BACKGROUND

Within three weeks of the destruction of the World Trade Center towers on September 11, 2001, the United States experienced a second assault in the form of anthrax spores delivered through the U.S. mail. The event initiated widespread changes in the scientific enterprise of the United States, in its federally-based funding priorities and in the regulatory and oversight mechanisms that strive to keep laboratories and communities safe.

"The events of September 11, 2001, and the anthrax attacks in October of that year re-shaped and changed, forever, the way we manage and conduct work in biological and clinical laboratories."[1]

Biosafety and biosecurity have dominated the policy discourse and the two have been inexorably intertwined. Biosafety and biosecurity are defined by the World Health Organization (WHO):[2] Biosafety comprises "the containment principles, technologies and practices that are implemented to prevent unintentional exposure to pathogens and toxins or their accidental release"; biosecurity is defined as "the protection, control and accountability for valuable biological materials (including information) in laboratories in order to prevent their unauthorized access, loss, theft, misuse, diversion or intentional release." The two terms are related but often used interchangeably and, as noted by Casedevall and Relman, differ significantly by the "crucial criterion of intent."[3] The U.S. research and regulatory communities are engaged in a long-term, evolving struggle to reconcile these terms and establish acceptable oversight mechanisms that satisfy both biosafety and biosecurity concerns. Here, we offer a short history of oversight and regulation of dangerous biological research in the United States and the ongoing debate over how such oversight should be carried out.

BRIEF HISTORY OF BIOSAFETY

Innovation and development of biosafety in the United States is reflected accurately in the history and pre-history of the American Biological Safety Association (ABSA). The first unofficial meeting was held on April 18, 1955 at Camp Detrick (now Fort Detrick) and involved members of the military representing Camp Detrick, Pine Bluff Arsenal, Arkansas (PBA), and Dugway Proving Grounds, Utah (DPG). In those days, the offensive BW program of the United States was in full swing: the opening keynote address was "The Role of Safety in the Biological Warfare Effort." Beginning in 1957, the yearly meetings began to include non-classified sessions to broaden the reach of the Association; representatives of the USDA were regular attendees through this "transition period." [4] There were striking changes in the meetings in 1964-1965: the NIH and CDC joined for the first time, along with a number of other relevant federal agencies. All classified information was removed accompanied by a concerted effort to declassify safety studies and release them for public knowledge and advantage. By 1966, the attendees included universities, private laboratories, hospitals, and industry. Gradually, federal regulations began to appear. In 1973, the impact of new OSHA regulations was analyzed and debated at the ASBA meeting; interestingly, there was a range of responses to the new regulations:

"Some view it as the most important social legislation since social security, or Our Savior Has Arrived; whereas others term it the most un-constitutional freedom-interfering repressive legislation since prohibition,"[5] according to Manuel Barbeito and Richard Kruse's historical analysis.

[1] U.S. National Institutes of Health and the Centers for Disease Control and Prevention, 2007. Biosafety in Microbiological and Biomedical Laboratories, 5th ed. L.C. Chosewood and D. E. Wilson, eds. Washington D.C. U.S. Government Printing Office; online version http://www.cdc.gov/od/ohs/biosfty/bmbl5/bmbl5toc.htm.

[2] (WHO. Biorisk management: Laboratory biosecurity guidance. *World Health Organization* [online] http:// www.who.int/csr/resources/publications/biosafety/ WHO_CDS_EPR_2006_6.pdf (2006).

[3] Casadevall, A and Relman, D.A. Microbial threat lists: obstacles in the quest for biosecurity? 2010. Nat Rev Microbiol Feb;8(2):149-54

[4] Manuel S. Barbeito and Richard H. Kruse, 1997, "A History of the American Biological Safety Association Part I: The First Ten Biological Safety Conferences 1955-1965." *JABSA, 2*(3): 7-19.

[5] Richard H. Kruse and Manuel S. Barbeito, 1997, "A History of the American Biological Safety Association Part II: Safety Conferences 1966-1977." *JABSA 2*(4): 10-25.

