Chapter 4
Considering US Proposals for Enhanced Biosafety, Biosecurity, and Research Oversight

Of the proposals that the US government tabled to stand in for a monitoring protocol for the Biological and Toxin Weapons Convention (BWC), the industry experts reacted most positively to those calling for BWC members to improve standards for biosafety, biosecurity, and oversight of genetic engineering research. They tempered their praise with criticism of the state-by-state structure of the proposals, which they saw as undercutting their potential efficacy. The industry group recommended instead that the United States advocate international adoption of common minimum standards in each of the areas, based on current US regulations and guidelines, or their equivalent.

Taking the US government's biosafety, biosecurity, and research oversight initiatives in turn, this chapter reviews the industry group's discussion of pertinent domestic efforts. The industry experts then explain why some changes are needed domestically and how to achieve them. Improvements at home will pave the way for the successful promotion of similar initiatives internationally. As one participant noted, "If we don't walk before we run, if we don't set up things at home first to serve as an international model, I'm not going to count on anyone else to do it."[1] In each topical area, the industry group makes specific recommendations to strengthen the US proposals. Prior to the discussion of the individual proposals, the discussion briefly focuses on three factors that will underpin the viability of any international moves to enhance biosecurity, biosafety, and oversight of genetic engineering research.

The first factor key to the success of any new standards will be the articulation of agreed lists of select human, animal, and plant pathogens. With such reference lists, scientists and institutions will no longer have to wonder whether their operations should trigger the use of certain biosafety, biosecurity, and research oversight practices. Select agent lists should: 1) stratify agents according to risk; and, 2) be no longer than necessary. Lists that do not meet these criteria defeat their own purpose because, as one industry expert observed, "Not everything can be high risk."[2] Facility operators find it too confusing and burdensome to work with exceedingly long lists.

The industry group cited as constructive models the Centers for Disease Control and Prevention's (CDC's) select agent list for human pathogens and toxins and the Australia Group's core and warning

[1] Dr. Jennie Hunter-Cevera, 10 August 2002. Dr. Jennie Hunter-Cevera, president of the University of Maryland Biotechnology Institute, holds a PhD in microbiology and has well over twenty years of research and managerial experience in US industry and research institutions.

[2] Dr. Robert Goldberg, 9 August 2002. Dr. Robert Goldberg, PhD in medical microbiology, has over thirty years of research and administrative experience in US industry and at the National Cancer Institute.

lists for human, animal, and plant microorganisms.[3] For examples of poorly conceived lists, they pointed to some of those maintained by US Department of Agriculture.[4]

The second factor central to the implementation of any new standards is education. The industry experts were disturbed that the academic institutions charged with instilling good scientific practices were not upholding their responsibilities, particularly regarding principles of biosafety. Two of the industry participants expressed alarm at the lax biosafety practices they had witnessed at some universities, which sometimes devote insufficient resources to this vital area.[5] Without appropriate instruction and supervision from biosafety officers, young scientists graduate with bad biosafety habits, virtually ignorant of the biosafety rules they go on to break routinely, sometimes at their peril.[6] The industry experts also recognized the need for colleges and universities to promote study of the "less glamorous scientific disciplines" (e.g., microbial forensics, maintenance of culture collections and databases, documentation,

[3] The CDC periodically reviews and updates its select agent list, which stands at thirty-six human toxins and pathogens. The relevant section of the federal code, 42 CFR 72, can be accessed at http://www.cdc.gov/od/ohs/lrsat/42cfr72.htm. The Australia Group is an export control cooperative of over thirty governments that harmonize export control policies for the purpose of hindering chemical and biological weapons proliferation. The Australia Group's control lists can be found at http://www.australiagroup.net/control_list/bio_agents.htm. For more on the Australia Group's operations, see Amy E. Smithson, *Separating Fact From Fiction: The Australia Group and the Chemical Weapons Convention* (Washington, DC: Henry L. Stimson Center, March 1997).

[4] Industry experts complained that some APHIS agent lists are too lengthy and do not sufficiently differentiate between different levels of risk, which creates inordinate delays to permit work with certain agents. The Regulated Plant List, available on APHIS' Plant Protection and Quarantine website at http://www.aphis.usda.gov/ppq/regpestlist, is eleven pages long and catalogs more than 400 different plant pathogens. In contrast, the new section of federal code created to fulfill the requirements of the *Public Health Security and Bioterrorism Preparedness and Response Act* lists only nine plant pathogens that US facilities must declare to APHIS. "The listed agents and toxins are viruses, bacteria, or fungi that can pose a severe threat to a number of important crops, including potatoes, rice, soybeans, corn, citrus, and stone fruit." "Agricultural Bioterrorism Protection Act of 2002; Listing of Biological Agents and Toxins and Requirements and Procedures for Notification of Possession," *Federal Register* 67, no. 155 (12 August 2002): 52383-52389. Discussed in more detail later in this chapter, the Public Health Security and Bioterrorism Preparedness and Response Act became Public Law 107-188 on 12 June 2002.

