of Biotechnology Activities. 1 Mar. 2005. <http://www4.od.nih.gov/oba/IBC/IBCindexpg.htm>.

[33] National Research Council. Committee on Research Standards and Practices to Prevent the Destructive Application of Biotechnology The Dual-Use Dilemma: Biotechnology Research in an Age of Terrorism. Washington, DC: National Academies Press, 2003.

[34] NIH, Guidelines for Research Involving Recombinant DNA Molecules.

[35] Ibid.

[36] Patterson, Amy. "Recombinant DNA Research and Institutional Biosafety Committees (Letter to All Institutions Receiving NIH Funding)." 2004. National Institutes of Health. 1 Feb. 2005. <http://www4.od.nih.gov/oba/IBC/rDNA_Compliance_Reminder.pdf>.

to provide a voluntary guide or code of practice as well as goals for upgrading operations."[37] Although the BMBL are referenced in sections of the select agent rules, the guidelines themselves remain suggestive rather than prescriptive. Determination of how best to apply the BMBL recommendations depends on the judgment of those responsible for local laboratory and institutional safety (the principal investigator, an institutional Biological Safety Officer – who may be a biosafety professional or a faculty member impressed into a term of service, and the IBC).

A statutory framework for protecting the health and safety of workers in the laboratory, as in other U.S. workplaces, resides in the Department of Labor's Occupational Safety and Health Administration (OSHA). OSHA regulations, and state regulations based upon them, focus mainly on preventing exposures to hazardous chemicals, toxins, or blood-borne pathogens in clinical and laboratory settings, and can be enforced through inspections and penalties for non-compliance.[38] Other regulatory frameworks govern the use of radioisotopes in bioscience research, as well as the safety of human subjects and the welfare of laboratory animals; these also rely largely on approval of protocols and monitoring at the institutional review level, with funding, accreditation, and licensing pressures for compliance.

PROTECTING PROPRIETARY INTERESTS.

Various forms of restriction on the sharing of proprietary data or materials with potential commercial value represent the controls on open scientific communication most familiar to the bioscience research community. The $200 billion per year biotechnology and drug development enterprise relies on patent and copyright laws, non-disclosure and confidentiality agreements (both within the industry and between for-profit and non-profit partners), technical licensing, material transfer agreements, and intellectual property protections of discoveries and databases.[39] Enforcement depends on a mesh of legally binding

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[37] Biosafety in Microbiology and Biomedical Laboratories, viii.

[38] Department of Labor. Occupational Safety and Health Administration. Occupational Health and Safety Standards 29 CFR Part 1910. Washington, DC: DOL. 1 Feb. 2005. <http://www.osha.gov/pls/oshaweb/owastand.display_standard_group?p_toc_level=1&p_part_number=1910>.

[39] Cook-Degan, Robert. "The Urge to Commercialize: Interactions Between Public and Private Research Development." The Role of Scientific and

contracts, university or company policies supported by financial or employment penalties, and enlightened self-interest in possible financial benefits.

Two major factors increasingly influence the application of proprietary concerns to openness in bioscience communications: the changing nature of research and the impact of the Bayh-Dole Act of 1980 (Public Law 96-517), which encouraged commercialization of the products of federally funded research. On the first point, the material products of research more frequently take the form of data (such as genomic sequences) that represent considerable investments with commercial value. U.S. government agencies usually support public access for databases generated with federal funds, while private companies often require subscriptions or fees.[40] Intellectual property laws, including copyright as well as database access laws, differ substantially in other nations; the European Union, for example, has its own database protection measures as well as encompassing individual nations' copyright laws.[41]

The patent and subsequent licensing process may accelerate movement of new technologies from basic research to development, but it also hedges traditional information and materials-sharing arrangements with a bureaucracy of commercial protections.

Second, under the Bayh-Dole Act, the U.S. government renounced any intellectual property claims to products of federally funded research at non-profit, non-government institutions, providing them with a financial

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Technical Data and Information in the Public Domain: Proceedings of a Symposium. Washington, DC: The National Academies Press, 2003.

[40] Commission on Physical Sciences. Mathematics, and Applications. A Question of Balance: Private Rights and the Public Interest in Scientific and Technical Databases. Washington, DC: The National Academies Press, 1999.

[41] Dreier, Thomas. "Overview of Legal Aspects in the European Union." Open Access and the Public Domain in Digital Data and Information for Science: Proceedings of an International Symposium. Washington, DC: The National Academies Press, 2004.

incentive to patent promising discoveries. The Supreme Court's decision in *Diamond vs. Chakrabarty* (the same year as Bayh-Dole) allowed patenting of genetically modified organisms, further strengthening patent protections and the commercial potential of the life sciences.[42] Between 1981 and 2001, the number of patents awarded to all academic institutions in the United States rose from less than 450 to more than 3,200 per year, with the greatest growth in the life sciences and biotechnology sectors.[43,44] Biotechnology firms that facilitate "the communication, transfer and adoption of new knowledge from universities to companies" burgeoned around major research universities during the same period.[45] The patent and subsequent licensing process may accelerate movement of new technologies from basic research to development, but it also hedges traditional information and materials-sharing arrangements with a bureaucracy of commercial protections.[46]

The debate about the impact of these commercial controls on the bioscience enterprise has continued in parallel with evolving discussions on whether, or how, to protect openly published information from potential misuse. There are those who question the impact of these factors in the longstanding principle of information-sharing and peer-reviewed publishing in the scientific community. In the words of the Committee on Responsibilities of Authorship in the Biological Sciences, "Whether or not the short-term gain of partial and restricted access to

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[42] National Science Board. Science and Engineering Indicators 2004 (Chapter 5, Academic Research and Development). Washington, DC: National Science Foundation, 2004. 1 Mar. 2005. <http://www.nsf.gov/sbe/srs/seind04/c5/c5s3.htm#c5s3l5>.

[43] National Science Board. Science and Engineering Indicators 2004. Appendix Table 5-54. Washington, DC: National Science Foundation, 2004. 1 Mar. 2005. <http://www.nsf.gov/sbe/srs/seind04/append/c5/at05-54.xls>.

[44] National Science Board. Science and Engineering Indicators 2004. Figure 5-47. Washington, DC: National Science Foundation, 2004. 1 Mar. 2005. <http://www.nsf.gov/sbe/srs/seind04/c5/fig05-47.htm>.

[45] Huttner, Susanne. "Knowledge and the Biotech Economy: A Case of Mistaken Identity." High-Level Forum on Measuring Knowledge in Learning Economies and Societies. Arlington, VA: Centre for Education Research and Innovation, Organisation for Economic and Cooperative Development, and National Science Foundation: 17-18 May 1999. 1 Mar. 2005. <http://www.oecd.org/dataoecd/18/23/1855200.pdf>.

[46] Kennedy, Donald. "Bayh-Dole: Almost 25." Science 307.5714 (2005): 1375.

data is worth the long-term setbacks to the system of publication is a matter of debate and difficult to prove."[47]

[47] Sharing Publication-Related Data and Materials: Responsibilities of Authorship in the Life Sciences, 66.

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BIOLOGICAL SECURITY IN THE POST-9/11 ENVIRONMENT – CONTROLLING KNOWLEDGE THROUGH ACCESS

Policymakers reacting to the anthrax assaults and terrorist attacks of 2001 concentrated on strategies to limit access to what some security analysts have termed "dangerous pathogens," or classed entirely as "dangerous research."[48] Efforts to develop this new biosecurity framework, however, drew more heavily from past experiences in safeguarding weapons materials than it did from the legacy of biosafety and confidentiality controls that characterized the pre-2001 regulatory framework in the biosciences.

LEGISLATIVE CONTROLS ON "DANGEROUS PATHOGENS."

Following the 1993 attack on the World Trade Center, the release of sarin nerve gas in the Tokyo subway by the cult Aum Shinrikyo in 1995, and the subsequent Oklahoma City bombing, policymakers and analysts voiced growing fears of catastrophic terrorism – including biological attacks – carried out by non-state actors.[49,50] The Antiterrorism and Effective Death Penalty Act of 1996 expanded the definition of

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[48] Greninger, Alex. "The Definition and Measurement of Dangerous Research." CISSM Controlling Dangerous Pathogens Working Paper. College Park, MD: Center for International and Security Studies at Maryland, 2004. 1 Feb. 2005. <http://www.cissm.umd.edu/documents/Greninger%20Paper%2007-16-04.pdf>.

[49] Smithson, Amy E., and Leslie-Ann Levy. Ataxia: The Chemical and Biological Terrorism Threat and the U.S. Response. Washington, DC: The Henry L. Stimson Center, 2000.

[50] Carter, Ashton B., John Deutch, and Philip Zelikow, "Catastrophic Terrorism: Tackling the New Danger," Foreign Affairs 77 (1998): 80.

biological weapons, made threatening their use (in addition to using them) a crime, and required the Secretary of Health and Human Services (HHS) to create a list of biological agents that posed a high threat to human health and to regulate the transfer of those agents between laboratories.[51] The resulting regulation gave rise to the first incarnation of the Select Agent Rule, mandating a system by which CDC would oversee the transfer of pathogens on the eponymous list.[52] By 1999, CDC had established a list of about 40 bacteria, viruses, rickettsiae, fungi, and toxins "with the potential to cause substantial harm to human health," and the agency registered 123 facilities that planned to ship or receive those agents.[53]

The anthrax assaults of fall 2001 further galvanized policymakers already sensitized by the September 11 attacks, particularly as Congress found its own members directly targeted, with no satisfactory list of probable suspects on hand. The USA PATRIOT Act of 2001 expanded the biological weapons statutes established in 1996 to create criminal penalties for the possession of "any biological agent, toxin, or delivery system of a type or in a quantity that, under the circumstances, is not reasonably justified by a prophylactic, protective, bona fide research, or other peaceful purpose," and created a class of "restricted persons" who cannot legally possess, transport, or ship any select agent.[54] Restricted persons under the USA PATRIOT Act include individuals indicted or convicted of crimes punishable by imprisonment for more than one year, fugitives from justice, illegal aliens, dishonorably discharged service members, any "unlawful user of any controlled substance," and anyone who has been "adjudicated as a mental defective" or committed to any mental institution.

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[51] The Anti-Terrorism and Effective Death Penalty Act (Public Law 104-132). 24 April 1996.

[52] Title 42 Part 72.6. Effective 15 April 1997.

[53] Ostroff, Stephen M. "Threat of Bioterrorism in America: Assessing the Adequacy of Federal Law Relating to Dangerous Biological Agents." Testimony before the House Committee on Commerce, Subcommittee on Oversight and Investigations. Washington, DC: Department of Health and Human Services, 1999. 1 Feb. 2005. <http://www.hhs.gov/asl/testify/t990520a.html>.

[54] The Uniting and Strengthening America by Providing Appropriate Tools Required to Intercept and Obstruct Terrorism Act of 2001 (Public Law 107-56). 26 Oct. 2001.

Subsequent legislation aimed at preventing the deliberate theft or misuse of pathogens from U.S. laboratories followed after months of debate. The Public Health Security and Bioterrorism Preparedness and Response Act of 2002 charged the Secretaries of HHS (in the case of human pathogens) and the U.S. Department of Agriculture (USDA, for pathogens of livestock and crops) with expanding upon the initial select agent rules.[55] The Bioterrorism Preparedness Act requires the two agencies to address a broad range of biosecurity issues, which include:

- Expanding and regularly updating the select agents list to include new pathogens or toxins of concern (at present, the list includes about 80 select agents, grouped into categories on the basis of risk level and whether they represent human, agricultural, or overlap pathogens);[56]
- Regulating safety, training, and physical security in laboratories that handle select agents;
- Registering both laboratories and individuals that possess and use select agents;
- Overseeing the inventory of the select agents themselves, including assembling a database of any characteristics that would allow strains or isolates to be identified as the product of a particular laboratory;
- Creating (with the Attorney General) a system for identifying individuals who fall into the category of restricted persons under the USA PATRIOT Act, or who might be "reasonably suspected" by a federal agency of being involved with an organization that plans terrorism or other violent actions, or of being an agent of a foreign power;
- Denying access to select agents to any person who falls within the category of restricted persons;
- Inspecting registered laboratories for adequate physical safeguards to prevent loss, theft, accidental release, or access by unregistered individuals to select agents.[57]

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[55] The Public Health Security and Bioterrorism Preparedness and Response Act of 2002 (Public Law 107-188). 12 June 2002.

[56] See "Select Agents List." Centers for Disease Control and Prevention. 1 Mar. 2005. <http://www.cdc.gov/od/sap/docs/salist.pdf>.

[57] Bioterrorism Preparedness Act, Public Law 107-188.

Violations of the Bioterrorism Preparedness Act can result in criminal penalties that include fines, imprisonment of up to five years, or both; civil penalties include fines of up to $250,000 for individuals and $500,000 for an institution.[58]

THE SELECT AGENT RULES – WHAT IS THE PRACTICAL IMPACT?

After the passage of a law, the agencies charged with responsibility for its provisions must develop and implement regulations based on their interpretation of the legislation, creating a set of working rules from a blueprint. The CDC (representing HHS) and the Animal and Plant Health Inspection Service (or APHIS, representing USDA) implement and enforce the regulations known as the select agent rules as modified by the Bioterrorism Preparedness Act. These regulations apply to academic institutions; commercial manufacturing facilities; federal, state, and local government agencies; other private research facilities; and individuals who intend to use, possess, or transfer select agents.[59,60]

Objections to the 2005 select agent rules reflect fundamental philosophical differences over whether the current system overemphasizes the 'guards, gates, and guns' approach to physical security.

To paraphrase an axiom, the devil is in the implementation. The final select agent rules appeared in March 2005, after more than two years of provisional administration based on interim rules and a mandated period for public commentary. Some of the complaints about the rules, and the

[58] Ibid.

[59] Department of Health and Human Services. Centers for Disease Control and Prevention. 42 CFR Parts 72 and 73, "Possession, Use, and Transfer of Select Agents and Toxins; Final Rule." Federal Register 70.52 (2005).

[60] Department of Agriculture. Animal and Plant Health Inspection Service. 7 CFR Part 331 and 9 CFR Part 121. "Agricultural Bioterrorism Protection Act of 2002; Possession, Use, and Transfer of Biological Agents and Toxins: Final Rule." Federal Register 70.52 (2005).

confusion surrounding their implementation in 2002 and 2003, may be regarded as predictable growing pains in a new system imposed upon a previously lightly regulated field. Other objections reflect fundamental philosophical differences over whether the current system overemphasizes the "guards, gates, and guns" approach to physical security, diverting resources that might be more fruitfully applied to research or different forms of security. Some observers predicted that the rules would have a chilling effect on research, a fear apparently offset by the surge in biodefense funding. In an attempt to understand the daily impact of these regulations on a typical select agent researcher, the Stimson Center invited more than 200 university-based biological researchers to participate in a secure, Web-based survey sent via e-mail. Those solicited for participation had been named as senior authors on manuscripts describing select agent research published in peer-reviewed journals between January 1, 1999, and December 31, 2001. A series of pilot interviews with senior infectious diseases/select agent researchers provided the text for the core of the survey. Twenty-eight researchers, with an average of more than 15 years' experience in studying select agents, completed the questionnaire, and several submitted additional comments on condition of confidentiality. Some of their responses are presented here as part of the analysis on the impact of the select agent rules.

Logistical issues and immediate impact. One of the chief growing pains during the early implementation of the select agent rules arose from confusion about how to interpret and meet the new requirements. During the public comment periods required by law prior to publication of the final select agent rules in the Federal Register, many institutions and professional societies such as ASM observed that sections of the rules lacked clarity, prompting some revisions in the wording of the final version.[61] Of the 28 experienced select agent researchers who responded to a survey on the daily impact of the select agent rules, only two found the CDC/USDA regulations clear and consistent. Echoing this, a survey on biosafety and biosecurity conducted for researchers at Sandia National Laboratories found that 42% of the 203 respondents believed that the regulations were "on the right track but need to be revised to provide clarity."[62] Based on comments shared by researchers, university administrators, and biosafety officers during a public workshop

[61] 42 CFR Parts 72 and 73, Final Rule.

[62] Rivera, Susan, Jennifer Gaudioso, and Reynolds Salerno, "Biosecurity in a Biosafety Environment." 47th Annual Biological Safety Conference. San Antonion, TX: American Biological Safety Association, 20 Oct. 2004.

convened by the Office of Science and Technology Policy (OSTP), individuals and institutions have clearly interpreted the regulations' demands differently, and thus the perceived impact of the new regulations may vary widely among institutions.[63]

Paperwork burden. The lack of clarity may also have contributed to the time burden associated with biosecurity compliance. In the Sandia biosecurity survey, Rivera et al. found that 62% of the 203 respondents cited the time necessary to comply with the new biosecurity requirements as a negative impact.[64] The 28 select agent researchers responding to the Stimson survey dedicated an average of just less than four hours each week to biosecurity compliance tasks (with individual estimates ranging from 15 to 0 hours weekly, some having delegated such tasks to other personnel). Nineteen found the biosecurity paperwork burden greater than similar regulatory demands, such as those associated with animal care, radioisotope, or human subjects regulations. Sixteen of the 28 respondents felt that their institutions had offered legal or administrative support in achieving compliance; only five of these 16 agreed or strongly agreed that their laboratory productivity had returned to baseline as they developed familiarity with the regulations. One respondent cited requirements for "overlap" agents – those regulated by both CDC and APHIS requirements – as a double demand due to inconsistent definitions and duplicate paperwork. (The final rules, in response to comments from many researchers, institutions, and professional societies, increased coordination between the two agencies.[65]) A second respondent worried that many laboratories would routinely experience three- to four-week time lags between filing requests and receiving approvals, a tremendous opportunity cost that could profoundly affect postdoctoral fellows and non-tenured faculty. Another commented more bluntly, "This is a remarkable drain on resources and time," and predicted that the influx of researchers newly diverted to the study of highly virulent pathogens due to the emphasis on biodefense funding would spend more time on paperwork than supervising safe research practices.