[5] Research grants do not contain line items for biosafety officers, and one expert recalled the example of a researcher who worked on *Staphylococcus aureus* for four months, thinking it was *Bacillus anthracis*. She continued: "When visiting some universities, I have been shocked at the lack of biosafety officers, procedures, guidelines, orientation, training for graduate students, undergraduates. It's just an accident waiting to happen." Dr. Jennie Hunter-Cevera, president of the University of Maryland Biotechnology Institute, 10 August 2002. Another expert brought up another example: "Remember that Yale researcher a couple years ago who inadvertently contaminated himself with a South American hemorrhagic fever virus and then got on the train to Boston? It was later found out that the institution did not realize that he did not have the proper controls in place, nor did he have the training to work with a Level III virus." Dr. Eric Utt, 9 August 2002. Dr. Eric Utt, health and safety manager at a large US pharmaceutical company, is a PhD microbiologist, widely published author, and patent holder.

[6] "In some academic settings, had I not known what was required, no one would have corrected the people who were bringing in soil samples containing pathogens from other states and all over the world. For example, in one location, they had no idea they needed the Plant Protection and Quarantine forms and the permits to work with those pathogens." Dr. Jennie Hunter-Cevera, president of the University of Maryland Biotechnology Institute, 10 August 2002. The group agreed that young scientists who join the industry ranks often get their first exposure to proper biosafety practices in that setting. The industry experts also decried the tendency of universities to use overhead from research grants to support English, history, and sociology departments instead of to hire biosafety officers. As one industry expert declared: "Chaucer never killed anybody, but hepatitis has." Dr. Robert Goldberg, PhD in medical microbiology and thirty-plus year industry and research veteran, 10 August 2002.

physiology) that are so important to the conduct of good science, not to mention the appropriate training of the support staff that assists scientists working with dangerous pathogens.[7]

Outside of academia, US commercial facilities tend to run their operations by the regulatory book, providing ongoing training for personnel. However, the industry experts doubted that all sites working at higher biosafety levels were continuing to educate their employees in proper, updated practices. The industry experts argued that from the time scientists first enter the laboratory until they retire, continual education in all scientific standards must be promoted as a fundamental tenet of safe, sound science.

Finally, but by no means least importantly, the industry experts stressed the need to articulate and enforce penalties for noncompliance with regulations. Absent stiff consequences and the occasional check-up from regulatory authorities to keep facility operators on their toes, many a rule would be ignored. According to the seriousness of the violation, the industry group suggested that individuals could be punished with loss of pay, fines, suspension, or loss of job. Penalties for institutions, which also must be held accountable, included fines, suspension or loss of licenses, and loss of government grants.[8]

Therefore, as part and parcel of any international standards for biosafety, biosecurity, and oversight of genetic engineering research, the industry specialists recommended the establishment of internationally agreed risk-stratified select agent lists for human, plant, and animal pathogens and toxins. They urged that universities and all organizations practicing the life sciences waste no time whatsoever in rectifying shortcomings in educating students in the basics of appropriate scientific practices and providing professionals with ongoing, updated training.[9] Next, they insisted the drafters of international standards stipulate penalties for noncompliance and create mechanisms to monitor compliance and administer punishment, when necessary.

PUTTING BACKBONE INTO THE US BIOSAFETY INITIATIVE

[7] For example, proper air handling is a key part of a barrier facility, yet there is a dearth of heating, ventilation, air conditioning specialists who are truly experts in the regulations and materials needed for a facility working with dangerous pathogens. Another example would be individuals who are fully versed in what types of biosafety cabinets are needed for what types of materials and activities. Without knowing what type of cabinet is needed, facilities might end up with equipment inappropriate to their needs.

[8] Expressing the group's consensus view: "Without effective sanction authorities and abilities to impose appropriate penalties, this is not going to work." Dr. George Pierce, 10 August 2002. Dr. George Pierce, a PhD microbiologist who is currently a professor of applied and environmental microbiology at Georgia State University, has over twenty years of experience in the US pharmaceutical industry.

[9] Although there is some movement at institutions of higher learning to develop more training programs, "In my mind, they can't move fast enough." Dr. Jennie Hunter-Cevera, president of the University of Maryland Biotechnology Institute, 10 August 2002.

The US government proposed that the members of the BWC individually commit to adopt and implement tough biosafety procedures for work with dangerous microorganisms based on the World Health Organization's guidelines for human pathogens or their equivalent, the Office of International Epizootics' guidelines for animal pathogens or their equivalent, and national guidelines for plant pathogens. In advancing this proposal, the US government observed, "biosafety procedures and practices vary enormously from country to country."[10]

In the United States, the disturbingly high occurrence of laboratory-acquired infections, which came to light in 1951, 1965, and 1976 surveys of 5,000 US laboratories, drove the development of US biosafety practices. This trio of surveys revealed that less than 20 percent of the 3,921 cases of research-related illnesses reported among laboratory workers were associated with a known accident, though in over 80 percent of the cases the infected individuals worked with the causative agent.[11] Evidence that even more robust biosafety practices are sorely needed can be found in the unacceptably high frequency with which laboratory researchers continue to be infected with such diseases as brucellosis, hepatitis, and tuberculosis.[12] Even the US military's premiere research laboratory is not immune to such incidents.[13]

Concerns about laboratory-associated illnesses moved the CDC and the National Institutes of Health (NIH) to compile the primary US resource manual for biosafety practices and standards, titled *Biosafety in Microbiological and Biomedical Laboratories*.[14] Referred to hereafter as the CDC/NIH *Biosafety Manual*, this core reference book describes recommended biosafety equipment, defines the four biosafety levels, and explains the recommended precautions to be taken with various dangerous pathogens. Though an excellent resource, the different editions of the CDC/NIH *Biosafety Manual* give

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[10] US Department of State, "New Ways to Strengthen the International Regime Against Biological Weapons," fact sheet, 19 October 2001, 8. Available at http://www.state.gov/t/ac/bw/fs/2001/7909.htm.