Registrations and physical security. The regulations now in place dictate that all laboratories handling select agents (except those exempted

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[63] "Laboratory Biosecurity: A Culture of Responsibility." Federal Register 69.56 (2004): 13527-13528.

[64] Ibid.

[65] 42 CFR Parts 72 and 73, Final Rule, 13302.

because they would obtain such agents incidentally from clinical, veterinary, or environmental samples) should have completed the registration and inspection process with CDC or APHIS. Laboratory registrations last up to three years, contingent on passing inspections and approvals for design and testing of plans related to physical security, incident response, and biosafety.[66] During the initial wave of laboratory registrations (as well as security risk assessments, described below), significant delays in the processing of applications occurred. Both the CDC and the FBI failed to meet statutory deadlines for completing the first round of inspections and assessments, respectively; an eleventh-hour amendment of the regulation allowed labs that had completed their applications to continue research, but required 125 out of the 322 laboratories that had then completed applications to operate under more restrictive provisional registrations until the inspection/approval process could be finished at these institutions.[67]

Twenty of the 26 select agent researchers in the Stimson survey who intended to continue select agent research believed that their laboratories required significant physical security upgrades. One researcher commented that the greatest part of the inspection process had been dedicated to creating an extremely detailed inventory – complete with freezer map – that then required its own security, demanded fastidious upkeep, and would still not detect the surreptitious removal of enough pathogen from a single vial to start a new culture. Another addressed the conspicuousness of the new physical security measures: Few colleagues had been aware of the researcher's years of select agent work in a laboratory that limited access with secured doors and other barriers as indicated by the BMBL until the new measures drew attention from the entire university community, as well as vocal complaints from inconvenienced colleagues.

At a public workshop on the select agent rules, a comment offered by Michael Durham, Director of Occupational and Environmental Safety at Louisiana State University – an institution noted for anthrax research expertise before the fall 2001 assaults – captured the frustration and costs experienced in adapting physical security measures to academic environments. "We put in $130,000 worth of security equipment in our building and then found, under an inspection made, we were still lacking. Recommendations go so far as to recommend bollards be placed in front of a building, concrete obstructions to keep someone from going in with

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[66] 42 CFR Part 73.11, Final Rule, 13322.

[67] Wilkie, Dana. "Select-Agent Security Clearance Stymies Research." The Scientist 18.10 (2004): 45.

a vehicle and blowing the building up. And this is a veterinary school, a veterinary clinic," Durham observed.[68] Such precautions might be appropriate to protect a nuclear or chemical facility, where sabotage might lead to the release of hazardous materials, but seem excessive for protecting heat-labile biologicals housed in finite quantities in freezers (assuming validity to the scenario that terrorists intend to target university pathogen collections for violent destruction, or accomplish theft of a pathogen through spectacular means).

Personnel security. The regulations require that any individuals with access to select agents undergo a security risk assessment conducted by the FBI; this process resembles the security clearance process with fewer administrative demands (a considerably slimmer application), less clear-cut questions, and more latitude in sharing the applicant's personal information with colleagues and others during the investigation process.[69,70] Although some researchers and administrators expressed anxiety about this sharing of information that could not be requested legally under many states' laws or institutional policies, legal opinions have not disputed the FBI's authority to do so under the broad statutory authority of the biosecurity laws and the Privacy Act.[71] As of December 2004, 72 out of approximately 13,000 individual applicants had been rejected as restricted persons, with six of these denials overturned on appeal, a low overall percentage of outright denials.[72]

Even if the personnel security system has legal standing, the indirect costs of lost productivity and the administrative burden remain less clear. The assessment must be renewed every five years or each time the individual begins working at a new laboratory or with a different select

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[68] Remarks, *USDA and HHS Public Meeting on the Interim Final Rule for Select Agents*, Washington, DC, December 16, 2002, 60.

[69] Federal Bureau of Investigation. Form FD-961. 1 Mar. 2005. <http://www.fbi.gov/terrorinfo/bioterrorfd961.htm>.

[70] Brickley, Peg. "Select Agent Security Checks." The Scientist 27 Mar. 2003. 1 Feb. 2005. <http://www.biomedcentral.com/news/20030327/03/>.

[71] "FBI revises instructions for completing select agent security risk assessments." AAU CFR Weekly Wrap-Up. 4 April 2003: 4. 1 Feb. 2005. <http://www.aau.edu/publications/Wrapup4.4.03.pdf>.

[72] Department of Justice. Office of the Inspector General. Inspection of the FBI's Security Risk Assessment Program for Individuals Requesting Access to Biological Agents and Toxins. I-2005-003. Washington, DC: 2005. 17.

agent, even if only changing projects within the same institution. The lack of "portability" in the security risk assessment (SRA) provides a challenge to laboratory management and research productivity. Although the final rule contains provisions for visits of registered researchers between registered labs, a researcher who has completed a security risk assessment at one registered lab and seeks a permanent or semi-permanent position at another registered lab – even involving work on the same select agent – must complete the process again.

In comments presented at the OSTP public workshop on biosecurity, ASM highlighted the cumbersome nature of current personnel security rules. "(I)t is our understanding that it takes 45 days to process an SRA and six months if further investigation is deemed necessary," ASM commented. "To accomplish the goal of conducting security assessments in an effective and timely manner, the Biopreparedness legislation provided for the prompt use of available electronic databases to carry out the clearance process."[73] A subsequent Department of Justice Inspector General's report on the SRA program confirmed these average times, but pointed out that some questions mandated in law and reflected on the SRA form are not amenable to a quick database scan (such as the open-ended inquiry about mental health history).[74] Several surveyed scientists noted that postdoctoral fellows could find months of their relatively short tenures consumed with waiting for clearance or "re-clearance" by the FBI, during which time they cannot access select agents in their new laboratories. Although organizations such as the Howard Hughes Medical Institute, in offering public comment on the select agent rules, suggested that security risk assessment approvals for individuals "be portable from entity to entity, from location to location, and from project to project" with appropriate administrative notices to CDC or APHIS, the final rule retained the status quo.[75] Both the FBI (through the interagency Select Biological Agents and Toxins Working Group) and the final rule rejected suggestions that researchers who

[73] ASM Comments Presented at the Public Workshop on Laboratory Biosecurity: A Culture of Responsibility. 12 Apr. 2004. Bethesda, MD. 1 Feb. 2006. <http://www.asm.org/Policy/index.asp?bid=26722>

[74] Inspection of the FBI's Security Risk Assessment Program for Individuals Requesting Access to Biological Agents and Toxins, 11-12.

[75] Howard Hughes Medical Institute, Office of Laboratory Safety. Comments on 42 CFR Part 73, Interim Final Rule Possession, Use and Transfer of Select Agents and Toxins. 21 Jan. 2003. 1 Feb. 2006. <http://www.hhmi.org/research/labsafe/rule/recommendations_cfr.html>

already hold high-level security clearances receive expedited security risk assessments – or, as per the request of the Deputy Under Secretary of Defense for Counterintelligence and Security, be exempted from the SRA altogether – as the underlying law made no exceptions.[76,77]

Measuring the real costs. The Regulatory Impact Analysis for the interim select agent rules estimated total annualized direct costs of $41 million (over 20 years) to implement the biosecurity requirements, with approximate individual annual costs for non-exempt laboratories ranging from $9,000 to $198,000, based on size and other factors.[78] The supplementary information to the final rule reported a decrease in the total annualized cost estimate to $16 million, based on the receipt of fewer requests for laboratory registrations, security risk assessments, and select agent transfers than expected.[79] Eight of those who commented on the final rule stated that the direct costs to their institutions would far exceed the preliminary estimates, a problem exacerbated by the fact that laboratories do not know if their security measures will prove adequate until after completion of the inspection process; grants to study select agents from the NIH include no funding to meet biosecurity regulations, requiring researchers to seek institutional support.[80,81] On the federal agency side, the Regulatory Impact Analysis estimated the direct annual costs to CDC at $1 million annually, although it seems unlikely this includes the costs for all staff involved in the Select Agent Program (HHS documents have referred to 21 full-time employee equivalents committed to select agent regulatory oversight).[82] Then there are the

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[76] 42 CFR Parts 72 and 72, Final Rule, 13304-5.

[77] Inspection of the FBI's Security Risk Assessment Program for Individuals Requesting Access to Biological Agents and Toxins, 18.

[78] Department of Health and Human Services. Centers for Disease Control and Prevention. Regulatory Impact Analysis, 42 CFR part 73, Select Biological Agents and Toxins, Interim Final Rule. Atlanta: CDC, 2002. 1 Feb. 2005.

[79] 42 CFR Parts 72 and 73, Final Rule, 13314.

[80] Ibid.

[81] Borrego, Anne Marie. "Regulatory Overkill?" The Chronicle of Higher Education 49.21 (2003): A25.

[82] Department of Health and Human Services. Office of the Inspector General. Summary Report on Select Agent Security at Universities (A-04-04-02000). Washington, DC: OIG, 2004.

regular oversight, inspection, and assessment costs incurred by other agencies and programs (such as NIH, USDA, and the FBI, which has cited a 9-member permanent staff for background checks[83]). Lastly, the intangible costs of lost productivity, samples destroyed, and the departure of veteran researchers from the field are even less straightforward.

Destroying pathogen stocks. The requirements for the physical security and inspection process, as interpreted by most institutions and researchers, appear to apply an all-or-nothing standard – demanding the same degree of protection, for example, for *Bacillus anthracis* and *Coccidioides immitis*, a poorly understood fungal disease endemic in the southwestern United States.[84] In comments to the interim final rule, ASM repeated its previous suggestions that the list of pathogens should be revisited by the broader microbiology community.[85] The final rule declined this suggestion; although conceding a need for slightly more flexibility in situation-specific security planning than the interim versions, it does not indicate how that will translate in practical terms). At present, a working group of subject matter experts drawn solely from federal government agencies advises the secretaries of HHS and USDA on requests to add or remove agents from the select agent list.[86]

In December 2002, CDC estimated that 817 entities would register under the new select agent rule, but only 350 had registered by the time of the final rule (105 of these being universities).[87,88] Some have interpreted this as an indication that many laboratories discontinued their work with select agents rather than incur the burden of the new rules; the

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[83] Wilkie, "Select-Agent Security Clearance Stymies Research."

[84] Fierer, Joshua and Theo Kirkland. "Questioning CDC's 'Select Agent' Criteria." Science 295.5552 (2002): 43.

[85] "ASM Comments to the CDC on the Interim Final Rule on the Possession, Use, and Transfer of Select Agents and Toxins." The American Society for Microbiology. 31 Jan. 2003. 1 Feb. 2005. <http://www.asm.org/Policy/index.asp?bid=8648>.

[86] "FAQ for Select Agent Regulation (42 CFR 73)." 1 Feb. 2006. Department of Health and Human Services, Centers for Disease Control and Prevention. < http://www.cdc.gov/od/sap/faq.htm>.

[87] Regulatory Impact Analysis, 2.

[88] 42 CFR Parts 72 and 73, Final Rule, 13315.

explanation in the final select agent rules states that this instead reflects a refinement of the "over-inclusive notification process we used to help ensure that all potentially affected entities would be made aware of the rule."[89,90] Whether this particular statistic accurately reflects the number of programs eliminated in response to the new regulations or not, some scientists and institutions clearly decided that the costs outweighed the benefits.

The final select agent rule states "we believe there will be few instances where universities abandon lines of research in response to the rule. Out of the 200 or so entities that transferred or destroyed their select agents rather than registering under the rule, we believe that the majority did so for reasons that do not threaten future research."[91] However, anecdotal reports and interviews suggest that, in addition to flamboyant institutional actions such as Iowa State University's destruction of its entire anthrax collection, an uncounted number of individual scientists in both academic and government laboratories destroyed pathogen collections prior to the initial registration process.[92,93,94] All 28 scientists who responded to the Stimson survey on select agent regulations indicated that they had eliminated at least one research project involving a select agent in response to the new biosecurity regulations, and that they personally knew colleagues who had done the same. Although OSTP asked institutions, through professional societies, to review decisions to destroy historical pathogen collections that might serve as "valuable research tools,"[95,96] the success of the temporary federal repository for such stocks at the CDC in rescuing unwanted cultures

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[89] Gaudioso, Jennifer and Reynolds M. Salerno. "Biosecurity and Research: Minimizing Adverse Impacts." Science 304.5671 (2004): 687.

[90] 42 CFR Parts 72 and 73, Final Rule, 13314.

[91] 42 CFR Parts 72 and 73, Final Rule, 13313.

[92] Schemo, Diana Jean. "After 9/11, Universities Destroying Bio Agents." NY Times 17 Dec. 2002, A20.

[93] Tucker, Jonathan B. "Research on Biodefense Can Get Generous Funds, but With Strings Attached." Chronicle of Higher Education 50.26 (2004): B10.

[94] Wilkie, "Select-Agent Security Clearance Stymies Research."

[95] Schemo, "After 9/11, Universities Destroying Bio Agents."

[96] Tucker, "Biodefense Research Can Get Generous Funds."

remains unclear. Until at least mid-2005, the CDC's Select Agent Program Web site "Frequently Asked Questions" page advised researchers considering destroying select agent collections due to financial constraints simply to follow the appropriate notification steps.

Provisions that allow exempt laboratories (such as diagnostic or testing centers) only seven calendar days after identifying a select agent to transfer it to a registered lab, destroy it, or seek special exemptions, may also have a negative effect on public health, either by prompting destruction of samples important to an epidemiological investigation or reducing the specimens available to researchers.[97] Such pressures can also make confirmation of results difficult or impossible, as in a recent case of falsely identified *Brucella abortus* in a Wyoming cattle herd, which required months of intensive investigation after the local diagnostic laboratory destroyed the original tissue samples in compliance with the select agent requirements.[98]

Select agent bureaucratic snafus involving diagnostic and testing centers may endanger quick responses to public health crises.

Epidemiological and research investigations into outbreaks. Select agent bureaucratic snafus involving diagnostic and testing centers may endanger quick responses to public health crises in yet other ways. One example involves the 2003 outbreak of exotic pet-borne monkeypox, a select agent, in the midwestern United States. Normally, cases of suspected bioterrorism or emerging infectious diseases would be referred from local to state laboratories as part of the Laboratory Response Network (a nationwide system established by the CDC to refer analysis of cases of suspected bioterrorism or emerging infections through a network of increasingly sophisticated laboratories for confirmation), and then onto the most capable federal labs if necessary.[99] Because the Wisconsin State Laboratory of Hygiene did not include monkeypox in its

[97] Wilkie, "Select-Agent Security Clearance Stymies Research."

[98] "Wyoming Case Could Lead to Lab Changes." Bioterrorism Week 27 Dec. 2004.

[99] "Facts about the Laboratory Response Network." Department of Health and Human Services. Centers for Disease Control and Prevention. 1 Mar. 2005. <http://www.bt.cdc.gov/lrn/factsheet.asp>.

original select agent registration, the clinic in Marshfield, Wisconsin, that first isolated the virus could not legally transfer the clinical specimens to the state laboratory; the specimens had to be transferred directly from the local clinic to CDC after much negotiation, "delaying definitive specimen identification, and prolonging response time."[100]

During a larger or more rapidly spreading outbreak, whether deliberate or naturally occurring, such delays could prove particularly damaging. The case of the severe acute respiratory syndrome (SARS) coronavirus provides one example of how critical the open exchange of scientific information can be during public health crises, and for subsequent research. Bold international cooperation allowed the containment of SARS only four months after its recognition, the sequencing and identification of the virus early in the epidemic, and rapid advances in understanding its natural history and molecular characteristics.[101] Fears that select agent status might endanger such progress prompted a group of researchers prominent in the characterization of SARS to urge the CDC to keep the virus off the list, a request that has so far been observed.[102]

In contrast, the classification of highly pathogenic avian influenza (HPAI, or "bird flu") as an agricultural select agent could present implications for global research openness during the current rapidly emerging international outbreak of H5N1 avian influenza in waterfowl and poultry, as well as during a possible pandemic. Concerns about biosecurity can mean slow approval for the exchange of viral samples between laboratories – even if both the shipper and recipient have stringent security protocols – leading to a delay of weeks or months in a situation demanding near real-time analysis.[103] The HHS Pandemic Influenza Plan notes, "If an avian influenza strain – or a human virus variant that evolves from it—causes an influenza pandemic, it might become necessary to re-evaluate biocontainment requirements and select

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[100] Mulcahy, R. Timothy. "An Uncertain Partnership." Science 302.5647 (2003): 949.

[101] Lingappa, "Wresting SARS from Uncertainty."

[102] Enserink, Martin. "Researchers Urge U.S. to Keep SARS Off Select Agent List." Science 304 (2004): 1726.

[103] Normile, Dennis. "Avian Influenza: Who Controls the Samples?" Science 309.5722 (2005): 372.

agent registration requirements for laboratory testing."[104] Although the select agent rules allow CDC and APHIS to grant temporary exemptions to institutions during public health or agricultural emergencies, smooth and timely implementation of this option during a pandemic is not guaranteed.

Impact on international collaborations. Arguably, the most significant immeasurable cost of the biosecurity regulations stems from restrictions placed on collaborations with foreign colleagues, traditionally a major conduit for the exchange of both samples and scientific information. Of 28 senior veteran select agent researchers surveyed by the Stimson Center, *all* had eliminated or changed one or more of their international collaborations in response to the new rules. The security risk assessment requirements nearly preclude the possibility that visiting scientists from other nations might work with a select agent in a U.S. laboratory, even if the foreign scientist initially obtained and shipped the specimens. NIAID announced in late 2004 that non-U.S. laboratories collaborating on a project with a U.S institution funded by a NIAID select agent research award must demonstrate that they have implemented select agent-handling protocols as rigorous as the U.S. regulations.[105] A December 2004 article in *Science* quoted unidentified U.S. select agent specialists as reporting that this requirement affects not only academic researchers receiving NIAID funding but their government counterparts, and has already affected research involving such emerging infectious diseases such as highly pathogenic avian influenza.[106] Scientists interviewed for the article pointed out that this measure unilaterally imposed the U.S. security model on other nations, rather than seeking harmonization of biosecurity regulations.

This regulatory framework may have a particularly devastating effect on U.S.-foreign partnerships to study the natural history of certain microorganisms or test high-priority vaccines against select agents where they occur as endemic or epidemic diseases. Examples of potentially

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[104] Department of Health and Human Services. HHS Pandemic Influenza Plan. Washington, DC: November 2005, 159. 1 Feb. 2006. <http://www.hhs.gov/pandemicflu/plan/>

[105] "NIAID Select Agent Policy for Foreign Institutions." National Institutes of Health. National Institute for Allergy and Infectious Diseases. 1 Feb. 2006. < http://www.niaid.nih.gov/ncn/qa/selagentfor.htm>.

[106] Stone, Richard. "Heightened Security or Neocolonial Science?" Science 306 (2004): 2177-78.

affected programs include U.S.-Asian joint ventures to study Japanese encephalitis virus (JEV), a mosquito-borne pathogen that is the leading cause of encephalitis in Asia as well as a threat to U.S. military personnel and travelers.[107] (The final select agent rule supplementary information acknowledged that the biosecurity regulations may affect research on JEV, such as high-priority efforts to develop an effective alternative to the currently licensed vaccine with less potential for serious adverse reactions, but declined to remove it from the list on the grounds that the virus can "cause severe disease in horses and swine for which there is no effective treatment and no domestically available veterinary vaccine."[108]) If the select agent regulations are found to apply more broadly to the rapidly expanding network of disease surveillance partnerships between U.S. agencies and foreign collaborators in their own nations, sentinel diagnostic laboratories and intensive microbial surveillance programs could be as profoundly affected as research and development efforts.

Responsibility or Fear? The threat of criminal penalties for even accidental violations of the select agent rules has engendered fears that many believe to be well-founded. Although decisions to destroy historical pathogen collections in U.S. institutions may merely represent, as the final rule supplementary information implies, clean-up of long-completed studies with no real impact on scientific research, such actions may also reflect researchers' anxieties about new biosecurity regulations. Three well-publicized cases of real or suspected biosecurity violations have elicited swiftly punitive responses from federal law enforcement:

- Dr. Thomas Butler, a respected senior researcher, was convicted of one count of improperly shipping samples and 44 unrelated counts of fraud against Texas Tech, after a confusing investigation into an initial report of missing plague vials to the FBI;[109]
- Tomas Foral, a graduate student at the University of Connecticut, was charged under the PATRIOT Act for retaining two vials of anthrax-tainted tissue after the

[107] Department of Health and Human Services. Centers for Disease Control and Prevention. "Inactivated Japanese Encephalitis Virus Vaccine: Recommendations of the Advisory Committee on Immunization Practices (ACIP)." MMWR 42.RR01 (1993): 1.

[108] 42 CFR Parts 72 and 73, Final Rule, 13249.

[109] Miller, John Dudley. "Butler Verdict Perplexes." The Scientist 8 Dec. 2003.

cleaning of a laboratory freezer, in what may have been a misunderstanding;[110] and

- Artist Steven Kurtz and geneticist Dr. Robert Ferrell were indicted for felony wire and mail fraud after an intense federal investigation triggered by the discovery of biotechnology apparata in Kurtz's apartment following his wife's sudden death. The investigation revealed only that Ferrell gave Kurtz non-pathogenic bacteria purchased from the American Type Culture Collection for use in performance art criticizing government biotechnology policies (a violation of a materials transfer agreement rather than biosecurity laws).[111,112] Their criminal cases continue to advance in federal court.[113]

In all three cases, the most compelling issue seems to be the message conveyed by the government's prosecutorial zeal rather than the question of guilt versus innocence (the researchers appear to have violated regulations, or at least university policies). The case of Thomas Butler, in particular, motivated many distinguished scientists to express their concerns about the impact on the infectious diseases research community; although the details of the case still remain unclear, his two-year prison sentence stemmed from one count of returning plague specimens to Tanzania without proper license or documentation, with the rest of the case based on "piled on" university contract disputes unrelated to the original charges of lying to the FBI, smuggling plague vials from Tanzania, or tax evasion.[114,115] The Kurtz-Ferrell case reinforced this

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[110] Tucker, "Research on Biodefense Can Get Generous Funds."

[111] Chamberlain, Allison. "Science and Security in the Post-9/11 Environment: Select Agent Rules (updated)." AAAS Science and Policy Program, 2004. 1 Mar. 2005. <http://www.aaas.org/spp/post911/agents/>.

[112] Snyder, Martin D. "State of the Profession: Dangerous Art." Academe Online January-February 2005. 1 Feb. 2005. <http://www.aaup.org/publications/Academe/2005/05jf/05jfSOTP.HTM>.

[113] Herbeck, Dan. "Federal judge gives the go-ahead to Kurtz case." *The Buffalo News*. 13 Jan. 2006.

[114] Letter from Bruce Alberts, president of the National Academy of Sciences, and Harvey Fineberg, president of the Institute of Medicine, to the Honorable John Ashcroft, Attorney General. 15 Aug. 2003.

message: A federal investigation into suspected biosecurity violations, once initiated, will not stop merely because it uncovers no real threat related to bioterrorism. Of 28 researchers polled in the Stimson survey, 23 admitted worrying that they, or a member of their labs, might unintentionally incur the serious civil and criminal penalties associated with the biosecurity regulations due to paperwork errors.

Growing pains or growing problem? There is as yet no comprehensive answer to the question of whether the barriers imposed by the select agent rules represent a real long-term drain on scientific productivity throughout the field of infectious diseases or simply an acceptable and temporary annoyance. Surveys of researchers and institutions, such as those cited in this analysis, rely on self-reported data undoubtedly biased by the impact of the regulations on those who choose to respond. On one hand, the biosecurity regulations represent an extremely focused control regime of physical and personnel security, and have so far affected a relatively defined universe of laboratories. "While there are problems associated with this, I think the law is pretty reasonable," Dr. Paul Keim of Northern Arizona University told *The Scientist* in an article on the select agent rules.[116] One-third of the respondents to the Sandia survey agreed that the regulations "impose prudent security measures," while only 11% felt that they represented the wrong approach (roughly equal to the number who felt that they didn't go far enough); most of the remainder felt that the regulations are "on the right track," but need to be revised for clarity.[117]

Will the barriers imposed by the select agent rules represent a real long-term drain on scientific productivity — or simply an acceptable and temporary annoyance?

On the other hand, it is not entirely clear that such measures have any effectiveness in the biological paradigm beyond reassuring the public

[115] Murray, Barbara E., et al. "Destroying the Life and Career of a Valued Physician-Scientist Who Tried to Protect Us from Plague: Was It Really Necessary?" *Clinical Infectious Diseases* 1 Jun. 2005. 40:1644.

[116] Wilkie, "Select-Agent Security Clearance Stymies Research."

[117] Rivera, Slide 6.

and policymakers. In a white paper, the American Biological Safety Association comments:

> Decades ago the U.S. Government defined and established security and personnel reliability programs in DOE and DOD nuclear and chemical facilities. The material being protected (i.e., processed nuclear material, warheads, chemical weapons) was bulky in size and would have to be stolen in substantial volume to be of use to a terrorist. The programs were sensitive to national security, often conducted at facilities that were closed to the general public, and relied heavily on the "guards, gates, guns, and two-man rule" approach to security and personnel reliability. This paradigm does not optimally meet the needs of security in biological facilities and may actually cause a false sense of protection….[118]

Apart from the direct costs, 16 of 26 surveyed select agent researchers felt that the new security measures presented barriers that objectively impede laboratory productivity. The decision of some laboratories to embrace the "two-man rule" developed for energy research, in which no researcher ever works alone with a select agent, can obviously halve productivity.[119] Even the first set of select agent rules, concerning only transfer of such agents, raised issues of whether regulations on transferring pathogens addressed a real risk and whether they might damage relationships between government agencies and researchers irrevocably. Testifying before a Congressional committee in 1999, Stephen Ostroff of CDC's National Center for Infectious Diseases commented, "CDC has worked extensively with our partners in the scientific community to develop and implement the regulation, even though we believe the regulatory framework has adversely impacted the longstanding working relationships with some of these partners."[120]

The objective benefits of the new biosecurity regulations remain as nebulous as the intangible costs. In order to evaluate the success of the

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[118] "Understanding Biosecurity." ABSA Biosecurity Task Force White Paper. Jan. 2003. 1 Feb. 2005. <http://www.absa.org/0301bstf.html>.

[119] Connell**,** Nancy. **"**The BSL3 Laboratory at New Jersey Medical School: A Short History." *National Security and Biological Research: What are the boundaries?* New York: New York Academy of Sciences, 2003. 1 Mar. 2005. <http://www.nyas.org/ebriefreps/main.asp?intSubsectionID=555>.

[120] Ostroff, "Threats of Bioterrorism in America."

program in meeting its intended goals, the first fundamental question to be addressed would be: Are we any safer than we were previously? To answer such a question, one must be able to define the threat and develop a metric for success, but neither is amenable to easy analysis. Proving the negative – that the system has worked, because the United States has experienced no biological attacks perpetrated with materials stolen from or misused in a U.S. laboratory since 2002 – may hold up in the court of public opinion, but it lacks compelling empirical evidence. The goals of the current biosecurity regulations include better inventory of pathogens and restricting the classes of researchers with access to "dangerous pathogens." The first of these could provide a false sense of security, sinking disproportionate resources into monitoring the minutiae of counting vials and locks at the expense of cultivating realistic risk assessment and broader awareness in the bioscience community. The second, restricted access, is an aim not inimical to initiatives to swell the ranks of American biodefense researchers and combat emerging infectious diseases before they arrive in the United States, but it is certainly not synergistic with them.

Determining the real cost-benefit ratio of the biosecurity regulatory framework would require a much more comprehensive study of both than has been offered to date by the government or universities. HHS has yet to reveal an analysis of the impact and benefits of the select agent rule, as mandated in the Bioterrorism Preparedness Act. Instead, the government has made its case for the cost-effectiveness of the final select agent rules by comparing the estimated annualized costs of implementing the rules to the estimated costs of responding to the 2001 anthrax attacks, a rather dubious comparison.[121]

The authorizations to appropriate funds under the Bioterrorism Preparedness Act expire in 2007, offering an obvious opportunity to discuss the law's impact on research and offer refinements. A more measured set of risk assessment parameters that would allow graded security measures for select agents, similar to the graded containment practices in the biosafety paradigm, might answer many scientists' concerns. At least one well-developed alternative model proposes "an intellectually defensible biosecurity methodology for the protection of high-risk agents and toxins" based on a matrix for classifying biosecurity levels as low, moderate, high, or extreme risk – in a system parallel to the biosafety guidelines – and scaling biosecurity measures accordingly.[122,123] The final rule advises that CDC and APHIS are

[121] 42 CFR Parts 72 and 73, Final Rule, 13315-6.

[122] Gaudioso and Salerno, 687.

currently in the process of drafting more specific guidance, with the input of interagency groups and security experts, with an eye toward more flexibility and specificity.[124]

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[123] Salerno, Reynolds. "A Possible Approach to Biosecurity for the BMBL." Laboratory Biosecurity: A Culture of Responsibility. Bethesda, MD: OSTP/NIH, 2004.

[124] 42 CFR Parts 72 and 73, Final Rule, 13306.

— 5 —
BIOSAFETY AND BIOSECURITY – NEVER THE TWAIN SHALL MEET?

Both biosafety and biosecurity comprise attempts to regulate unintentional exposures to laboratory pathogens through clear definition of possible hazards and careful risk management. The longstanding U.S. biosafety system, as noted above, relies on a combination of voluntary measures adopted by researchers in order to protect themselves, their co-workers, and the public, and mandatory compliance in order to maintain institutional eligibility for NIH funding. The new biosecurity regulations comprise a system of government regulation, with civil and criminal penalties, aimed at strengthening physical and personnel security of labs that handle specific pathogens – a strategy neither incompatible nor integrated fully with the first.

The current (fourth) edition of the BMBL references security issues in Appendix F, a five-page 2002 update that summarizes the new biosecurity regulations and outlines risk assessment methods.[125] However, confusion lingers about what the BMBL construes for biosecurity requirements. A March 2004 report on select agent security at 11 U.S. universities issued by the HHS Office of the Inspector General "took exception" to the affirmation by several universities that the BMBL constitutes "a general guideline and not a requirement." HHS commented: "Although issued as a guidelines, the BMBL had been formally incorporated into the select agent regulation (42 CFR § 72.6(a)(5)) and was in effect at the time of our reviews."[126] The section in question, like the final select agent rules, appears to incorporate the BMBL "by reference" rather than codifying the BMBL (incorporating it into law), a step that would make editing the BMBL in the future a much

[125] Biosafety in Microbiology and Biomedical Laboratories, 230.

[126] Department of Health and Human Services, Office of the Inspector General, 5.

more cumbersome process.[127] Clarifying the legal standing of the BMBL in the context of biosecurity could help institutions and laboratories in interpreting the regulations.

There are signs that incipient policies may better coordinate, or at least recognize, the intersection of biosafety and biosecurity protocols. The final select agent rule references biosafety practices far more explicitly than the interim versions, mandating that "entities must not only develop and implement a safety plan, but must develop a plan that is commensurate with the risk of the agent or toxin, given its intended use."[128] OSTP convened a public workshop, described above, "to solicit comments on the successes and challenges associated with implementing biosecurity procedures and protocols," including suggestions of what information should be included in a chapter on biosecurity in the fifth edition of the BMBL, anticipated in 2005 but not yet released at the time of this publication.[129] The public workshop on the BMBL featured, amid feedback from researchers and biosafety officers charged with biosecurity compliance, a lively discussion on clarifying the demands of the two systems, including a presentation on the proposed risk assessment matrix described above.[130]

In the meantime, the World Health Organization's (WHO) newly revised *Laboratory Biosafety Manual*, produced with support from the CDC, provides a glimpse of growing enthusiasm for combining biosecurity and biosafety into a seamless logical whole. These WHO guidelines serve as a template for national codes; the 2004 revision contains a new section on laboratory biosecurity which (although cursory at two pages) affirms:

> Effective biosafety practices are the very foundation of laboratory biosecurity activities. Through risk assessments, performed as an integral part of an institution's biosafety programme, information is gathered regarding the type of organisms available, their physical location, the personnel who require access to them, and the identification of those responsible

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[127] 42 CFR 72.6(a)(5), Part 72, "Interstate Shipment of Etiologic Agents," updated October 1, 2004.

[128] 42 CFR Parts 72 and 73, Final Rule, 13308.

[129] "Laboratory Biosecurity: A Culture of Responsibility." Federal Register 69.56 (2004): 13527-13528.

[130] Salerno, "A Possible Approach to Biosecurity for the BMBL."

> for them. This information can be used to assess whether an institution possesses biological materials that are attractive to those who may wish to use them improperly.[131]

Although 80% of the 203 scientists responding to the Sandia survey believed that biosecurity and biosafety are compatible,[132] an excessive focus on biosecurity compliance demands may actually detract from monitoring safe laboratory practices by consuming the primary investigators' and biosafety officers' time and energy. The final select agent rules address this by mandating biosafety planning and training as part of the biosecurity inspection process – thus indirectly tying civil and criminal penalties to biosafety guidelines for select agent researchers, and approaching the problem by increasing the regulatory burden. Whether the new BMBL will help align the goals of the U.S. biosafety and biosecurity strategies, and thus provide guidance to researchers without creating still more compliance issues, remains to be seen.

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[131] World Health Organization. Laboratory Biosafety Manual, Third Ed. Geneva, Switzerland: WHO, 2004.

[132] Rivera et al., "Biosecurity in a Biosafety Environment."

— 6 —
DEFINING DUAL-USE TECHNOLOGIES

The select agent rules approach issues of biosecurity by controlling access to pathogens, thus treating biological agents very much like nuclear materials: a finite resource whose acquisition serves as a bottleneck in any potential weapons program. In the last few years, however, the science policy and policymaking communities have extensively explored how the capabilities that might be acquired through many fields of biological research unrelated to select agents might themselves represent a risk just as profound but far less manageable.

The term "dual-use technologies" has two meanings: The first encompasses any technology that might be applied to a purpose outside of the original intent, and includes those with "both military utility and sufficient commercial potential to support a viable industrial base," deliberately cultivated by federal agencies seeking to stretch limited research and development resources.[133] The second definition, expanded from nuclear and munitions export control paradigms to include biological and chemical threats, includes those applications whose legitimate research, commercial, or military uses might be subverted to malicious ends.