[11] S.E. Sulkin and R.M. Pike's research is summarized in the introduction of US Department of Health and Human Services, Centers for Disease Control and Prevention (CDC) and the National Institutes of Health (NIH), *Biosafety in Microbiological and Biomedical Laboratories*, 4th ed. (Washington, DC: General Printing Office, 1999), 1-2.

[12] Reasons for certain diseases appearing more commonly may include the lack of an effective vaccine, high infectivity virulence, or frequency of use in research. For example, less than ten *brucella* organisms can cause a brucellosis infection, and an effective vaccine is still lacking for this disease. Dr. George Pierce, professor of applied and environmental microbiology at Georgia State University and twenty-plus year veteran of US industry, 10 August 2002. For discussions of laboratory infections from brucella, see Pier Luigi Fiori et al., "*Brucella abortus* Infection Acquired in Microbiology Laboratories," *Journal of Clinical Microbiology* 38, no. 5 (May 2000): 2005-6; E. Martin-Mazuelos et al., "Outbreak of *Brucella melitensis* among Microbiology Laboratory Workers," *Journal of Clinical Microbiology* 32, no. 8 (August 1994): 2035-36.

[13] In May 2000, a microbiologist at the US Army Institute for Infectious Diseases (USAMRIID) contracted glanders after handling laboratory equipment without wearing gloves. Previously, the last case of glanders seen in the United States was in 1945. Centers for Disease Control and Prevention, "Laboratory-Acquired Human Glanders – Maryland, May 2000," *Morbidity and Mortality Weekly Report* 49, no. 24 (23 June 2000): 532. Earlier this year, also at USAMRIID, a civilian scientist tested positive for anthrax exposure, but having been vaccinated, did not contract the illness. David Dishneau, "Fort Detrick worker tests positive for anthrax exposure," Associated Press, 19 April 2002.

[14] CDC and NIH, *Biosafety in Microbiological and Biomedical Laboratories*, 4th ed. (1999).

uneven coverage to different pathogens. In the most recent version, anthrax, tularemia, and brucella received two pages of coverage apiece, while the discussion of prions spanned thirteen pages.[15] Accordingly, those just learning biosafety practices could get skewed impressions of the infectivity and relative biosafety risks of various diseases based on their length of coverage in the CDC/NIH *Biosafety Manual*.[16] Industry experts advised that future editions not just update information on pathogens, but also retain previously published data.

The CDC/NIH *Biosafety Manual* has a great deal in common with the Laboratory Biosafety Manual issued by the World Health Organization's Communicable Disease Unit. Industry experts said that other models for the implementation of stronger biosafety practices can be found in the cooperation of the US nuclear and chemical industries with their respective government administrators, the Nuclear Regulatory Commission and the Occupational Safety and Health Administration, in regulating the possession, transfer, and use of nuclear materials and hazardous chemicals. The industry experts noted that other countries (e.g., Canada, the United Kingdom) have also issued biosafety guidance that is essentially equivalent to US standards. Indeed, they noted that incorporating some foreign standards could elevate US practices.[17] The industry group was widely critical of the fact that the CDC/NIH *Biosafety Manual*, unlike the Canadian and British biosafety measures, is only advisory.

Only two categories of US facilities reliably observe biosafety guidelines. Facilities receiving US government monies follow the guidelines because they can lose their grants if they do not. Commercial manufacturers also comply because the overall US regulatory environment propels scrupulous attention to good laboratory and manufacturing practices, quality assurance, and quality control. For other institutions, the CDC/NIH *Biosafety Manual* guidelines are optional. Bemoaned one of the experts, the US biosafety system is therefore "based on voluntary compliance and the good intentions of the individuals attempting to comply."[18] The recent explosion of bioterrorism research monies could well

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[15] CDC and NIH, *Biosafety in Microbiological and Biomedical Laboratories*, 89-92, 99-100, 134-47.

[16] "This manual does not maintain an historical database of agents of concern. Although there is a lot of information, it's just not what you'd call one-stop shopping." Dr. George Pierce, professor of applied and environmental microbiology at Georgia State University and twenty-plus year veteran of US industry, 10 August 2002. Another group member countered, "It isn't supposed to be a textbook." Dr. Robert Goldberg, PhD in medical microbiology and thirty-plus year industry and research veteran, 10 August 2002.

[17] Europeans and Canadians have elevated disposal to a chapter in their regulations because of the danger of not properly disposing of organisms and waste. If not properly trained, researchers might think that simply autoclaving used laboratory tools and equipment is sufficient, not realizing that it is necessary to have validated autoclaves and load patterns. Many students come out of universities thinking that "121 degrees Centigrade for fifteen minutes will kill everything; but the problem is it has to hit every place and you have to demonstrate it." Expert 1, 10 August 2002. Expert 1, a senior vice president overseeing operations, product development and manufacturing at a US biopharmaceutical company, has over twenty years of experience in the pharmaceutical industry and holds a PhD in biology.