The anthrax assaults of 2001 drew particular scrutiny to the biosciences as a field in which almost every technology can be termed dual-use in the latter sense. Few of the tools fundamental to legitimate biological research and development can be distinguished on a purely technical basis from those necessary to the first steps in weapons production. Although the intent behind the production of an inactivated bacterial vaccine to prevent disease differs radically from the intent to create a biological weapon incorporating the same bacterium, the same basic

[133] "Definition of the U.S. Department of Defense, Dual-Use Science and Technology Program." Defense Technical Information Center. 1 Feb. 2006. <http://www.acq.osd.mil/ott/dust/summary.html>.

microbiological culturing capabilities would be critical to initiating either process.

Access to advanced biotechnologies will continue to increase as cost and technical barriers decrease.

Concerns about dual-use capacities in the biosciences and biotechnology expand far beyond the borders of microbiology research alone. In an address to a meeting on scientific openness and national security convened in early 2003 by the National Academies and the Center for Strategic and International Studies, Dr. George Poste of the Defense Science Board and Health Technology Networks emphasized that specific advances in immunology, gene therapy, molecular biology, signal transduction, neurology, and the emerging field of systems biology could be subverted through "malignant utilization of magnificent technological advance."[134] The growing importance of the life sciences to national security issues, he suggested, in terms of protecting populations against instability brought about by diseases and other environmental factors, is accompanied by a profound naiveté throughout the biosciences community about their potential misuse. The tools, skills, and knowledge to manipulate biological materials have become ubiquitously distributed throughout an increasingly global bioscience research enterprise, and access to advanced biotechnologies will continue to increase as cost and technical barriers decrease – witness, for example, the onerous laboratory technique that becomes a "kit" in the span of only a few years.

Even a cursory consideration of these observations highlights the false sense of security inherent in the focus on select agents: If a scientist who truly intends to create a biological weapon can learn to manipulate unregulated pathogens in a U.S. laboratory, the researcher could then with minor ingenuity obtain a virulent strain from a natural outbreak or from a repository in another nation. Knowledge and tools in common use now would allow a skilled laboratorian to modify some microorganisms closely related to select agents to make them resemble their pathogenic cousins. Given advances in biotechnology, a researcher bent on malicious use of the biosciences could enhance the virulence of a benign pathogen through a number of increasingly complex mechanisms, or simply exploit strategies to manipulate human biological systems

[134] Poste, George. Remarks to the Scientific Openness and National Security Workshop. Washington, DC: National Research Council, 2003. 1 Feb. 2005. <http://www.csis.org/tech/ssi/sonsw/>.

directly. Such a program would be easily hidden among legitimate research efforts. Intent, rather than content, of the research program would be the only distinguishing factor. However, regulating every biotechnology that could possibly be misused would clearly be impractical, as well as being an undesirable obstacle to the progress of legitimate research with the potential to protect human, environmental, and economic health.

Until quite recently, the majority of bioscientists who engaged in federal policy debates enjoyed the luxury of focusing on funding rather than dual-use technology issues. While many of their counterparts in the field of physics – caught by the legacies of the Manhattan Project, Cold War, and space race – have contended with security implications of their work for decades, the number of biomedical researchers involved in any major government programs involving national security remained relatively small even before the United States renounced its offensive biological weapons program in 1969.[135] Until the mid-1990s, discussions of deliberate misuse of pathogens or biotechnologies in basic research laboratories mainly took place in the context of debates on state-sponsored biological weapons programs and mechanisms that could be used to detect the circumvention of treaties and norms proscribing their development. Few in the life sciences had to confront the concept that "the bedrock attributes of science and technology," as described by Massachusetts Institute of Technology Professor Emeritus Eugene Skolnikoff, dictate that "all technologies are dual-use. There is no such thing as a technology that cannot be used for evil or malign purposes. Some are closer to weapons, but all of them have that capability."[136]

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[135] Fischer, Julie E. Speaking Data to Power: Science, Technology, and Health Expertise in the National Biological Security Policy Process. Washington, DC: The Henry L. Stimson Center, 2004.

[136] Skolnikoff, Eugene B. "Research Universities and National Security: Can Traditional Values Survive?" Science and Technology in A Vulnerable World. Eds. Albert H. Teich, Stephen D. Nelson, and Stephen J. Lita, Washington, DC: American Association for the Advancement of Science, 2002.

— 7 —
CONTROLLING KNOWLEDGE: THE HISTORY OF SCIENTIFIC SECRETS

For many bioscientists, the fifty-year-old debate on how best to balance the potential benefits of an unrestricted flow of scientific information against any conceivable threat to U.S. national security interests recently transmuted from an issue for intellectual curiosity, affecting a very limited subset of their peers, to a vivid and personal quandary. On the other hand, scientists engaged in disciplines related to energy, computer sciences, space, and cryptography research have coped with information and technology control regimes for decades. The newly minted debate within the bioscience field thus takes place against the background of, and must be informed by, a much longer history of national security demands and constraints on scientific openness.

ATOMIC ENERGY AND THE BIRTH OF CLASSIFIED SCIENCE.

The modern U.S. system of national security emerged from voluntary censorship on sharing of any nuclear weapons information assumed by the non-governmental scientists engaged in atomic energy research prior to World War II (many of them refugees who feared Hitler's atomic aspirations), a system that became institutionalized during the Manhattan Project and formalized in law and practice during the Cold War.[137] A wartime committee on scientific publications convened by the National Academy of Sciences and the National Research Council sanctioned and

[137] Blanton, Thomas S. "National Security and Open Government in the United States: Beyond the Balancing Test." National Security and Open Government: Striking the Right Balance. Syracuse, NY: Campbell Public Affairs Institute, The Maxwell School of Syracuse University, 2003.

supported publication controls to protect atomic research details.[138] Congress codified this paradigm of scientific secrecy in the name of national defense; the resulting regulatory framework established that any atomic energy-related information is automatically "born classified" as "restricted data" unless specified otherwise, even if produced outside of U.S. government programs.[139,140,141]

The laws and regulations related to controlling information on atomic energy, under-girded by massive government investment in and influence over research during the Cold War and the space race, collectively fostered the idea that scientific research could and should be subject to information controls to prevent acquisition of knowledge by enemies, secure U.S. technological superiority, and even limit interference in controversial projects by the public or other parts of the government.[142] The atomic energy paradigm also provided the foundation for U.S. policy on information controls and scientific communication: Those areas subject to controls should be identified clearly (prior to the conduct of the research itself) and classification should be the primary mechanism for protecting information. Regardless of perceptions about its possible over-application, the legal framework that controls classification – with its terms defined in a presidential directive subject to amendment by each new administration – provides a clearly defined set of criteria for levels of and authority over sensitive information.[143] Major research universities have a choice: Accept and

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[138] Shea, Dana A. Balancing Scientific Publication and National Security Concerns: Issues for Congress. Congressional Research Service Report RL31695. Washington, DC: Library of Congress, 2004.

[139] Blanton, 39-41.

[140] The Atomic Energy Act of 1946, Public Law 79-585 (1 Aug. 1946), as amended by the Atomic Energy Act of 1954, Public Law 83-703 (30 Aug. 1954).

[141] Knezo, Genevieve J. "Sensitive But Unclassified" and Other Federal Security Controls on Scientific and Technical Information: History and Current Controversy. Congressional Research Service Report RL31845. Washington, DC: Library of Congress, 2004.

[142] Blanton, 39-41.

[143] Relyea, Harold C. "Emerging Threats: Over-classification and Pseudoclassification." Statement before the House Government Reform Subcommittee on National Security, Emerging Threats, and International Relations.. 2 Mar. 2005.

sequester classified research projects in order to minimize their impact on other facets of academic life (for example, confining such research to off-campus facilities, a strategy embraced by universities such as MIT and John Hopkins), consider each project on a case-by-base basis, or decline classified research altogether as does the University of Chicago.[144,145,146]

DUAL-USE TECHNOLOGIES AND EXPORT CONTROLS.

In the 1950s, a federal government heavily involved in space and defense research sought another mechanism to deny its Cold War adversaries access to dual-use technologies developed outside of government laboratories (and, therefore, not necessarily born classified): controlling the export of tools and knowledge. The International Traffic in Arms Regulations (ITAR), implemented by the Department of State, focus on any hardware or technical knowledge related to "defense articles" on the U.S. Munitions List, which includes the category "biological agents" as well as many more specific classes of technologies with military applications.[147] The ITAR requires a license to export controlled materials or knowledge with military uses, making no distinction between those produced through government or private funding.[148] The ITAR excludes fundamental research, including technical information commonly taught in academic institutions and any results of basic or applied research that will be presented at scientific meetings and published without restrictions.[149,150]

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[144] Shea, 10.

[145] Malakoff, David. "Universities Review Policies for On-Site Classified Research." Science 295.5559 (2002): 1438.

[146] "Guidelines for Grant and Contract Management." University of Chicago. 1 Mar. 2005. <http://researchadmin.uchicago.edu/guidelines/200/224.shtml>.

[147] International Traffic in Arms Regulations, Part 121: The United States Munitions List (22 CFR 120.10). 1 Feb. 2005. <http://fas.org/spp/starwars/offdocs/itar/p121.htm>.

[148] Knezo, "Sensitive But Unclassified."

[149] Exemptions for U.S. Institutions of Higher Learning, 22 CFR Parts 123 and 125. Federal Register 67.61 (2002): 15099-15111.

[150] Knezo, "Sensitive But Unclassified."

A second set of export controls on dual-use technologies addresses both economic and national security concerns. The Export Administration Regulations (EAR), implemented by the Department of Commerce, require licenses for the export of materials or technical data related to commercial dual-use technologies.[151] As these regulations evolved from the post-World War II era through the late 1970s, "export control laws, long a mechanism to control the transfer of goods having *military* applications, became a means to limit the export of goods or technologies having *commercial* value," explains Alice Gast, PhD, vice president for research and associate provost of the Massachusetts Institute of Technology.[152] Under the EAR, "any release of technology or source code subject to the EAR to a foreign national...is deemed to be an export to the home country or countries of the foreign national," even if such an exchange takes place in the United States.[153] EAR apply to the export of a long list of plant and animal pathogens, toxins, and genetically modified organisms, so that many laboratories which ship samples to foreign collaborators must now comply with both the Commerce Department and the select agent rules.

Export controls remain a centerpiece of the traditional approach to national security, with lessons for and applicability to the bioscience community. But despite long experience with both military and commercial export control regimes, ambiguities remain, especially with regard to "deemed exports" of technical knowledge shared with a foreign national. Universities, professional societies, and individual researchers still struggle to clarify where and with whom they can hold technical discussions that fall under export control rules. In a recent example, a 1999 policy change expanded ITAR to include the export of information (including discussions) about basic research involving satellites and space instruments. In 2002 – in response to requests for clarity from academic and professional institutions – the State Department released new guidance on university exemptions for licensing technical information related to basic research, loosening restrictions on interactions with researchers from certain nations deemed friendly to

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[151] Commerce Export Control List (15 CFR Part 774). U.S. Government Printing Office. 1 Feb. 2005. <http://www.access.gpo.gov/bis/ear/pdf/ccl1.pdf>.

[152] Gast, Alice P. "The Impact of Restricting Information Access on Science and Technology." The American Association of Universities. 1 Feb. 2005. <http://www.aau.edu/research/Gast.pdf>.

[153] "Scope of the Export Administration Regulations." Export Administration Regulations Part 734. 9 Dec. 2004. 1 Feb. 2005. <http://www.access.gpo.gov/bis/ear/ear_data.html>.

U.S. interests. The new rules, however, still failed to resolve many concerns, such as whether the original researchers hold responsibility for "downstream" sharing of knowledge.[154,155]

Incidents such as the uncertainty over academic research involving satellites show the difficulties in implementing these regulations even in a relatively established system. This is an important issue for any newly proposed regimes to regulate bioscience information, but especially in the bioscience field, where the broad rubric of "biological agents" provides room for flexible interpretation. "ITAR is comprehensive, complex, time-consuming, and often inconsistent," writes Eugene Skolnikoff, PhD, Professor of Political Science Emeritus at MIT. "It often requires legal interpretation. Note that none of this has to do with whether information is classified or not. Unclassified information is also covered. Furthermore, it is important to note that anyone accused or convicted of violating ITAR is subject not just to fines, but to imprisonment."[156]

EAR exempt information related to fundamental research from licensing requirements, with the caveat that these must be *openly published*; acceptance of any restrictions on publication other than pre-publication review for proprietary information negates the exception.[157] Whether an author's acquiescence to biosecurity screening requirements adopted by scientific journals constitutes such a publication restriction, and thus leaves basic research involving the same list of organisms or toxins open to deemed export controls, remains unclear.[158] A recent report issued by the Department of Commerce's Office of Inspector General recommended tighter controls on deemed exports to foreign nationals

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[154] Knezo, 5-6.

[155] Skolnikoff, 66-67.

[156] Ibid.

[157] Shea, 10-11.

[158] Jones, Diane Auer. "Export Control Compliance Reports: Implications for Academic Research." Government University Industry Research Roundtable Technology Across Borders and Barriers: Visas and Export Meeting. Washington, DC: National Academies, 2004. 1 Feb. 2005. <http://www7.nationalacademies.org/guirr/Jones.ppt>.

working in U.S. laboratories, even on fundamental research, and the proposed changes remain under consideration.[159]

PRE-PUBLICATION RESTRICTIONS.

The final direct mechanism for government control of scientific information comes in the form of conditions on publication included in funding contracts or grants. Some government agencies (most notably the Departments of Defense and Energy) have historically relied upon pre-publication review agreements aimed not at entire fields of research but at specific projects that may have defense implications or rely upon classified information.[160] As with classified research, universities can elect to segregate or decline any projects requiring pre-publication review.

The heightened Cold War tensions of the late 1970s and early 1980s inspired zeal for controlling science and technology information, especially in denying deemed exports of technical knowledge to foreign nationals.

CONTENTIOUS TRENDS, THE CORSON REPORT, AND BACK TO CLASSIFICATION.

By the 1950s, the heavy government influence on university research funding began itself to elicit unease from a science community confronting new regimes for controlling scientific information produced through federally funded research, the vast majority of the U.S. research portfolio.[161] With détente, federal influence began to relax, but the

[159] Department of Commerce. Office of the Inspector General. Deemed Export Controls May Not Stop the Transfer of Sensitive Technology to Foreign Nationals in the U.S. Final Inspection Report No. IPE-16176. Washington, DC: OIG, 2004.

[160] Shea, 12-13.

[161] Relyea, Harold C. *Silencing* Science: National Security Controls and Scientific Communication. Norwood, NJ: Ablex Publishing Corporation, 1994.

heightened Cold War tensions of the late 1970s and early 1980s inspired a concomitant zeal for controlling science and technology information, especially in denying deemed exports of technical knowledge to foreign nationals – even the results of fundamental research presented openly at professional conferences.[162] The Reagan administration reversed a trend of classification reform by expanding categories of classifiable information, mandating classification within these areas, authorizing the reclassification of documents, encouraging agencies to err on the side of secrecy, and eliminating automatic declassification mechanisms.[163] President Reagan's executive order on classification excluded basic research "not clearly related to national security," a definition with widely debated meaning, even as the government cracked down on open presentation of basic research findings at scientific meetings attended by certain foreign nationals.[164]

Concerns in the scientific community about increasingly stringent information controls, and the recommendations of a university-Department of Defense forum, led to the convening of a panel on national security and scientific openness by the National Research Council (NRC).[165] Called the "Corson Report" after its study chair, the resulting 1982 publication concluded that "most university research should be unrestricted," and that "the best way to ensure long-term national security lies in a strategy of security by accomplishment, and that an essential ingredient of technological accomplishment is open and free scientific communication."[166] The Corson Report did note that a few areas of research clearly required strong information security in the form of classification; research in nebulous gray areas characterized by rapid development and direct military applications might merit other types of controls, but these should be clearly drawn and monitored.[167] In 1985,

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[162] Gast, 1-2.

[163] Relyea, "Emerging Threats."

[164] Crowley, John C. "Science and Secrecy: NSDD 189 – Prologue to a New Debate?" Washington, DC: AAAS R&D Policy Colloquium, 2003. 1 Feb. 2005. <http://www.aaas.org/spp/rd/JCC.ppt>.

[165] Ibid.

[166] Panel on Scientific Communication and National Security. Scientific Communication and National Security. Washington, DC: National Academies Press, 1982.

[167] Ibid.

the Reagan Administration issued National Security Decision Directive 189 (NSDD 189), which incorporated and specifically cited the recommendations of the Corson Report. NSDD 189 affirmed:

> It is the policy of this Administration that, to the maximum extent possible, the products of fundamental research remain unrestricted. It is also the policy of this Administration that, where the national security requires control, the mechanism for control of information generated during federally-funded fundamental research in science, technology and engineering at colleges, universities and laboratories is classification. Each federal government agency is responsible for: a) determining whether classification is appropriate prior to the award of a research grant, contract, or cooperative agreement and, if so, controlling the research results through standard classification procedures; b) periodically reviewing all research grants, contracts, or cooperative agreements for potential classification. No restrictions may be placed upon the conduct or reporting of federally-funded fundamental research that has not received national security classification, except as provided in applicable U.S. Statutes.[168]

Neither NSDD 189 nor its foundation documents address the biosciences directly. The Corson Report's sole discussion on biology (rather than weapons or energy) research cited monoclonal antibody technology as a negative example: an emerging technology that should not be subject to information controls due to the lack of apparent military applications.[169]

INFORMATION, RESEARCH, AND THE POST -9/11 ENVIRONMENT.

A November 2001 letter authored by then-National Security Advisor Condoleezza Rice provided some reassurance to a research community concerned about information controls in the wake of the year's terrorist attacks, affirming the value of basic and open research to U.S. national security, and confirming that "the policy on the transfer of scientific,

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[168] "National Policy on the Transfer of Scientific, Technical, and Engineering Information." The White House Press Office. 21 Sept. 1985. 1 Feb. 2005. <http://www.fas.org/irp/offdocs/nsdd/nsdd-189.htm>.

[169] Scientific Communication and National Security, 49.

technical, and engineering information set forth in NSDD l89 shall remain in effect."[170] A month later, a group representing both research and security professionals convened at the National Academies to consider what the new policy environment implied for open scientific communication.[171] Its report to the presidents of the National Academies began by reiterating the findings of the Corson Report two decades earlier, but expanded into a different vein:

> It is rarely feasible or desirable to restrict access to scientific information, knowledge, and education. Some categories of information, such as protocols for constructing and deploying weapons of mass destruction, however, should be restricted. With respect to scientific materials, restrictions are both feasible and desirable for a number of reasons including but not limited to terrorism. Defining the various categories of information and materials, the appropriate level of access/restriction, and the appropriate body to regulate such information and materials need to be carefully considered.[172]

The group also recommended a strengthened working relationship between the academic and national security communities, and it discussed the idea of creating new guidelines for protecting information outside of the bipolar classification system, possibly relying upon a self-regulated, risk-based matrix.[173]

The following months revealed a pattern in which Bush Administration policies generally expanded the categories of data that should be considered sensitive, regardless of classification status – including directing the systematic denial of Freedom of Information Act (FOIA)

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[170] Letter from Dr. Condoleezza Rice to Dr. Harold Brown, co-chairman, Center for Strategic and International Studies. Federation of American Scientists. 2001. 1 Feb. 2005. <http://www.fas.org/sgp/bush/cr110101.html>.

[171] Balancing National Security and Open Scientific Communication: Implications of September 11th for the Research Community. Washington, DC: The National Academies, 2001.

[172] Hasselmo, Nils and Robert Rich, co-chairs. "National Academies' Report on Post-September 11 Scientific Openness at Universities." The American Association of Universities. 2002. 1 Feb. 2005. <http://www.aau.edu/research/NAReport.html>.

[173] Ibid.

requests when a "sound legal basis" exists.[174] Although federal agencies have for decades used dozens of special access markings, such as "limited official use," that have no statutory standing but serve as internal shorthand for controlling public access to unclassified or "pseudo-classified" information,[175] some analysts suggest that "(t)he status of sensitive information outside of the present classification system is murkier than ever."[176] More than a decade earlier, in response to several contentious executive decisions, the Computer Security Act of 1987 (Public Law 100-325) defined the previously nebulous "sensitive information" as unclassified data which could adversely affect national interests, the conduct of federal programs, or individual privacy if lost or misused, but the law granted federal agencies broad latitude in defining and protecting sensitive information in their own systems.[177] "Sensitive but Unclassified" (SBU) became one of the most popular of the administrative control labels in the late 1990s, used by the Departments of State, Energy, and Defense, among others, to protect documents ranging from employees' personal information to logistical planning – some agencies or branches simply declared all unclassified internal documents to be SBU.[178]

The Homeland Security Act of 2002 created a new category of SBU information, codifying "sensitive homeland security information" as potentially protected and requiring the executive branch to issue guidance on safeguarding such information.[179] In March 2002, the White House released a memo signed by Chief of Staff Andrew Card that called upon agencies to review all of their publicly available data on weapons of mass destruction or homeland security, and to evaluate whether this data – including previously unclassified or declassified materials – should be protected by classification or by handling the documents as SBU.[180,181] (This policy may have been sparked by a January 13, 2002,

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[174] Knezo, 24-25.

[175] Relyea, "Emerging Threats," 10-17.

[176] JASON Program Office.HORIZONTAL INTEGRATION: Broader Access Models for Realizing Information Dominance. McLean, VA: Mitre Corporation, 2004.

[177] Knezo, 13-14.

[178] Knezo, 18-20.

[179] The Homeland Security Act of 2002 (PL 107-296), 23 Jan. 2002.

[180] Knezo, 23.

New York Times article called "U.S. Selling Papers Showing How to Make Germ Weapons," which revealed to the public that government protocols on bioweapons declassified years before could be ordered openly.[182]) Together, these policies escalated the significance of the SBU category, and have been interpreted as requiring security clearances for viewing certain types of SBU or sensitive homeland security information.[183]

A 2002 statement from the presidents of the National Academies cautioned about enthusiasm for extending SBU controls to research. "We believe it to be essential," the document said, "that these distinctions not include poorly defined categories of 'sensitive but unclassified' information that do not provide precise guidance on what information should be restricted from public access. Experience shows that vague criteria of this kind generate deep uncertainties among both scientists and officials responsible for enforcing regulations."[184] However, 2002 also saw the application of SBU-like restrictions to a National Academy of Sciences (NAS) committee report on agricultural terrorism vulnerabilities, which NAS agreed to censor under the broad interpretation of sound legal bases to reject FOIA requests.[185] Although the White House Office of Homeland Security and reviewers from the law enforcement and security communities found no classified data in the report, the Academy yielded to the concerns of USDA, the report's

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[181] "Memorandum for the Heads of Executive Departments and Agencies from Andrew H. Card, Jr., The White House: Action to Safeguard Information Regarding Weapons of Mass Destruction and Other Sensitive Documents Related to Homeland Security." U.S. Department of Justice. 2002. 1 Feb. 2005. <http://www.usdoj.gov/oip/foiapost/2002foiapost10.htm>.

[182] Blanton, 60-61.

[183] Knezo, 27.

[184] Alberts, Bruce, Wm. A. Wulf, and Harvey Fineberg. "Statement on Science and Security in an Age of Terrorism." 18 Oct. 2002. The National Academies. 1 Feb. 2005. <http://www4.nationalacademies.org/news.nsf/isbn/s10182002b?OpenDocument>.

[185] Enserink, Martin. "Entering the Twilight Zone of What Material to Censor." Science 298 (2002): 1548.

sponsor, that even information assembled completely from open-source information might compromise national security.[186]

Also in 2002, the Department of Defense drafted guidelines that would have required all researchers receiving military grant funding to obtain permission before discussing or publishing the results of their unclassified research projects, a proposal subsequently withdrawn in the face of strenuous objections from universities.[187] Universities also began to note, and balk at, wider use of restrictive language incorporated into other federal funding agreements. In 2003, the Association of American Universities and the Council on Government Relations assembled a task force of 20 academic institutions and asked them to review six months' of their federal contracts or grants for basic research. The task force identified 138 examples of restrictive language that contradicted university guidelines – mostly involving restrictions on publication or research by foreign nationals – that resulted in long negotiations or refusal of the federal funding altogether.[188] Dr. John Marburger, OSTP director, defended such restrictions as consistent with prior policies.[189]

OUTRIGHT CLASSIFICATION.

In March 2003, President Bush issued Executive Order 13292, which specified that categories eligible for classification include "scientific, technological, or economic matters relating to the national security, which includes defense against transnational terrorism." Although the order reiterates that "(b)asic scientific research information not clearly related to the national security shall not be classified," maintaining the national policy set in NSDD 189,[190] the reference to science and

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[186] Monastersky, Richard. "Publish and Perish?" Chronicle of Higher Education 11 Oct. 2002: A16.

[187] Southwick, Ron. "Pentagon Backs Away From Strict Controls on Basic Research." Chronicle of Higher Education, 31 May 2002.

[188] Association of American Universities/Council on Government Relations Task Force. "Restrictions on Research Awards: Troublesome Clauses." 8 April 2004.

[189] Marburger, John. Remarks at the National Academies of Science Roundtable on Scientific Communication and National Security. 19 June 2003.

[190] "Further Amendment to Executive Order 12958, as Amended, Classified National Security Information." 25 Mar. 2003. White House Office of the Press Secretary. 1 Feb. 2005.

technological matters that might be broadly linked to either national security or defense provides a platform for more generous inclusion of biosciences research in the face of future policy shifts.

PEER-REVIEW AND EDITING AS AN EMBARGOED SERVICE.

In 2003, the Treasury Department's Office of Foreign Assets Control concluded that the process of peer-reviewing and editing scientific manuscripts for publication constitutes an illegal service for authors from trade-embargoed nations, even prohibiting correction of punctuation.[191] In December 2004, following months of objections from publishers, the Treasury Department removed these restrictions. Although unrelated to proposed mechanisms to control the content of scientific publications, the initial decision to regulate the normal scientific publishing process as an export in specific contexts elicited strong reactions from professional societies and scientific journal editors that paralleled the concurrent debate on openness in scientific communications.[192]

<http://a257.g.akamaitech.net/7/257/2422/14mar20010800/edocket.access.gpo.gov/2003/pdf/03-7736.pdf>.

[191] Kingman, Sharon. "Scientific Publishers Divided over U.S. Trade Embargo Ruling." Bulletin of the World Health Organization 82.4 (2004): 312.

[192] Bhattacharjee, Yudhijit. "Editing No Longer Infringes U.S. Trade Sanctions." Science 306.5705 (2004): 2170.

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INFORMATION CONTROLS IN THE BIOSCIENCES: OUT WITH THE OPEN, IN WITH….?

In addition to the general trend for closer controls on all classes of technical information, a handful of scientific publications in 2001 and 2002 called the attention of policymakers to openness in the biosciences. In February 2001, a paper published in an ASM journal by an Australian research group demonstrated that expression of the cytokine IL-4 by a recombinant mousepox virus rendered the infection lethal to normally resistant mice, even those that had been previously immunized.[193] The results could be considered unsurprising, as previous observations had shown that IL-4 expression increases the virulence of mousepox and other poxvirus vectors, but the paper perhaps represented a necessary incremental advance in understanding how to apply immunomodulatory molecules in the design of immunocontraceptive vaccines.[194,195] In a May 2002 publication in the *Proceedings of the National Academy of Sciences*, researchers engineered and characterized a protein from variola (smallpox) virus, demonstrating that it acts as a virulence factor and thus

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[193] Jackson, Ronald J. et al. "Expression of Mouse Interleukin-4 by a Recombinant Ectromelia Virus Suppresses Cytolytic Lymphocyte Responses and Overcomes Genetic Resistance to Mousepox," Journal of Virology 75.3 (2001): 1205.

[194] Johnson, Teresa R., Julie E. Fischer, and Barney S. Graham. "Construction and Characterization of Recombinant Vaccinia Viruses Co-Expressing a Respiratory Syncytial Virus Protein and a Cytokine." Journal of General Virology 82.9 (2001): 2107.

[195] Ramshaw, Ian A. et al. **"**Cytokines and immunity to viral infections." Immunology Reviews 159 (1997): 119.

a possible target for therapeutic or vaccine interventions.[196] A few months later, *Science* published a manuscript demonstrating the production of infectious poliovirus from a full-length complementary DNA synthesized *de novo* from the published sequence.[197] The production of infectious poliovirus from complementary DNA alone had been demonstrated more than 20 years previously,[198] making the novelty of this experiment the completely synthetic assembly of the template from chemical building blocks. Other scientists alternatively praised the technical achievement and decried the experiment as a "cheap stunt."[199,200]

SCIENTIFIC PUBLICATIONS AND HEIGHTENED CONCERNS.

Had any of these papers been published prior to 2000, they likely would have drawn little but technical interest. However, in the atmosphere of newly heightened sensitivity to potential security threats, they attracted the attention of Congressional representatives and security analysts, as well as apprehension from researchers. Critics of the recombinant mousepox paper suggested that it provided a template for making other poxviruses (such as vaccinia, the virus used as a smallpox vaccine) lethal, and leveled similar accusations at the research that described the smallpox virulence factor.[201] As to the publication showing the ability to construct the relatively simple poliovirus "from scratch" in two years,

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[196] Rosengard, Ariella M. et al**. "**Variola Virus Immune Evasion Design: Expression of a Highly Efficient Inhibitor of Human Complement." *Proceedings of the National Academy of Sciences of the United States of America* 99.13 (2002): 8808.

[197] Cello, Jeronimo, Aniko V. Paul, and Eckard Wimmer**.** "Chemical Synthesis of Poliovirus cDNA: Generation of Infectious Virus in the Absence of Natural Template." Science 297.5583 (2002): 1016.

[198] Racaniello, Vincent R. and David Baltimore. "Cloned Poliovirus Complementary DNA is Infectious in Mammalian Cells." Science 214.4523 (1981): 916.

[199] Couzin, Jennifer. "Active Poliovirus Baked from Scratch." Science 297.5579 (2002): 174.

[200] Block, Stephen M. and Donald Kennedy. "A Not-So-Cheap Stunt" and response. Science 297.5582 (2002): 769.

[201] Monastersky, "Publish and Perish?"

some researchers lamented publicly what it implied for WHO's polio eradication plans and for biosecurity – not because the publication or the virus itself posed any risk to national security but because it drew attention to bioscience's technical capabilities.[202,203] For those seeking examples of "contentious research," these publications became case studies of experiments that "could have immediate weapons implications and that therefore raise questions concerning whether and how that research should be conducted and disseminated."[204]

Much of the popular media coverage focused on the sensational, even if acknowledging that none of these experiments introduced new technologies and that construction of more complex viruses from "mail-order" sequences remains an unlikely threat for a number of reasons.[205] The poliovirus experiment, in particular, sparked public fears and a continuing debate over whether the commercial DNA synthesis industry and oligonucleotide synthesizers, the machines that produce very short strands of DNA for use in molecular biology, should be regulated as dual-use technologies.[206] In response, Congressman Dave Weldon (R-FL) and seven co-sponsors introduced a House resolution condemning both AAAS and the researchers for "publishing a blueprint for creating a polio virus and other harmful pathogens that could be released on the population of the United States," and calling upon the science community and the Administration to reexamine publication policies.[207]

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[202] Couzin, "Active Poliovirus Baked from Scratch."

[203] Block, "A Not-So-Cheap Stunt."

[204] Epstein, Gerald L. "Controlling Biological Warfare Threats: Resolving Potential Tensions among the Research Community, Industry, and the National Security Community." Critical Reviews in Microbiology 27.4 (2001): 321.

[205] "Mail-Order Virus Could Pose Threat." 11 July 202. Associated Press/CBS News.com. 1 Feb. 2005. <http://www.cbsnews.com/stories/2002/07/11/health/main514906.shtml>.

[206] Weiss, Rick. "Mail Order Molecules Brew a Terrorism Debate." Washington Post 17 July 2002, A01.

[207] House Resolution 514, "Expressing serious concern regarding the publication of instructions on how to create a synthetic human polio virus, and for other purposes." 26 July 2002.

In October 2002, the House Committee on Science called a hearing on scientific communication and national security.[208] Among the witnesses, then-ASM president Ronald Atlas noted in his testimony that the scientific community shared policymakers' concerns about the possible misuse of technical information, but that a reactionary impulse to restrict publications would have consequences:

> The ASM recognizes the legitimacy of concerns about the publication and dissemination of scientific information and supports reasonable, balanced, and sensible restrictions on access to select agents that pose a high risk to public health and safety. The ASM agrees that we must deny scientific and technical information to terrorists and enhance laboratory security. At the same time, we must avoid restraining the exchange of scientific information in a manner that inhibits scientific research and medical progress, thereby adversely affecting public health. …The best defense against anthrax or any other infectious disease is information; information in a form that can be used by scientists and public representatives to guide rational and effective actions to ensure public safety.[209]

Dr. Atlas also warned of the difficulties in determining exactly what information should be restricted, when almost any biotechnology could be considered dual-use. In her testimony, Chancellor M.R.C. Greenwood of the University of California-Santa Cruz, cautioned: "We should take care not to break what works well and not to attempt to fix what isn't broken. … I am not here today to suggest that the nation's universities should simply be left alone but rather to try to inject a note of caution about overreacting. Trying to put into place new restrictions to prevent research in areas where an imaginary scenario might suggest a danger is probably not productive. We should consider new areas of classification only where there are real, agreed-upon threats."[210]

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[208] U.S. House of Representatives Committee on Science. "Conducting Research During the War on Terrorism: Balancing Openness and Security." Washington, DC: USHR, 2002.

[209] Atlas, Ronald M. on behalf of the American Society for Microbiology. Testimony before the House Science Committee. Washington, DC, 10 Oct. 2002.

[210] Greenwood, M.R.C. Testimony before the House Science Committee. Washington, DC, 10 Oct. 2002.

Despite concerns articulated in the (un-passed) House Resolution, and those expressed during several hearings, Congress has passed no new laws restricting bioscience research beyond the PATRIOT Act and the Bioterrorism Preparedness Act. Also, despite months of ominous meetings between OSTP and representatives of the science and technology community on the nuances of sensitive homeland security information in the sciences, the most recent executive branch actions on biosecurity (in addition to the release of the final select agent rule) have largely followed the recommendations of a report advocating a system modeled on the NIH guidelines for studying recombinant DNA.

RECOMMENDATIONS: DRAWING THE LINES.

Several meetings and reports sponsored by the National Academies played a role in developing self-regulation systems that have been adopted to varying degrees in the past two years. In addition to hosting several previously mentioned conferences on scientific openness, the National Academies sponsored two studies that specifically addressed issues central to security and the biosciences: one on biotechnology's "dual-use dilemma," and the second on genome research in the age of terrorism.

The latter study focused on genome data, "a source of raw material that, although not inherently dangerous, can be enabling for potentially destructive agendas."[211] The committee weighed the advantages of restricting access to genome data – removing a tool that could be used by a relatively sophisticated malefactor to enhance the virulence of a pathogen – against the benefits of openly shared data for researchers characterizing and countering the already virulent pathogens created by nature.