[18] Dr. George Pierce, professor of applied and environmental microbiology at Georgia State University and twenty-plus year veteran of US industry, 10 August 2002. To which another group member rejoined, "The path to hell is paved with those good intentions." Dr. Robert Goldberg, PhD in medical microbiology and thirty-plus year industry and research veteran, 10 August 2002.

compound these unfortunate circumstances as a dramatic influx of scientists unlikely to have proper biosafety training (e.g., chemists, physicists, microbiologists, engineers) embark on projects that entail work with dangerous pathogens.[19]

In contrast, the group observed, facilities that employ animals in research and tests are governed by a detailed regulatory system that requires licenses for such operations and annual compliance inspections.[20] Under this system, a principal investigator works with other facility personnel to develop specific practices or protocols for animal handling, experimentation, and emergencies. The biosafety officer at an animal facility is considered a critical node in the research team, whereas when facilities conducting other types of research appoint a biosafety officer, this individual can be a less actively involved administrative functionary. Animal research facilities are required to have an Institutional Animal Care and Use Committee to review and approve all pertinent research activities. Because certification takes place at the institutional level and the lack thereof could bring operations to a halt, the facility director bears personal responsibility for overseeing compliance.[21] Since the animal use regulations are in the federal code, a breach equates to breaking the law. The US biosafety "guidelines" simply do not garner the same respect and adherence. For this reason, the group overwhelmingly recommended a domestic change to full regulatory status, with a continuing relaxed approach for clinical laboratories.[22]

Until the 1996 US law regulating the transfer of certain dangerous human pathogens,[23] there was virtually no oversight to determine whether facilities requesting dangerous strains from culture collections had the proper biosafety set-up to handle those organisms. One industry expert marveled: "I found it amazing that you had to get a license to put a deck on your house, but anybody with a Bachelor's degree

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[19] Grant-making agencies and institutions would be well advised to confirm the biosafety background of potential grantees before awarding monies.

[20] For more detail on how the U.S. Department of Agriculture's Animal and Plant Health Inspection Service administers the Animal Welfare Act, including licensure and unannounced inspections of every registered facility in the country, go to http://www.aphis.usda.gov/oa/pubs/inspect.html. Organizations that receive funding from a public health service agency (e.g., CDC, NIH) are bound by a separate set of regulations enforced by the Office of Laboratory Animal Welfare at NIH. More information can be found at http://grants2.nih.gov/grants/olaw/references/phspol.htm.

[21] "At most institutions the chairman of the IACUC is a senior facility member, and in industry senior personnel also serve on the IACUC to make sure things happen correctly." Dr. Eric Utt, health and safety manager at a large US pharmaceutical company, 10 August 2002.

[22] Under current US guidelines, clinical laboratories are allowed to conduct activities that would otherwise be considered biosafety level 3 under biosafety level 2 precautions. This approach is advisable due to the sheer volume of unknown samples that clinical laboratories receive daily.

[23] This law was prompted by Larry Wayne Harris' use of a false facility letterhead to acquire three vials of *Y. pestis*, the causative agent of bubonic plague, from the American Type Culture Collection. The transfer regulations are contained in 18 USC, Sections 175-178 and 2332, 42 CFR 72. For more on the biological misadventures of Larry Wayne Harris see, briefly, Box. 2.5 in Amy E. Smithson and Leslie-Anne Levy, *Ataxia: The Chemical and Biological Terrorism Threat and the US Response*, (Washington, DC: Henry L. Stimson Center, October 2000), 41-2.

could work with any organism."[24] Quipped another: "They told you how to open the vial or container, but they never bothered to ask or check if your facility had the appropriate facilities or training to handle that organism. The biological safety officer was supposed to do that, but some institutions have biosafety officers in name only."[25] If biosafety licensure was until recently an erratic affair in the United States, which is considered to be a biosafety pacesetter, the industry group shuddered at what might be found elsewhere.

Instead of relying on national preferences that may materialize unevenly and slowly, the industry experts recommended strengthening the US biosafety proposal by requiring an international biosafety standard. A proposal that leaves states the leeway to follow or disregard guidelines and the flexibility to craft the basic principals of their own domestic practices fails to deal with the very problems that the US government seeks to address, namely the complete absence of biosafety practices in some countries and the wide variance of such practices in others. Moreover, the industry experts suggested that while the World Health Organization guidelines would be an improvement, a higher minimum standard would be comprised of the best practices from current domestic guidelines, with the generally high-caliber CDC/NIH *Biosafety Manual* serving as the basis for new international standards.

All countries, in other words, should be obligated to adhere to mandatory universal biosafety standards, complete with noncompliance penalties.[26] The group rejected the idea that facilities would find compliance with such biosafety practices onerous or burdensome.[27] One participant summed up the group's thoughts as follows: "In many cases, biosafety defines a certain level of more rigorous science. It improves science."[28]

STRENGTHENING THE US BIOSECURITY INITIATIVE

[24] Dr. Robert Goldberg, PhD in medical microbiology and thirty-plus year industry and research veteran, 10 August 2002.

[25] Dr. Jennie Hunter-Cevera, president of the University of Maryland Biotechnology Institute, 10 August 2002. Note that many biosafety officers may not even be aware that such strains were requested, unless the researcher informs them. Similar to the standard practice in the chemical industry, the Canadian health ministry has created material safety data sheets for individual biological agents that provide information such as infectivity levels, methods of transmissions, and recommended precautions. These sheets are accessible online from the Office of Laboratory Security, Population and Public Health Branch, HealthCanada at http://www.hc-sc.gc.ca/pphb-dgspsp/msds-ftss/index.html.