Examples of the increasing utility of genomics in meeting public health crises cited by the committee included that of the SARS virus outbreak in 2003. Within six weeks of the WHO's first global health alert concerning a newly identified atypical pneumonia, the virus that caused the disease had been isolated, cultured, and sequenced. The ability to publish the sequence openly allowed the organism to be identified conclusively as a coronavirus most likely of natural origin rather than a bioweapon, and also provided the basis for developing diagnostic tests

[211] National Research Council. Committee on Genomics Databases for Bioterrorism Threat Agents. Seeking Security: Pathogens, Open Access, and Genome Databases. Washington, DC: National Academies Press, 2004.

and candidate therapeutics.[212,213] Collaborators at the National Microbiology Laboratory, Canada; University of California at San Francisco; Erasmus University, Rotterdam; and Bernhard-Nocht Institute, Hamburg, contributed to the full-length sequence announced by the CDC in April 2003.[214] Had access to either the samples of this virus or the genomic sequences been controlled, such speed and international collaboration would clearly have been difficult or impossible.

The U.S. National Center for Biotechnology Information's publicly available Genbank data repository now includes genetic maps of more than one hundred bacteria and viruses, and coordinates its data regularly with similar databases in Japan and Europe.

In its full examination of genomic research, the National Academies committee stressed that the practicality of trying to contain genome data remains doubtful, even if the risks outweighed the benefits. The U.S. National Center for Biotechnology Information's publicly available Genbank data repository now includes genetic maps of more than one hundred bacteria and viruses, and coordinates its data regularly with similar databases in Japan and Europe.[215] Focusing on the genomes of just the select agents would not necessarily make restriction of such information more practical, as sequences from all of those pathogens classed as Category A, or highest risk, by CDC have already been released in the public domain, and information from closely related "non-select" organisms

[212] Committee on Genomics Databases for Bioterrorism Threat Agents, 31-32.

[213] Lingappa, Jairam R. et al. "Wresting SARS from Uncertainty." Emerging Infectious Diseases 10.2 (2004): 167.

[214] Department of Health and Human Services. Centers for Disease Control and Prevention. "SARS-Associated Coronavirus (SARS-CoV) Sequencing**."** Atlanta: CDC, 2004. 1 Feb. 2005. <http://www.cdc.gov/ncidod/sars/sequence.htm>.

[215] "Genomic Biology." The National Center for Biotechnology Information. 1 Feb. 2005. <http://www.ncbi.nlm.nih.gov/Genomes/>.

might provide just as many insights.[216] Even if a decision should be made to restrict access to genomic data in the future through classification, or through the less severe measure of requiring researchers to become registered users of databases, many sequences have been publicly available for months or years – the proverbial horse has already left the barn. In addition, these types of restrictions would be meaningless unless adopted also by all foreign colleagues and by commercial and other non-profit databases. Based on these analyses, the National Academies committee recommended that policies on microbial genome data obtained through basic research continue to emphasize openness and rapid publication, but that an entity with appropriate scientific expertise and connections to diverse federal agencies provide a forum where scientists and security experts could meet regularly to discuss new advances in genomics.[217]

While the deliberations on genomic data were complicated enough, the first National Research Council committee focused on the much larger question of how to deal with all implications of biotechnology's fundamentally dual-use character without unduly restricting research or inadvertently providing tools that might be intentionally misused. The committee considered the history of biological weapons, recognized recently raised concerns about openness in biosciences publishing, and evaluated the effectiveness of the current regulatory frameworks for both biosafety and biosecurity. The resulting October 2003 report, frequently called the Fink Report after panel chairman Dr. Gerald Fink, proposed a new system for guiding "dual-use" biotechnologies. The new system would maintain the current select agent rules for controlling access to pathogens but add a system of self-regulation to address "experiments of concern" before they can be performed and deal with unexpected results prior to publication. The recommendations included:

- Educating scientists about risks and responsibilities linked to dual-use technologies in the biosciences through professional societies and other relevant forums, and adopting appropriate codes of ethics for work in the biosciences.
- Identifying "experiments of concern" – those intended to enhance a microorganism's virulence, increase a pathogen's transmissibility or host range, make a pathogen more suitable to weaponization, or render a pathogen capable of

[216] Seeking Security: Pathogens, Open Access, and Genome Databases, 45.

[217] Seeking Security: Pathogens, Open Access, and Genome Databases, 52-59.

evading vaccine-induced immunity, therapeutically effective antibiotics or antivirals, or diagnostic/detection systems – and reviewing these before they are performed. Because most, if not all, of the experiments in this category would already fall under the existing NIH guidelines for experiments involving recombinant DNA, the Fink Report proposed adding dual-use biotechnology criteria into the current biosafety regulatory system, allowing for institutional review by IBCs with federal oversight by an expanded RAC.

- Relying on self-governance by scientific journals to review manuscripts for potential security risks. The mousepox IL-4 study provides a good example of an experiment that would not necessarily be identified as inherently risky through the criteria described above (as its goal was to enhance antibody production in an immunocontraceptive vaccine rather than to enhance the vector's virulence), but produced "unexpected results" that raised security issues. The Fink Report suggested that an adequately informed, self-directed reviewing process at scientific journals, incorporating lessons learned from policies already adopted by ASM journals, would detect manuscripts evincing security concerns, and that the editorial staff and authors could then decide whether to publish the paper as proposed, or require modification in order to prevent dissemination of "how to" guides facilitating weapons production.
- Creating a National Science Advisory Board for Biosecurity (NSABB) to serve as a liaison between the scientific and security communities and as a source of independent technical advice on select agents, "experiments of concern," educational tools, and other issues to relevant federal agencies.
- Maintaining the select agent rules without further security requirements, but reviewing and updating them as necessary through the NSABB.
- Strengthening channels of communication between life scientists and the national security and law enforcement communities.
- Creating an International Forum on Biosecurity to develop harmonized national, regional, and international regulatory frameworks. [218]

[218] *Dual-Use Dilemma,* 111-126.

The committee advised caution "so that the intended ends will be achieved without creating 'unintended consequences,'" but warned that "the potential threat from the misuse of current and future biological research is a challenge to which policymakers and the scientific community must respond."[219]

REALIZING THE NSABB.

In March 2004, then-HHS Secretary Tommy Thompson announced that some of the recommendations in the Fink Report would be embodied in Administration policy with the creation of the proposed NSABB. [220] As described in its charter, the NSABB incorporates responsibilities that the Fink Report divided between an advisory board and the expanded biosafety network, including developing:

- criteria to identify and strategies to oversee all dual-use research, including guidelines for risk-benefit analysis;
- guidelines for conducting life sciences research, disseminating "potentially sensitive" research results, and educating researchers about biosecurity at all federally funded institutions;
- a template code of conduct for the life sciences; and
- strategies for international cooperation on biosecurity issues.[221]

In addition, NSABB is charged with developing policies to adapt the institutional review process to dual-use research, formulating criteria for the IBCs to use in reviewing and referring such research, revising these policies through the review of cases deemed complex or novel by a local IBC (the role of the RAC in the biosafety network), and responding to requests by institutions to clarify how the guidelines will be applied to specific research proposals in the case of an IBC rejection.[222] The

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[219] *Dual-Use Dilemma*, 126.

[220] "HHS Will Lead Government-Wide Effort to Enhance Biosecurity in 'Dual-Use' Research." 4 Mar. 2004. Department of Health and Human Services. 1 Mar. 2005. <http://www.biosecurityboard.gov/NSABB_press_release.pdf>.

[221] "Charter: National Science Advisory Board for Biosecurity." 4 Mar. 2004. Department of Health and Human Services. 1 Mar. 2005. <http://www.biosecurityboard.gov/SIGNED%20NSABB%20Charter.pdf>.

[222] Ibid.

NSABB will not, however, review proposals rejected by an IBC on appeal. The charter calls for up to 25 voting members, chosen for expertise in a range of relevant fields and holding security clearances rated secret or higher, to be appointed by the HHS Secretary in consultation with the heads of other federal departments and agencies that support life sciences research. These will also supply non-voting *ex officio* members. The charter calls for the NSABB to meet quarterly, or as needed at the discretion of the "HHS Designated Federal Official" who sets the agenda and attends all meetings.[223]

The NSABB offers the framework for an official federal policy for biosecurity built largely on the existing successful model of self-regulation, with a system of institutional and federal review.

In concept, this offers the framework for an official federal policy for biosecurity built largely on the existing successful model of self-regulation, with a system of institutional and federal review guided by technical experts and enforced by federal funding pressures. Because the Administration's adaptation of the Fink Report recommendations includes only two tiers of review (rather than the intermediate review committee envisioned in the report), this system will expand the roles, the scope, and the necessary number of IBCs. The broad range of responsibilities assigned to the NSABB makes the adequacy of a quarterly meeting appear questionable, especially in light of the many new questions to be addressed in the first months following its inception. The NSABB's charter covers only federally funded research, and specifically excludes classified research; compliance with its recommendations in commercial, government, and private laboratories that do not receive NIH funding will depend, like the larger biosafety system, on voluntary adoption.

The realization of the board itself progressed with less than lightning speed from charter to embodiment.[224] Almost one year into its two-year charter, the Secretary of HHS appointed Thomas V. Holohan, MD, as the

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[223] Ibid.

[224] Miller, John Dudley. "Biosecurity a No-Show." The Scientist 18.24(2004): 12.

first NSABB executive director. The inaugural NSABB meeting on June 30, 2005, featured expert presentations on a range of issues related to dual-use research, and working groups of NSABB members began sketching approaches for implementing the board's charter at its second meeting in November 2005.[225] The NSABB (assuming that its existence will be extended by executive order) may grow to fill a very real need: a senior advisory body grounded in research culture and informed about real security threats, capable of plumbing the complexities of potentially dual-use biological research to set enduring precedents. Over time, such an organization could become an unremarkable and fully integrated part of the institutional review process, and of broader biomedical research culture. However, its early months have seen NSABB first freighted by great expectations that might exceed its available resources, then overstepping its original boundaries by intervening directly in scientific publishing, as described below. Whether the NSABB will ultimately succeed remains to be seen.

SELF-REGULATION OR SELF-CENSORSHIP?

Awareness that bioscience professional societies and journal editors needed to establish policies on publishing "sensitive biological research" pre-dated the Fink Report, in the context of debates on SBU categories in science and the threat of top-down government regulation. This issue became particularly pressing for journals that accept numerous manuscripts on microbiology research, such as those published by ASM. In early December 2001, the editors of ASM's journals announced an addition to the peer-review process: a step requesting that reviewers indicate if they believe that the work represents a misuse of microbiology or data, or might pose a threat to public health and safety. A positive answer would trigger a process of detailed consideration by the editor and possible referral to the ASM Publications Board, leading finally to either resumption of the review process or return of the paper to the author.[226,227] All accepted manuscripts involving select agents would

[225] "National Science Security Advisory Board for Biosecurity Meetings." Department of Health and Human Services. 1 Mar. 2005. <http://www.biosecurityboard.gov/meetings.asp>.

[226] "Policy Guidelines of the Publications Board of the ASM in the Handling of Manuscripts Dealing with Microbiological Sensitive Issues." American Society for Microbiology. 1 Feb. 2005. <http://journals.asm.org/misc/Pathogens_and_Toxins.shtml>.

undergo a second mandatory screening. This policy also states explicitly that authors must disclose complete materials and methods, and share unique materials and data as permitted under current regulations to allow replication of the published experiments.

Samuel Kaplan, chair of the ASM Publications Board, discussed the impact of this decision at a workshop on scientific openness in the context of national security issues held by the National Academies and the Center for Strategic and International Studies (CSIS). First, he emphasized, the sheer volume of publications at ASM (and in the life sciences in general) makes administering such controls less than trivial: In 2001-2002, ASM publications reviewed nearly 14,000 submitted manuscripts (involving four to five authors each on average, with about 60% of those of non-U.S. origin, from about 100 foreign countries), and depended upon the services of about 6,000 volunteer editors, editorial board members, and ad hoc reviewers (15-20% from outside of the United States). Because of this volume, attempts to screen manuscripts prior to review would be incredibly difficult to implement. Of the approximately 6,000 manuscripts and 134 "select agent manuscripts," accepted for publication in that year, two had been selected for detailed review, with both eventually accepted for publication with modifications.

A meeting of journal editors, authors, and science policy professionals immediately followed the workshop on scientific openness, and its participants subsequently released a joint statement that appeared in *Science*, *Nature*, and the *Proceedings of the National Academy of Sciences*. The group recognized that openly published scientific information might be used maliciously but advocated balancing such concerns against the benefits of open publication to public health and biodefense research. Its four specific declarations include, in summary:

1. In order to protect scientific integrity, published manuscripts must contain sufficient detail to permit independent researchers to reproduce, verify, and build upon the results.
2. The editors recognize legitimate concerns about the misuse of published information, and are committed to recognizing and dealing with safety and security issues in manuscripts.
3. Scientists and journals must find ways to implement reviews of papers that raise security concerns, applying lessons learned from journals that have already attracted such papers.

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[227] Kaplan, Samuel. "Remarks at Scientific Openness and National Security Workshop." 9 Jan. 2003. National Research Council. 1 Feb. 2005. <http://www.csis.org/tech/ssi/sonsw/>.

4. If an editor or professional society concludes that the theoretical harm of openly sharing specific data outweighs the potential benefits, the information should be modified, or not published – a stricture extending to communications in meetings and any other forum.[228]

Commenting on the first statement, the commitment to avoiding "partial censorship" by withholding materials and methods, participant Ronald Atlas explained, "In our war against infectious diseases, and in our quest to find effective defenses against biothreat agents, we cannot afford to go down false roads because of lack of verifiability."[229]

How have these recommendations been implemented by the approximately 20 general and specialty biomedical journals represented? As an example, editor Robert R. Rich indicated, in publishing the joint statement, that the *Journal of Immunology* would ask reviewers and editors to be aware that information in a manuscript might be misused, and to refer papers that they consider worrisome to the editorial staff for further review.[230] At the same time, he pointed out the difficulties in assessing the risks of publication versus the many intangible risks of non-publication, suggesting that many manuscripts would be subject to increased scrutiny but few would be likely candidates for outright rejection:

> How likely is it that we will see information rise through the rigor of our peer review system to be regarded as sufficiently meritorious to warrant publication in *The JI,* but that is also thought to present a risk of misuse sufficient to justify modification or rejection on that basis alone? I believe it is quite unlikely. For example, a "how to" methods paper that would assist a scientifically unsophisticated terrorist in weaponizing an

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[228] Journal Editors and Authors Group. "Uncensored Exchange of Scientific Results." Proceedings of the National Academy of Sciences of the United States of America 100.4 (2003): 1464.

[229] Atlas, Ronald. "Scientific Publishing in the Age of Bioterrorism." 2003. Academe Online. 1 Feb. 2005. <http://www.aaup.org/publications/Academe/2003/03so/03soatla.htm>.

[230] Rich, Robert R. "Benefit Versus Risk." Journal of Immunology 170.6 (2003): 2793.

> infectious agent, if ever submitted to *The JI,* would almost certainly be rejected for lack of scientific interest.[231]

Very little data exist to determine the frequency with which researchers have decided to censor their own results as a result of security concerns. In the Stimson survey of 28 experienced select agent researchers cited above, responses appeared polarized: Only two researchers strongly agreed that they have decided against publishing data or techniques that they feared might be misused, while 17 disagreed strongly that they would make such a decision. Based on available information, it appears that neither the self-imposed biosecurity review policy adopted by ASM nor the select agent rules have appreciably affected the number of submissions to specialty microbiology journals.[232] However, several authors have questioned ASM's policy requiring that accepted papers be published with reproducible materials and methods sections, based on the authors' own assessments that their publications could be misused.[233] A few have decided to withhold their papers based on their own independent judgments.[234]

Whether or not self-censorship represents a concern among more than a fraction of select agent researchers is an issue deserving more intense study, particularly because of the potential career impact of such decisions. Peer-reviewed publications play an important role not only in scientific progress but in connecting "the people who are paying the bills and employing the scientists and the scientists themselves…. Not only do [the authors] get feedback, they also derive personal recognition from their peers and establish a professional reputation, and they signal their value to the marketplace."[235] As articulated in a report from the American Association of University Professors, "The academic

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[231] Ibid.

[232] Shoemaker, Janet, director of public affairs, American Society for Microbiology. Personal communication.

[233] Ibid.

[234] Atlas, Ronald M. "National Security and the Biological Research Community." Science 298 (2002): 753.

[235] Lewis, Tracy. "Academics as a Natural Haven for Open Science and Public-Domain Resources: How Far Can We Stray?" The Role of Scientific and Technical Data and Information in the Public Domain: Proceedings of a Symposium. Washington, DC: National Academies Press, 2003.

community must be careful not to impose on itself a regulatory burden that differs from the government's only in the locus of administration. No evidence suggests that self-governance by the scientific community has been purchased at the price of individual freedom."[236]

A FIRST TEST.