[26] Note that a relaxed approach would continue to be appropriate for clinical laboratories.

[27] This activity was likened to the creation of Occupational Safety and Health Administration regulations and the institution of quality assurance laws in the 1960s and 1970s. Once these laws were on the books, facilities that did not abide by them went out of business. Douglas Jaeger, 10 August 2002. Douglas Jaeger, current president of the Society for Industrial Microbiologists and holder of two master's degrees, recently retired after a thirty-five year career with a major US pharmaceutical company where he rose to the manager of custom fermentation and bioprocessing.

[28] Dr. George Pierce, professor of applied and environmental microbiology at Georgia State University and twenty-plus year veteran of US industry, 10 August 2002.

Similar to its biosafety proposal, the US government's biosecurity initiative asked individual states to commit to adopt national regulations governing access to and transfer of dangerous pathogens, including possible restrictions on where work with dangerous pathogens may be conducted and who may obtain and possess specific microorganisms for such purposes. The US government also proposed that nations report to international authorities any "adverse events" (e.g., accidental release of a dangerous pathogen) that could affect other countries.[29]

Although specific laws regarding the transfer of etiologic agents have been on the books for over twenty years, the industry experts said there is still an abundance of confusion, ignorance, and disturbing casualness exhibited in the transfer of dangerous organisms. Any US scientist trying to determine the right procedures to ship hazardous biological materials has to wade through the regulations and guidelines posted by at least a dozen different government agencies and international organizations, as Table 4.1 denotes. When faced with this regulatory hydra, no wonder many scientists find it easier to tuck a tube into their suit jacket pocket and board a plane.[30]

Spurred by two bioterrorist incidents that highlighted the weaknesses in the US regulatory system,[31] Congress passed laws to regulate the transfer and receipt of dangerous human pathogens and to monitor more closely the facilities dealing with dangerous human, animal, and plant pathogens.[32] Under a 1996 law, the CDC began to certify the facilities applying to receive dangerous human pathogens on the

[29] US Department of State, "New Ways to Strengthen the International Regime," 4.

[30] Other types of rules are also broken despite the extensive training on the various shipping requirements that new scientists in industry receive. For instance, strains still arrive in laboratories daily, improperly marked or not designated as dangerous at all. Dr. Jennie Hunter-Cevera, president of the University of Maryland Biotechnology Institute, 10 August 2002.

[31] The first of these incidents involved Larry Wayne Harris, as footnote 23 describes, the second were the anthrax letter attacks of the fall of 2001, which indicated a possible theft of this pathogen from a facility. Steve Fainaru and Joby Warrick, "Deadly Anthrax Strain Leaves a Muddy Trail," *Washington Post*, 25 November 2001; Rick Weiss and Susan Schmidt, "Capitol Hill Anthrax Matches Army's Stocks; 5 Labs Can Trace Spores to Ft. Detrick," *Washington Post*, 16 December 2001; William J. Broad and Judith Miller, "Inquiry Includes Possibility of Killer from a U.S. Lab," *New York Times*, 2 December 2001.

[32] On 12 June 2002, the Public Health Security and Bioterrorism Preparedness and Response Act became Public Law 107-188.

Table 4.1: Current Regulations for the Shipment of Dangerous Pathogens.**

Organization	Type of Regulation or Guidelines
US Centers for Disease Control and Prevention	Importation, Transfer, and Receiving of Select Human Pathogens
US Animal and Plant Health Inspection Service	Importation of Etiologic Agents of Animals and Plants
US Public Health Service	Interstate Shipment of Etiologic Agents
US Postal Service	Mailability of Etiologic Agents
US Department of Transportation	Shipment of Hazardous Materials
US Occupational Safety and Health Administration	Occupational Exposure to Dangerous Pathogens
US Department of Commerce	Exportation of Select Human, Animal, and Plant Pathogens
International Air Transport Association	Dangerous Goods Regulations
International Civil Aviation Organization	Sending of Dangerous Pathogens via the International Mail System
World Health Organization	Transfer of Dangerous Biological Materials
Universal Postal Union	Mailing of Dangerous Pathogens
World Federation of Culture Collections	Shipment of Dangerous Pathogens
United Nations Committee of Experts on the Transport of Dangerous Goods	Shipment of Dangerous Pathogens

** The CDC certifies facilities to receive and handle dangerous pathogens and administers regulations governing the Importation of Etiologic Agents of Human Disease, as regulated in the federal code in 42 CFR 72 and 42 CFR 71 and 71.54. APHIS oversees the regulations regarding the importation of etiological agents of livestock, poultry, and other animal diseases and the federal plant pest regulations, respectively, see 9 CFR 92, 94, 95, 96, 122 and 130 and 7 CFR 330. The Commerce Department's export rules are specified in 15 CFR 730 to 799, and the US Postal Service's regulations on mailing etiologic agents are in 39 CFR 111. The regulations of the US Transportation Department are located in 19 CFR 171-178, and the Occupational Safety and Health Administration's rules related to exposure to bloodborne pathogens are in 29 CFR 1910.1030.

International Air Transport Association's Dangerous Goods Regulations require that packaging for dangerous biological materials meet the standards set out in IATA packing instruction 602 (class 6.2). See International Air Transport Association, Dangerous Goods Regulations, 39th ed. (Montreal: IATA, 1998). The International Air Transport Association developed its packaging rules in conjunction with the International Civil Aviation Organization. Pertinent guidance from World Health Organization is contained in Guidelines for the Safe Transport of Infectious Substances and Diagnostic Specimens (Geneva: World Health Organization, 1997); Intergovernmental Committee for the Cartagena Protocol on Biosafety, "Handling, Transport, Packaging and Identification (Article 18)," Document UNEP/CBD/ICCP/1/6, 25 September 2000.

The World Federation for Culture Collections maintains a list of guidelines that encourage member organizations to adhere to applicable international or national standards., including one for the shipment of cultures: See World Federation for Culture Collections, Guidelines for the Establishment and Operation of Collections of Microorganisms, 2nd ed., 1999. Similarly, the United Nations (UN) Committee of Experts on the Transport of Dangerous Goods presents model regulations, including suggested lists of principal dangerous goods, general packing requirements, etc. United Nations Economic and Social Council, Committee of Experts on the Transport of Dangerous Goods, UN Model Regulations on the Transport of Dangerous Goods, 12th ed., foreword. Available at http://www.unece.org/trans/danger/publi/unrec/mr_nature_e.html.

select agent list.[33] While the CDC has only a few years of experience administering these transfer regulations, the industry experts also pointed to the tight system that the Nuclear Regulatory Commission has long overseen as a model for certifying the fitness of facilities to receive hazardous materials.[34]

A second law, passed in 2001, stipulated a deadline for some 190,000 US facilities that might have involvement with past or ongoing dangerous pathogens work to inventory the holdings in their culture collections and report to federal authorities the possession of any agents found that are on designated lists of human, animal, and plant pathogens.[35] The rationale behind this requirement is that transfer and receipt regulations address the activities of facilities from the point in time in which they are implemented, leaving the culture collection holdings of a multitude of facilities in place. If unaddressed, individuals with access to the freezers in these facilities could rummage through their contents in search of dangerous pathogens for foul play. Hence, this law requires that facilities inventory culture collections and "clean the house" of dangerous pathogens that they have no legitimate need to keep on hand.

The industry experts explained that many facilities do not have a firm idea of just what is in their freezers, partly because of the aforementioned tendency of scientists to slip sample vials into their jacket pockets. Moreover, it is not uncommon for scientists to change jobs or retire, leaving behind their personal cache of special samples.[36] Tucked unobtrusively amidst a sea of other vials, these personal collections often remain undisturbed for years in corporate or university freezers.[37]

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[33] These transfer regulations, which grew out of the Antiterrorism and Effective Death Penalty Act, are in 18 USC, Sections 175-178 and 2332, 42 CFR 72.

[34] Under the Nuclear Regulatory Commission's well-policed regulations, "when an institution receives a radio-labeled or radioactive package, that package is quarantined until it is swipe-tested to make sure there is no contamination on the outside. Then that package is released only to a trained individual who signs for the package and whose laboratory is enrolled in the Radio/Chemical Safety Program. That laboratory is inspected regularly." Dr. Eric Utt, health and safety manager at a large US pharmaceutical company, 10 August 2002. Other industry experts held the Nuclear Regulatory Commission's transfer, access, and safety regulations in similarly high regard, partly because both researchers and administrators are required to be aware of the regulations and noncompliance penalties.

[35] These regulations were born out of the aforementioned Public Health Security and Bioterrorism Preparedness and Response Act passed on the heels of the anthrax letter attacks in the fall of 2001. The select agent lists, published in the Federal Register, comprised thirty-six human pathogens (eighteen of which are also contained in the animal pathogen list, because they threaten both humans and animals), twenty-four livestock diseases, and nine plant pathogens. Reporting forms were mailed directly to facilities and also made available online. By 10 September 2002, facilities were to return their human pathogens inventory results to the CDC and their plant and animal pathogens inventory results to USDA's Animal and Plant Health Inspection Service. A copy of the law can be found at http://www.cdc.gov/od/ohs/lrsat/bioterro.htm. See also, Stephen Mitchell, "Feds Scramble to List Bioterror Holdings," United Press International, 13 August 2002; Diane Jean Schemo, "Sept. 11 Strikes at Labs' Doors," *New York Times*, 12 August 2002.

[36] When asked what percentage of strains in facility freezers were properly certified and documented, answers varied according to type of facility. The group estimated 100 percent for manufacturing plants, 65 to 80 percent for development facilities, but only 10 to 25 percent of the freezer contents would be properly registered in research laboratories.

[37] For example, in a March 2002 audit of US Agriculture Department laboratories, investigators discovered that a retired scientist had left behind a sample of *Salmonella*, a biosafety level 2 agent, in the freezer of a government laboratory. The

With these very circumstances in mind, the industry experts recommended bolstering the US biosecurity proposal by requiring nations to bring their biosecurity practices up to an agreed minimal international standard, patterned after the US transfer and access regulations.[38] To account for the dangerous pathogens present in laboratory freezers around the world, the industry experts proposed adding a clean house requirement for facilities globally. They estimated that within three months facilities could inventory their holdings and notify appropriate national authorities if they discover any human, animal, or plant pathogens on select agent lists not included in their current registration. While consulting with national authorities about the proper disposal of any such select-list pathogens, the vial(s) in questions would be stored securely.[39]

In addition, the industry experts suggested that governments consider another aspect of biosecurity—physical security requirements. Due to break-ins and vandalism from animal activists, [40] many industrial, university, and government laboratories have found it advisable to upgrade the physical security on their premises, installing security cameras, alarm systems, and card key entry procedures. As accounting and reporting procedures are put in place for facilities working with select-list agents, these facilities will become more readily identifiable because of reported information and/or the required posting of certain warning signs.