In 2002, experts in research and security participating in a workshop on the publication of potentially "sensitive" data identified molecular details of the 1918 Spanish flu strain as an example of an inherently dual-use finding that could be used to combat future pandemics or "facilitate the deliberate engineering of lethal variants of influenza virus."[237] In October 2005, a team of researchers from the Armed Forces Institute of Pathology, CDC, USDA, and Mount Sinai School of Medicine capped a 10-year research effort with publications in the journals *Science* and *Nature* characterizing the infectivity of and genetic sequences from a reconstructed 1918 Spanish flu virus. Because the authors and editors recognized the obligation to balance security concerns against the need to provide scientists with a better understanding of the characteristics of influenza strains with pandemic potential, the editors of *Science* in this case demanded unusual scrutiny, including requiring the authors to obtain approval to publish from CDC Director Julie Gerberding and NIAID Director Anthony Fauci.[238] Unexpectedly, HHS Secretary Michael Leavitt also asked that the NSABB directly review both manuscripts just prior to publication; the board cleared both after a brief, hectic consulting period, requesting only the addition of two comments on security measures and the work's significance for public health.[239] In an editorial that appeared in the same issue of *Science*, molecular biologist and Nobel laureate Phillip A. Sharp discussed the decision to publish the findings in the interest of both public health and national security, concluding:

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[236] "Academic Freedom and National Security in a Time of Crisis." 3 Oct. 2003. American Association of University Professors, 1 Feb. 2005. <http://www.aaup.org/statements/REPORTS/911report.htm>.

[237] Zilinskas, Raymond A., and Tucker, Jonathan B. "Limiting the Contribution of the Open Scientific Literature to the Biological Weapons Threat." December 2002. 1 Feb. 2006. <http://www.homelandsecurity.org/journal/Articles/tucker.html>

[238] Kaiser, Jocelyn. "Resurrected Influenza Virus Yields Secrets of Deadly 1918 Pandemic." Science. 310.5745 (2005): 28.

[239] Ibid.

> It is reassuring that the NSABB was asked to consider these papers before publication and concluded that the scientific benefit of the future use of this information far outweighs the potential risk of misuse. People may be reassured that the system is working, because agencies representing the public, the scientific community, and the publishing journals were involved in the decision.[240]

However, an editorial published in the same journal one week later by *Science* editor-in-chief Donald Kennedy pointed out that the NSABB's final unanimous decision in favor of publication should not be construed as a happy ending, but only one facet of a story rich with lessons on managing dual-use research findings. The last-minute intervention of HHS officials – including the Secretary – to invoke an NSABB vote on a matter beyond the scope of its original charter (screening individual manuscripts rather than setting policy for doing so) did not merely inconvenience the editorial staff of one of the world's premier scientific journals, but created questions about federal authority over non-classified research. "Government officials can advise, and should be listened to thoughtfully," wrote Kennedy. "But they can't order the nonpublication of a paper just because they consider the findings 'sensitive.' No such category short of classification exists, as the Reagan-era Executive Order National Security Decision Directive 189, still in force, makes clear. If a paper should not be published because of biosecurity risks, then it should be classified."[241]

Stewart Simonson, Assistant Secretary for Public Health Emergency Preparedness, offered a mild rebuke in a letter to the editor of *Science* suggesting that Kennedy's editorial "appears to misunderstand the role" of the NSABB and the flexibility under its charter to address any issue at the request of the HHS Secretary. "While it was never the Department's intention to screen all dual-use papers," explained the letter, "it was understood that special cases would occur from time to time and that the Secretary would need to seek advice on individual papers."[242]

Although the federal intervention neither prevented nor delayed the publication of these two manuscripts, the sequence of events

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[240] Sharp, Phillip A. "1918 Flu and Responsible Science." Science 310.5745 (2005): 17.

[241] Kennedy, Donald. "Better Never than Late." Science 310.5746 (2005): 195.

[242] Simonson, Stewart. "Advising on Publication." Science. 311.5759 (2006): 311.

demonstrates that the parallel processes of self-regulation by scientists and scientific journals and federal oversight have not yet achieved harmony. The debate on when and if any federal organization, including the NSABB, should be involved in screening manuscripts – carried out in the pages of the largest circulation peer-reviewed general science journal in the world – may at last have drawn the attention of the broader research community.

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STEWARDSHIP AND THE "CULTURE OF RESPONSIBILITY"

In a 2003 publication, Gigi Kwik and colleagues outlined the requirements for an effective self-governance system in the context of "responsible stewardship of bioscience." Echoing many of the recommendations made by academic researchers in recent years, she identifies as critical an increased awareness of biosecurity and bioterrorism risks for scientists and their leaders, security provisions "organic" to the culture and practices of biological research, "bottom-up" approaches, processes for regularly assessing success, and an increasingly global approach.[243] Despite these thoroughly sensible suggestions, the biosecurity regulatory framework still hinges first on federally regulated and enforced pathogen control mechanisms, while self-governance mechanisms remain in fledgling form.

A culture of fear may breed compliance, but does little to engage bioscientists in a culture of responsibility based on shared values and consensus. At the same time, it deliberately casts scientists, law enforcement, and security professionals in an adversarial relationship. Any biosecurity regulatory framework destined to endure as a part of daily research life will do so only with "buy-in" from the research community. A snapshot of the current culture suggests that a small percentage of scientists have embraced the government's biosecurity paradigm fully – in some cases so enthusiastically that they question the stringency of the self-regulation adopted by scientific journals and urge tighter controls on dual-use materials and information. The majority has demonstrated ambivalence, with some concern about the possibility of a biological attack but a sense of mild skepticism about the need for or effectiveness of controls outside of securing "high-risk" pathogens. Although no community-wide surveys exist to bolster anecdotal observations, few scientists who conduct research with select agents or other pathogens appear to feel engaged in the policy-making process underlying either biodefense or biosecurity paradigms. In general, sensitivity to dual-use technologies as potential threats appears even

[243] Kwik, Gigi et al. "Biosecurity: Responsible Stewardship of Bioscience." Biosecurity and Bioterrorism 1.1 (2003): 27.

lower in fields where biodefense funding has made little impact and select agent concerns have required few changes in laboratory practices. At the other extreme, a fraction of scientists have regarded the movement toward increased biosecurity cynically, pointing to the polemics surrounding all issues related to "weapons of mass destruction," the technical obstacles to making any biotechnologies or pathogens into such weapons, and the channeling of resources into protection against unlikely scenarios. As articulated by Dr. Gerald Epstein: "[As] a basic requirement for anything to work, it's got to be fully supported by the people who are going to be subject to it, and the people who are going to be implementing it. So, that's again the notion that dialogue between the research community and the security community – the people who can identify the problems, the people who know what the consequences of that policy approach are going to be – is absolutely essential."[244]

The lack of buy-in for the current biodefense/biosecurity paradigm among scientists working in a relevant discipline can be seen in a March 2005 open letter to the director of NIH signed by 758 microbiologists, criticizing large increases for biodefense research funding at the perceived expense of basic microbial research.[245] Citing a steep increase from 2001-2005 in the number of grants awarded to study six pathogens prioritized as possible bioweapons, and a concomitant decrease in grants to study non-biodefense microorganisms, the authors stated that "the diversion of research funds from projects of high public-health importance to projects of high biodefense but low public-health importance represents a misdirection of NIH priorities and a crisis for NIH-supported microbiological research." NIH leaders quickly refuted both the substance of the letter and the supporting data, stating that funding for basic microbial research continued to grow at the same pace as the general NIH budget while the admittedly generous funding increases for biodefense research represent new funds, added to a budget that would never have seen such an increase without policymakers' concerns about bioterrorism.[246] "More broadly," replied NIAID director

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[244] Epstein, Gerald L. "Panel Discussion: Preventing the Misuse of Biotechnology." 15 Nov. 2002. Carnegie International Non-Proliferation Conference. 1 Feb. 2005. <http://www.ceip.org/files/projects/npp/pdf/conference/lottmantranscripts/Epstein.pdf>.

[245] Altman, S. et al. "An Open Letter to Elias Zerhouni." Science 307.5714 (2005): 1409-1410.

[246] Fauci, Anthony S. and Elias A. Zerhouni. "NIH Response to Open Letter." Science 308.5718 (2005): 49.

Anthony Fauci and NIH director Elias Zerhouni, "we disagree with the notion that biodefense concerns are of 'low public-health significance.' The United States has experienced an anthrax attack, and security experts repeatedly express concern that future attacks with biological weapons are likely, if not inevitable."

Although the microbiologists' objections relate to biodefense research priorities rather than biosecurity regulations, they certainly reflect a viewpoint that does not wholeheartedly concur with the leaders of government research organizations. While the dramatic increases in funding for pathogen research dedicated to Category A select agents would most likely not exist without political will to combat bioterrorism, these researchers clearly deemed the build-up in biodefense research – and, by implication, assumptions about the public health importance of biodefense – a strategic miscalculation.

Does the current U.S. paradigm for biodefense research go too far in dedicating public health resources to a handful of pathogens that could be used as weapons–or not far enough in preparing for a deliberate epidemic?

The perceptions of these microbiologists demand two questions: First, is there a real threat to be countered? If the answer is yes, what can be done to engage the entire biosciences community – not just the fraction most affected by select agents research, or seeking biodefense funding – in a productive dialogue to help the security community define the threats of high-risk pathogens and dual-use technologies accurately? By the same token, how can we arrive at a reasonable biosecurity strategy that matches the most appropriate solutions to the potential problems and fosters a biodefense agenda that can prove dual-use in the sense of approaching both man-made and natural threats to human, agricultural, and environmental health?

DEFINING THE THREAT, SEEKING SOLUTIONS.

Does the current biosecurity regime represent a satisfactory, if occasionally annoying, solution to a serious threat of pathogen diversion in domestic laboratories, or an exaggerated response to a hypothetical problem? Similarly, does the current U.S. paradigm for biodefense research go too far in dedicating public health resources to a handful of pathogens that could be used as weapons, or not far enough in preparing for a deliberate epidemic? The answer to both questions is an unsatisfactory, "it depends who you ask," as there is continuing discord within the bioscience community's leadership as well as between experts in biological security.[247] The only way to arrive at a better answer is to strengthen channels of communication between the broader biosciences community and those charged with overseeing national security, a prospect hampered not only by mistrust and cultural differences but by the simple dearth of a strong forum. Several formal and informal channels exist to provide technical advice to stakeholders in the national biological security policy process, but a lack of shared vocabulary and the dissociation of the larger biosciences community from policy decision-making processes present challenges to establishing buy-in from both sides.[248] Embarrassing gaffes in the last few years, including a minor fracas over whether the report on an unclassified session for microbiologists to discuss scientific openness with the intelligence community would itself be classified, have done little to build trust.[249]

The alternative to developing a stronger relationship between the bioscience and security communities would probably prove more painful for the former. Many scientists remain unconvinced of the necessity to pursue more stringent biosecurity regulations and adopt greater controls on open sharing of scientific information – not unreasonably, as many of the warnings from the security and policy analysis communities have taken the form of dire portents that seem technically far-fetched. Nonetheless, on the other side of the argument, the consensus about a real threat seems firm. To help evaluate real threats accurately and define acceptable costs for mitigating them, the biosciences community as a whole must openly and thoughtfully consider assumptions advanced

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[247] Enserink, Martin and Jocelyn Kaiser. "Has Biodefense Gone Overboard?" Science 307 (2005): 1396-1398.

[248] Fischer, 24-41.

[249] Brickley, Peg. "CIA Openness Report to be Classified?" The Scientist 7 April 2003.

by security analysts about the possible misuse of scientific information. Otherwise, the broader biosciences community risks being excluded from ongoing discussions of biosecurity regimes deliberately, rather than through simple neglect. As emphasized by George Poste, chair of the Bioterrorism Task Force for the Defense Science Board of the office of the U.S. Secretary of Defense, between the security and science communities there continues to be "a very profound climate of distrust, which just cannot be dismissed as merely the ramblings of non-scientific Philistines. This is a potential collision course that we are on, and I would submit that denial of this risk or obfuscation by the science and technology community would not only damage credibility with political leadership, but also the public, and, thus, predispose us to what several people have said would be well-intentioned but nonetheless flawed policies to control access to information and materials."[250]

While it appears unlikely that a non-state terrorist group would invest the resources necessary to pursue high-risk, cutting-edge technologies that *might* lead to a novel biological weapon when more conservative technologies (such as explosives, chemicals, or even weaponized pathogens purchased from a defunct state-sponsored program) would be more reliable, the apparent success of groups such as al-Qaeda and Aum Shinrikyo in recruiting individuals with biosciences expertise makes it necessary to consider vulnerabilities.[251] The NSABB can and should play a major role in bridging the chasms between the science and security communities, helping to establish a technically sound understanding of the threats posed by pathogen diversion and biotechnologies in general. Although classification will undoubtedly continue to be an issue (both cultural and practical), the ability of the security and intelligence communities to delineate the threats to NSABB members, and their dexterity in "translating" these issues to researchers through professional societies, meetings, and publications, will be fundamental to building trust between the two communities.

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[250] Poste, George. Remarks to the Scientific Openness and National Security Workshop. Washington, DC: National Research Council, 2003. 1 Feb. 2005. <http://www.csis.org/tech/ssi/sonsw/>.

[251] Petro, James B. and David A. Relman. "Understanding Threats to Scientific Openness." Science 302 (2003): 1898.

WHAT IS THE STRATEGY?

So far, the biosecurity paradigms embraced by the security and research communities have shown a predictable dichotomy: The initial reaction to the terrorist attacks and anthrax assaults of 2001, and the direction still supported by many security and law enforcement professionals, involves government-directed regulation of materials, technologies, people, and information. In contrast, the research community has tentatively tested systems for self-governance, attempting to reassure the public without imposing a stringent regulatory burden on scientists and publishers. The former model assumes that sensitive information can be identified and contained if necessary through a variety of mechanisms. The latter postulates that – with a few possible egregious exceptions likely to be recognized by technical experts – if *any* technology can be used malevolently, then the best strategy is complete transparency to allow the scientific community to "outrace" the menace of disease, whether deliberately released or naturally occurring.

A telling exercise lies in the attempt to develop a metric of success for the select agent rules – representing top-down regulations – and self-regulation of potentially sensitive information through internal manuscript review policies. The success of the select agent rules might be measured as the number of potential bioterrorists denied access to pathogen materials, a very difficult matter to quantify without a denominator (the number of potential bioterrorists who might have stolen or diverted pathogens in the absence of restrictions). The metric for evaluating the framework of self-regulation adopted by several scientific journals would focus on the awareness of reviewers and the number of papers screened, flagged for further review, and finally either withdrawn or published successfully with the concurrence of the author after careful consideration.

Together, the two approaches share a common goal – denying easy access to materials or tools that could be misused to produce a biological weapon – but embrace divergent strategies. The George W. Bush administration has articulated a government-wide biodefense strategy, citing a need to prevent biological weapons attacks through the "expansion of current multilateral initiatives to limit the access of agents, technology, and know-how to countries, groups, or individuals seeking to develop, produce, and use these agents."[252] Efforts to streamline policies across the entire federal government, and prevent both inadvertent and

[252] "Biodefense for the 21st Century." 28 April 2004. White House. 1 Feb. 2005. <http://www.whitehouse.gov/homeland/20040430.html>.

intentional exposures of the public to the products of laboratory research will require both short- and long-term strategies for biosafety and biosecurity. Again, the collaborative work of both the bioscience and security communities, facilitated through the NSABB or an equivalent task force, will be required to produce a technologically sound approach that builds a strategy on a series of general questions:

- What dual-use biotechnologies represent a realistic threat, meaning that they are technically feasible, affordable, accessible to state or non-state actors, reliable, and deployable without requiring extremely specialized tools (or wild surmise)?
- Do any of these threats appear so clear-cut that they should be born classified?
- For all other classes of dual-use technology threats, can an objective matrix be drawn that ties specifically prescribed precautions to incrementally increasing degrees of danger? (As a start, can researchers and security experts agree on a set of effective physical and personnel security measures for pathogens, tied to the risk that they realistically pose to public health or the economy if accidentally or deliberately released, that incorporates lessons learned from the first three years of the select agent rules? Can similar measures be developed – if necessary – for "contentious research" or "experiments of concern?" What about biotechnologies that *could* be used, in theory, to develop novel threats?)
- Once the threats have been described, what are the specific goals that can be met to limit them, without halting the progress of biological and biomedical research?
- How can these threats be described accurately to scientists without security clearance?
- How do these goals fit together in a larger strategy to increase transparency of data and facilitate communication among researchers working on legitimate and beneficial projects (the vast majority), and to minimize accidental or intentional exposures of researchers and the public to potentially hazardous pathogens or other materials of laboratory origin? Can the science and security communities mutually agree on this larger strategy?

BUILDING PUBLIC TRUST.

That public trust in science and scientists oscillates through periods of profound misgivings hardly qualifies as news. Since the anthrax assaults engendered a sudden awareness of bioterrorism in an already fragile national psyche, stories of potentially mishandled clinical trials, conflicts of interest, and emotionally charged cloning and stem cell questions have joined the ongoing debate about genetically modified organisms in the news headlines. Biodefense strategies have raised concerns of their own, first with the announcement that the government would dramatically expand the amount of Biosafety Level 3 and 4 laboratory space available in the United States in the next few years.[253] News that one of three new Biosafety Level 4 containment laboratories had been awarded to Boston University provoked local dissent, within the scientific community as well as the general public, and in other states awarded funding to expand lower-level facilities, citizens' groups objected to the proliferation of the Orwellian-sounding "biosafety laboratories."[254] A spate of laboratory incidents involving select agents fanned such anxieties. In one case, a laboratory worker was exposed to Ebola virus at Fort Detrick. In another, a failure to inactivate a *Bacillus anthracis* culture inadvertently exposed seven California researchers to anthrax. Meanwhile, three Boston University laboratory workers were alleged to have contracted tularemia, and three SARS incidents were reported in Asian laboratories.[255, 256, 257, 258]

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[253] Miller, John Dudley. "U.S. Government Launches Biolab Building Spree." The Scientist 18.10 (2004): 48.