Consequently, the industry specialists warned that terrorists seeking biological agents for harmful purposes might consider institutions working with dangerous pathogens worthy targets for theft or terrorism. No US regulations require enhanced physical security for industrial or academic facilities working with dangerous pathogens.[41] To reduce the possibility of theft of a virulent strain or sabotage at such facilities, the industry group advised institutional, national, and international policy makers to make heightened physical security precautions (e.g., guards, fences) at pertinent facilities an item on the priority list.

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sample remained in the inventory, unbeknownst to laboratory officials, even after the laboratory ceased to operate at that biosafety level. US Department of Agriculture, *Audit Report: Oversight and Security of Biological Agents* (Washington, DC: Office of the Inspector General, March 2002), 8-9.

[38] The industry experts argued for a flexible construction that could be adapted to technical changes.

[39] Note that the industry experts argued that facilities operators should not be required to identify the contents of any vials that are unlabeled or that have labels that cannot be read. Instead, they should be allowed to destroy the contents of such vials using appropriate safety precautions.

[40] In the Department of Agriculture's audit, investigators documented five break-ins at the department's biosafety level 2 laboratories. "Although officials…did not express any concerns that biological material could have been removed, only two of the laboratories had current inventories that could be used to make such a determination." US Department of Agriculture, *Audit Report: Oversight and Security of Biological Agents*, 13.

[41] A *de facto* approach to physical security (e.g., building entry codes) exists at some facilities.

CREATING MORE RIGOROUS OVERSIGHT OF GENETIC ENGINEERING RESEARCH

To contend with proliferation dangers presented by modern genetic engineering research, the Bush administration proposed that nations that belong to the BWC "sensitize" scientists to the "possible biological weapons implications" of genetic engineering research. The United States also suggested that individual countries "explore" national oversight concepts with nongovernmental organizations (e.g., professional societies, national academies of science), possibly formulating recommendations for the review of proposed genetic engineering experiments.[42]

The industry experts had high praise for the NIH's prescient approach to guiding safe recombinant DNA research, which dates to the mid-1970s.[43] Since the publication of the original NIH *Guidelines for Research Involving Recombinant DNA Molecules*, regulatory progress has kept pace with what many have described as a revolution in the life sciences.[44] Not all of the outcomes that this revolution enabled have been benign. For example, Soviet scientists engineered various biowarfare agents to make them resistant to antibiotic treatment.[45] Experiments with good intentions also went bad. In January 2001, scientists and non-scientists alike were shaken when Australian researchers announced that during experiments with the mousepox virus, they had unintentionally created a more lethal virus that destroyed the immune systems of the mice.[46] Such developments have disturbing implications for countries or terrorists seeking an advanced biowarfare capability. Yet, amidst this scientific revolution, the industry group lauded the NIH's guidelines as a "reasonable, rational, living document that provides a beautiful framework for any institution to conduct DNA recombinant research safely and sanely."[47]

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[42] US Department of State, "New Ways to Strengthen the International Regime Against Biological Weapons," 5.

[43] In 1975, the government convened experts pertinent to recombinant DNA research for discussions in Asilomar, California. The outcome of this meeting was the framework for the first edition of the NIH guidelines. Recalled one of the industry experts, "Some of the first experiments in DNA recombinant research were done at the NIH when I was there. Even then, oversight was in place. You had to go into the BL4 facility at Frederick, make the application, list the protocols, and go through a lot of hoops to get access to that facility." Dr. Robert Goldberg, PhD in medical microbiology and thirty-plus year industry and research veteran, 10 August 2002.

[44] For a discussion of what scientific advances may portend for bioweapons, see chapters 5 and 6, Malcolm Dando, *Biological Warfare in the 21st Century: Biotechnology and the Proliferation of Biological Weapons*, (New York: Brassey's, 1994), 86-129.

[45] See Ken Alibek with Stephen Handelman, *Biohazard* (New York: Random House, 1999).

[46] Researchers at Australian National University urged strengthening of the Biological Weapons Convention after their experiment on mouse contraception went off track. Ronald J. Jackson, et al., "Expression of Mouse Interleukin-4 by a Recombinant Ectromelia Virus Suppresses Cytolytic Lymphocyte Responses and Overcomes Genetic Resistance to Mousepox," *Journal of Virology* 75, no. 3 (February 2001): 1205-10. Available at http://jvi.asm.org. See also, Clive Cookson, "Scientists Convert Virus into Killer," *Financial Times*, 12 January 2001.

[47] Dr. Robert Goldberg, PhD in medical microbiology and thirty-plus year industry and research veteran, 10 August 2002.