[254] Field, Kelly. "Residents Fight Boston U.'s 'Biosafety' Laboratory." Chronicle of Higher Education 50.42 (2004): A28.

[255] Starr, Barbara. "Researcher Isolated After Possible Ebola Exposure." 19 Feb. 2004. CNN.com. 1 Feb. 2005. <http://www.cnn.com/2004/HEALTH/02/19/ebola.exposure/>.

[256] Kunkle, Fredrick. "Md. Lab Ships Live Anthrax in Error." Washington Post 12 June 2004, B05.

[257] Shane, Scott. "Exposure at Germ Lab Reignites a Public Health Debate." New York Times 24 Jan. 2005, A13.

[258] Brown, David. "SARS Cases in Asia Show Labs' Risk." Washington Post 29 May 2004, A01.

Any biosecurity regulatory framework, and particularly one based on self-regulation, must do more than just satisfy science and security professionals: It must engage the public's trust. Abigail Salyers, former president of ASM, explains it this way:

> Although scientists themselves are well aware of the importance of the free exchange of information within the research community, a community that transcends national boundaries, the public may not necessarily be convinced that scientists can be trusted to this extent. There remains an undercurrent of public discomfort with what is seen by some, however wrongly, as freedom without responsibility. This generalized discomfort has been evident during the debates on the safety of genetically modified foods and the ethics of stem cell research. All of us in the scientific community, either individually or through our professional societies, must be prepared to make a strong and well-documented case for the importance of the free flow of information if such a defense becomes necessary. It is no longer sufficient to tell the public: "Trust us, we know what is good for you." We need to be able to explain why our position is in the public interest.[259]

Policymakers will respond to public concerns, and a public that fears the consequences of open scientific communication will support draconian safety measures if less stringent schemes appear ineffective. Professional societies that have already taken steps toward self-governance in publishing must keep the public apprised of such decisions and their implications.

WHERE ARE THE REASONABLE COMPROMISES?

Assurances from OSTP Director John Marburger have not completely assuaged fears that the Administration might still withdraw its support from the principle that "determinations relating to the reporting of federally funded research be made *prior to the award*. Only in rare and exceptional circumstances should it be necessary to invoke additional controls after the award, and such cases should not be regarded as establishing a precedent."[260] The effectiveness of the still-new system of

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[259] Salyers, Abigail. "Science, Censorship, and Public Health." Science 296.5568 (2002): 617.

[260] Marburger, John. "Remarks at Scientific Openness and National Security Workshop," 9 Jan. 2003. National Research Council. 1 Feb. 2005. <http://www.csis.org/tech/ssi/sonsw/>.

self-regulation in biosciences publishing, with assessment built into the peer-review process, has already been scrutinized during the publication of the 1918 Spanish flu manuscripts – undoubtedly not the last time that this will happen – and NSABB will apparently be expected to advise relevant federal agencies on dual-use publication policies while participating directly in the publication process.

Questions about the real costs of short delays or partial censorship have not been answered clearly by the research community any more than the exact nature of extant threats has been explained by the security community.

Ronald Atlas notes: "Review for 'sensitive' information is difficult and complicated. There is no common definition of what is dangerous or sensitive information and no individual is empowered to decide what is potentially dangerous knowledge."[261] Questions about the real costs of short delays or partial censorship have not been answered clearly by the research community any more than the exact nature of extant threats has been explained by the security community. Specific proposals from some security experts have included registration schemes for access to scientific publications as well as genome databases, with publicly available versions of articles omitting technical details from materials and methods sections that would be available to registered institutional users.[262] Others have suggested a stalling tactic. In this stratagem, where the open and rapid publication of research results "will improve the hands-on 'know how' of how to handle dangerous pathogens, or may help a terrorist organization or proliferant state to avoid long and costly dead-end lines of research, or overcome other technical obstacles, a *modest* delay before

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[261] Atlas, Ronald M. Testimony before the House Science Committee.

[262] Gansler, Jacques S. and William Lucyshyn, The Unintended Audience: Balancing Openness and Security. Washington, DC: National Defense University, 2004.

communication for the purposes of security review would not be inappropriate."[263]

While continuing the current plan of primarily self-regulation in biosciences publishing, the broader biomedical research community should thoughtfully evaluate the arguments for stricter limits on scientific communication and either develop well-articulated, supported counterarguments, or decide what points can be conceded without violating the integrity of the scientific process. For example, a decision to restrict detailed materials and methods sections to institutional subscribers would clearly contradict the principles of open access, and affect collaborators in developing nations disproportionately, but specific examples of how this might affect research productivity, collaborations, or public health emergencies would provide a more compelling case than objections based in philosophical argument.

INTERNATIONAL HARMONIZATION.

The Fink Report pointed out that any efforts to reduce the potential risks of dual-use research "must ultimately be international in scope, because the technologies that could be misused are available and being developed throughout the globe."[264] From 1988 to 2001, the number of internationally co-authored papers (with authors representing institutions in more than one country) more than doubled from 8 to 18%, with U.S. authors represented in 44% of these in 2001.[265] In that year, the United States accounted for about one-third of all published science and engineering articles – the largest percentage of any single nation, but no monopoly.[266] Whether self-imposed or developed with government guidance in the future, consistent application of a U.S. standard for "sensitive information" to manuscripts from nations with discordant security requirements would undoubtedly have an impact on international collegiality, and not inconceivably on publishing patterns.

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[263] Wallerstein, Mitchel B. Remarks at Scientific Openness and National Security Workshop," 9 Jan. 2003. National Research Council. 1 Feb. 2005. <http://www.csis.org/tech/ssi/sonsw/>.

[264] *Biotechnology Research in an Age of Terrorism*, 124.

[265] National Science Board. Science and Engineer Indicators 2004 (Chapter 5: Academic Research and Development). Washington, DC: National Science Foundation, 2004. 1 Mar. 2005. <http://www.nsf.gov/sbe/srs/seind04/c5/c5s3.htm#c5s3l5>.

[266] Science Board, Science and Engineer Indicators 2004, Table 5-18.

Biosecurity regulations that constrain the open sharing of scientific information by U.S. researchers and journals in the context of an increasingly global research enterprise would "certainly adversely impact biomedical research in the United States. Whether it could help deter bioterrorism is far from clear."[267]

The lack of international harmonization presents very practical problems for infectious diseases researchers. The mousepox paper cited above illustrates part of the dilemma. Although published in a U.S. journal, the research in question was conducted in Australia. Procedurally, then, decisions about whether this line of inquiry represents contentious research that should be carefully reviewed for risks and benefits prior to advancing would depend upon another nation's review system, and only the decision to publish or reject the manuscript would be left to U.S. journals. In the past few years, other high-output research nations (including the United Kingdom, France, Germany, Japan, Israel, and Canada) have passed domestic laboratory biosecurity legislation, and the European Union issued a 2003 directive calling for best practices to help guide national legislation for controlling access to pathogens and toxins.[268] Thus far, the current Administration has resisted any multilateral efforts to negotiate international biosecurity guidelines on the basis that these might "water down the U.S. standards."[269] However, the lack of a single best-practices model could result in a "patchwork of inconsistent regulations," leading to problematic international collaborations at best and venue-shopping for weak regulatory frameworks at worst.[270] The former has already become apparent. The announcement that foreign researchers working with U.S. researchers on federally funded select agent projects will have to meet the equivalent of U.S. biosecurity standards could pressure resource-poor collaborators "to serve as mere sample exporters."[271] Sharp disparities in biosecurity requirements and available resources can exaggerate the burdens of

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[267] Atlas, "National Security and the Biological Research Community," 754.

[268] Tucker, Jonathan B. Biosecurity: Limiting Access to Deadly Pathogens. Washington, DC: U.S. Institute of Peace, 2003.

[269] Tucker, Jonathan B. "A Strategy for International Harmonization of Biosecurity Standards Under SCR 1540." 3 Dec. 2004. Workshop on U.N. Security Council Resolution 1540 as it Pertains to Biological Weapons,

[270] Tucker, Biosecurity: Limiting Access to Deadly Pathogens, 24.

[271] Stone, 2177.

compliance for all laboratories and researchers involved. No additional funding resources have been made available to help individual U.S. laboratories bring their foreign collaborators' laboratories up to U.S. physical and personnel security standards.

At the same time, three separate laboratory-based outbreaks leading to at least nine cases of SARS infections in China, Taiwan, and Singapore have drawn attention to variable compliance with specific biosafety guidelines issued by the WHO, let alone general suggestions that laboratories should incorporate biosecurity risk assessments.[272] In May 2005, the World Health Assembly called upon its member nations, with the technical assistance of WHO, to improve laboratory biosafety at the local and national levels.[273] A realistic risk matrix that integrates biosecurity and biosafety strategies more closely could prove as valuable for providing common ground for international harmonization efforts as it could for optimizing risk-benefit in U.S. domestic biosecurity regulations. The institutional review model for biosafety, for example, has been widely adopted internationally, not because the United States imposed its template upon the WHO or other nations but because it provides a practical model for relatively unobtrusive and cost-effective regulation of experiments that might pose a hazard to researchers or the public.

The NSABB has been charged, among its many responsibilities, with developing the international forum for harmonizing biosecurity regulations recommended by the Fink Report. Efforts to achieve international harmonization of biosecurity regulations do not begin with a blank slate. Unsuccessful efforts to develop strong compliance protocols acceptable to all state parties of the Biological Weapons Convention have left a legacy of frustration, particularly with the George W. Bush administration's rejection of a biosecurity regime that would have included inspections of pharmaceutical and biotech laboratories as well as government facilities. The WHO has developed long-term biosecurity strategies with wider acceptance, such as ongoing regulation of sensitive smallpox research and guidance on laboratory safety, but has done so largely in the absence of enforcement authority. The Australia Group, which harmonizes export controls for certain chemical and biological materials, has demonstrated that a group of advanced industrialized nations with similar resources and goals can develop a

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[272] Brown "SARS Cases in Asia Show Labs' Risk."

[273] World Health Organization, 58th World Health Assembly. (Draft) A58/62. 25 May 2005. < http://www.who.int/gb/ebwha/pdf_files/WHA58/A58_62-en.pdf>.

consensus list of dual-use biotechnologies that should be subject to controls in return for certain intra-group trade conveniences; unfortunately, the Group's history also shows that excluding less technologically advanced nations from both the advantages and requirements of membership can engender resentment.[274]

While reaching international consensus is daunting, forcing the U.S. select agent list and guidelines on researchers in other nations seems an equally unlikely model for success. First, perceptions of high-risk pathogens differ based on nations' varying epidemic and endemic diseases profiles. Second, such demands – focusing largely on the personnel and physical security emphasized by the select agent rules – may be seen as ranging from wildly impractical to imperialistic. Finally, until the United States has demonstrated that the benefits of the select agent rules and the evolving dual-use biotechnology regulatory paradigm outweigh the costs to the satisfaction of its own research community, convincing other nations will remain challenging.

CODES OF CONDUCT.

Codes of conduct have been proposed as both an educational tool to explain risks to individual researchers and a compact between those scientists and society by the Fink Report and other analyses. A template code flexible enough to incorporate national practices, but universal enough to capture a shared ethos, could provide one method for "bottom-up" international harmonization of biosecurity practices. The NSABB has been charged with developing a code of conduct for biosecurity, but this can and should involve an iterative process with input from professional societies, institutions, and individual scientists. Many questions remain about the type of code to be adopted (with models of aspirational, educational, and enforceable codes to be considered), as well as how to make such codes relevant to life sciences researchers.[275] If the true strategy of the biosecurity regulatory framework lies in developing a culture of responsibility that transcends national law, individual scientists must feel ownership in, as well as necessity for, vital codes of conduct or ethics.

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[274] Tucker, Biosecurity: Limiting Access to Deadly Pathogens, 25-27.
[275] Rappert, Brian. "Towards a Life Sciences Code: Countering the Threats from Biological Weapons." Strengthening the Biological Weapons Convention, Briefing Paper No. 13. Bradford, UK: University of Bradford, 2004.

TIME FOR ANOTHER ASILOMAR – OR TWO?

The biosciences community cannot simply wait for the NSABB to fill all of its potential roles, especially as the committee will probably stagger under its considerable workload for some time to come. The National Academies and policy analysis organizations have facilitated meetings between scientists, science policy analysts, security and intelligence professionals, and policymakers that should continue despite previous misunderstandings – and even in the absence of a recent bioterrorism event. Professional societies, especially those whose members do not gravitate naturally toward select agents or pathogens issues, can also play a role by convening discussion sessions at national meetings, developing educational curricula on the issues at hand, and creating policies on a range of scientific openness issues that can be shared with the NSABB and directly with policymakers. In partnership, professional societies and policy organizations can also play a key role in developing realistic case studies that examine the consequences of delayed or restricted research publications objectively, as a matter for serious analysis, rather than simply asserting the desirability of open scientific communications.

Some leaders in the field of biodefense have called for a second Asilomar, a reincarnation of the 1975 conference that outlined the current working system for biosafety and gave rise to the institutional review system.[276] Such a meeting could provide a manageable forum for addressing the many issues raised above: defining the real risks, identifying short-term goals and long-term strategies for dealing with those risks in the context of responsible self-regulation where possible, and determining how these would affect both individual researchers and the overall state of scientific communication in biological and biomedical research. Like the first Asilomar Conference, such a program would have to engage stakeholders from beyond the most directly affected community of researchers, involving the public through media coverage and participation by stakeholders from various community and policy sectors. Building on lessons learned in the last three decades, such a conference should also include discussions of ethical, legal, and social issues, in addition to the technical issues of concern.

Asilomar may not provide exactly the right model, as the hazards of biodefense research have been debated publicly now for several years, by-passing the opportunity to engage in thoughtful scientific debate about the perceived risks before broaching the subject with the general

[276] Atlas, Ronald M. "National Security and the Biological Research Community," 754.

public and policymakers. However, a summit for interested members of the biosciences community to focus on the entire range of issues related to open scientific communication, including public trust, remains desperately needed. Due to the scope of community involvement required, the correct answer might be a series of Asilomars, or meetings repeated with an identical agenda, distributed either by geography or held after the regular conferences of various large professional societies. Such a series would provide a means through which the newly selected members of the NSABB might judge the current interests and needs of bioscientists from various disciplines or institutions. Regardless of whether this community-wide summit takes place as a single conference or a series of meetings, a venue for addressing the whole range of concerns that surround issues of biodefense, biosecurity, and open scientific communication might offer an opportunity to explore divisions within the biosciences community, as well as to improve public understanding.

THE ROLE OF THE INDIVIDUAL.

As in every community, the involvement of individual scientists in political and policy issues ranges from intense involvement in advocacy issues to almost complete disengagement apart from paying annual dues to a professional society. Following the anthrax assaults and the subsequently imposed biosecurity regulations, several scientists have become articulate advocates for scientific openness and related issues. However, many assumptions about the impact of current and proposed regulatory measures stem from the observations of those vocal few, or from limited surveys inherently biased through self-selection. Stronger channels for feedback from individual scientists on specific biosecurity and biosafety issues – designed to avoid professional repercussions and maximize responses – would help decision-makers, professional organizations, and institutions perform the kind of evaluations necessary to foster a successful and sustainable biosecurity framework.

Although federal workshops occasionally allow individuals to address such issues, few researchers have the time or resources to travel to Washington, DC-area meetings solely to provide comments on national policies. Professional societies and institutions will most likely provide the most appropriate conduit for conveying individual concerns to the NSABB or other appropriate forums at the federal level. They could provide an inestimable service through the joint development of a more active, standardized mechanism for monitoring scientists' awareness of and response to biosecurity issues than can be generated by researchers in a single study. Such information could at least establish a true

baseline for understanding the impact of the current biosecurity regulatory framework.

The science community must rely on individual scientists to engage the issue, learning as much as possible about the policy and political aspects of the biosecurity debate. An educated researcher steeped in these details as well as the technical facets of the biosecurity regulation challenge can serve as a far more effective advocate for reasonable approaches to understanding and averting the threat of dual-use technologies. The security community does not take the "right to research" for granted. Neither can scientists.

AT-A-GLANCE: LEGISLATION & CASES

Bayh-Dole Act of 1980 (Public Law 96-517): Created a uniform patent policy among federal agencies that fund extramural research, allowing universities and other non-profit organizations to retain title to innovations developed with federal funding.

DIAMOND v. CHAKRABARTY, 447 U.S. 303 (1980): Allowed patenting of living genetically modified organisms, enhancing the commercial potential of the life sciences.

Antiterrorism and Effective Death Penalty Act of 1996 (Public Law 104-132): Expanded the definition of biological weapons, made threatening their use (in addition to using them) a crime, and required the Secretary of Health and Human Services to create a list of biological agents that posed a high threat to human health and to regulate the transfer of those agents between laboratories.

USA PATRIOT Act of 2001 (Public Law 107-56): Expanded the biological weapons statutes established in 1996 to create criminal penalties for the possession of "any biological agent, toxin, or delivery system of a type or in a quantity that, under the circumstances, is not reasonably justified by a prophylactic, protective, bona fide research, or other peaceful purpose," and created a class of "restricted persons" who cannot legally possess, transport, or ship any select agent.

Public Health Security and Bioterrorism Preparedness and Response Act of 2002 (Public Law 107-188): Codified the criteria for classifying pathogens as select agents, required the Secretaries of HHS and USDA to regulate safety of possession and use as well as transfer of select agents, mandated laboratory inspections as necessary to ensure safeguarding of select agents, required HHS and USDA to work with the Department of Justice to identify "restricted persons," and created civil penalties for violation of the select agent regulations. (Other provisions cover state and national emergency medical preparedness and food and water security.)