While the industry experts supported the US government's inclination to address the potential biological weapons proliferation threat resident in genetic engineering research, they declared that the US proposal significantly misgauged the urgency of the matter by stopping at requests that states sensitize scientists to proliferation risks and look into possible national oversight measures. Given the rapid advancements in the field, the industry group recommended a more distinct and targeted approach, based on the NIH's guidelines as the best foundation for the standards that should ultimately oversee such research worldwide.[48] Rather than having a stifling effect on genetic research, the industry group characterized the NIH guidelines as a "good road map for people working in the area."[49]

Just as Rome was not built in a day, research institutions and countries must gradually work toward the NIH guidelines. Accordingly, the industry experts suggested beginning with just the reporting requirements, working progressively toward adopting minimum research oversight standards as a next step, and eventually adopting the NIH guidelines in total.[50] Implemented in incremental fashion, an international standard would foster increasing transparency, coordination, and oversight of genetic engineering research.

CONCLUDING THOUGHTS ABOUT IMPLEMENTATION

To achieve the US government's desired aim of strengthening the international regime against biological weapons, the industry experts believed that the international community should push forward with the agreement and enactment of common minimum standards that include penalties for infractions of biosafety, biosecurity, and genetic research oversight regulations. This trio of regulations should work separately but also in concert, reinforcing one another so that closer tabs can be kept on possibly dangerous biological activities. Appreciative of the complexities of regulating biosafety, biosecurity, and genetic engineering research, the industry group counseled a step-by-step approach to ease institutions and governments into the implementation of universal standards. Once international standards are agreed, nations would pass laws requiring pertinent institutions to operate accordingly. On the heels of these steps, countries would establish national regulatory infrastructures, progress that would eventually be capped by the creation of international coordination and oversight capacities.

In each functional area, individual institutions that have not previously practiced biosafety, biosecurity, and/or oversight of genetic engineering research would have much to do. For example,

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[48] The group also gave high marks to the extensive British guidelines for overseeing genetic research.

[49] Dr. George Pierce, professor of applied and environmental microbiology at Georgia State University and twenty-plus year veteran of US industry, 10 August 2002.

[50] Of the initial step that countries must take, one industry expert said: "Just as there are basic levels for biological safety; there should be basic levels for recombinant DNA work, which implies basic types of reporting." Dr. George Pierce, professor of applied and environmental microbiology at Georgia State University and twenty-plus year veteran of US industry, 10 August 2002.

facilities working with dangerous pathogens need to have a well-trained biosafety officer as well as an institutional biosafety committee composed of fully trained, competent individuals. This infrastructure would assure fulfillment of the institution's responsibility to provide ongoing biosafety training of its employees. The biosafety officer would also check the adherence of project personnel to biosafety protocols throughout the lifetime of a project. Should problems occur, the biosafety officer would play a key role in the investigation and subsequent adjustment of biosafety practices to reduce the possibility that problems would recur. For proposed projects, the biosafety officer would assist in the principal investigator's assessment of safety risks, the suitability of the facility's containment, materials handling, and waste treatment procedures, and other factors pertinent to safe conduct of the envisioned research.

In the area of biosecurity, the biosafety officer would inaugurate, if necessary, the requisite protocols to receive dangerous pathogens and ensure that only essential personnel have access to them. The biosafety officer would ensure that personnel working with or nearby dangerous pathogens received refresher training about workplace rules, doing the same for those engaged in genetic engineering research. While an institutional biosafety committee could grant permission for less hazardous types of advanced research, scientists planning to initiate certain types of experiments (e.g., cloning toxins with certain levels of lethality, introducing antibiotic resistance into an organism) would first have to obtain the permission of the recombinant DNA advisory committee.

Similarly, nations that lack government offices to administer biosafety, biosecurity, and genetic research oversight regulations would need to establish such a capacity. After a reasonable agreed upon grace period to allow institutions to come up to speed, national authorities would be responsible for monitoring adherence with various regulations through reporting requirements and inspections, as necessary. Specifically with regard to genetic engineering research, a national oversight authority would review and approve experiments, certify personnel and facilities, and assume, vis-à-vis the laboratories, responsibility for assessing risk and setting levels of containment. The national authorities would then track individual projects, including the disposition of all genetically modified organisms. National authorities would also hand out fines and other penalties to institutions and individuals found in violation of the biosafety, biosecurity, and research oversight rules.

Ultimately, years from now, the industry group could foresee the creation of an international organization that would perform some of the tasks described above for the national authorities, but at an international level. First, this body would be charged with coordination of national efforts and updating of standards, monitoring tools, select agent lists, and penalties to keep pace with technical developments. International authorities would also oversee the progress of biosafety and biosecurity monitoring efforts. With regard to oversight of genetic engineering research, this body would ramp up gradually, beginning just with the registration of DNA recombinant experiments with Class III and IV organisms to compile an index of such activities worldwide. Eventually, the industry experts envisioned that international authorities would play an important role in the review and approval of proposed genetic engineering research.

While the industry experts believed that implementing this suite of biosafety, biosecurity, and research oversight recommendations would strengthen international efforts to retard biological weapons proliferation, the industry experts also noted that these actions would have additional positive repercussions. Facilities that employ proper safety and containment protocols will reduce the potential for accidental release of dangerous diseases. The biosafety and biosecurity standards that the industry experts endorsed constitute good laboratory and manufacturing practices. As the pharmaceutical and biotechnology facilities in other countries adopt such standards, they will encounter easier access to US and other advanced markets. Finally, in the event that additional research and field trials prove the feasibility of a monitoring system for the BWC, as Chapter 2 discusses, inspectors would find the documentation, standard operating procedures, and oversight activities that the biosafety, biosecurity, and genetic engineering research standards require useful benchmarks in helping to determine whether a particular facility's operations are consistent with its stated purpose(s).