Biological Agents in the Laboratory - The Regulatory Issues

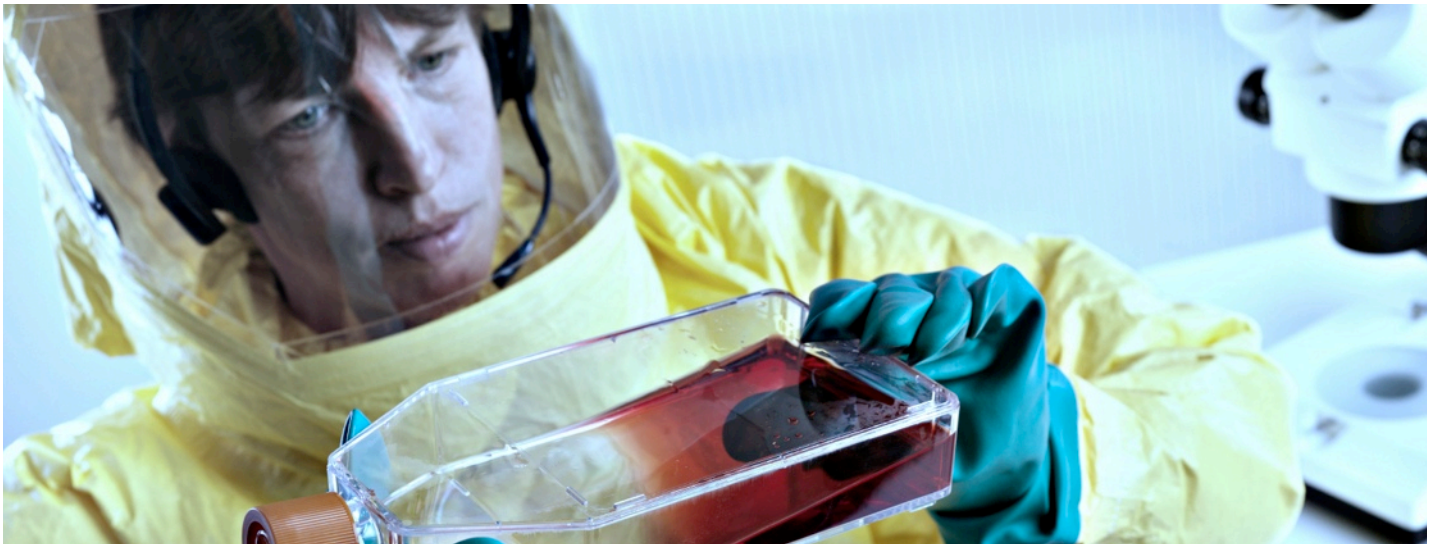
— BY NANCY CONNELL

In 1974, the United States Postal Service and Department of Transportation introduced regulations for shipping of etiologic agents (microorganisms and toxins that cause disease in humans). New safety programs and trainings were introduced. The designation of 4 levels of biosafety originated in the mid-1970s,[6] and the safety requirements for research with recombinant DNA were hotly debated. A survey of the ABSA meetings in the 1980s reveals increased focus on individual agents or groups of agents and coordination of international safety issues.[7] ABSA now represents biosafety professionals in 20 countries, and reflects the organic nature of the topic: biosafety is a fast-moving field with constant research into and reevaluation of its tenets as threat perception change and technologies advance.

CURRENT U.S. REGULATIONS FOR BIOSAFETY AND BIOCONTAINMENT

The Public Health Security and Bioterrorism Preparedness and Response Act of 2002[8] required institutions to notify HHS and/or the USDA of possession of select agents or high-consequence pathogens and instituted increased oversight mechanisms for use of and access to the agents. Currently, multiple federal, state, local and institutional agencies are involved in oversight of dangerous pathogens and toxins, and the overlap of these oversight systems can be thought to ensure a positive outcome. The primary agencies involved are the Department of Labor (DOL), Occupational Safety and Health Administration (OSHA), Health and Human Services (HHS) Centers for Disease Control and Prevention (CDC), and the U.S. Department of Agriculture (USDA) Animal and Plant Health Inspection Service (APHIS).

[6] There are four basic biosafety levels as determined by CDC and NIH which describe the microbiological techniques, lab practices, safety equipment and lab facilities necessary to protect workers and the environment.
[7] Richard H. Kruse and Manuel S. Barbeito, 1997, "A History of the American Biological Safety Association Part III: Safety Conferences 1978-1987." *JABSA 3*(1): 11-25.
[8] 2002 ACT



The relevant regulations and guidelines are found in four places, listed below. Note that the collection includes one coded law, one set of standards, one set of regulations and a set of guidelines, not federally mandated.

(1) Code of Federal Regulations: Select Agent and Toxins Rule, HHS and USDA (42CFR part 73, effective March 2005)[9]
(2) OSHA: the *General Duty Clause*, *Bloodborne Pathogens Standard*, and *Personal Protective Equipment Standards*[10]
(3) CDC permit regulations for work with high-consequence pathogens
(4) NIH and CDC guidelines, entitled *Biosafety in Microbiological and Biomedical Laboratories*; and the *NIH Guidelines for Research Involving Recombinant DNA Molecules* ("the NIH Guidelines")[11]

There are a number of basic aspects to working with Select Agents that are codified under 42 CFR part 73: the Select Agent list, laboratory registration, laboratory security, personnel oversight, notifications of loss or theft, restricted experiments, incident response, training programs, records and inventory, and biosafety requirements.

THE SELECT AGENT LIST

The original list of select agents and toxins was published in the Federal Register in 1996 in Appendix A to 42 CFR part 72. In the wake of the anthrax mailings of 2011, the Public Health Safety and Bioterrorism Preparedness and Response Act of 2002 specified that HHS establish a list of biological agents and toxins that "have the potential to pose a severe threat to public health and safety." A list of approximately 80 bacteria, viruses, fungi and toxins was established by HHS and USDA. A combination of considerations is used to determine an agent's inclusion on the Select Agent and Toxin List (SATL): past or potential use as biological weapon, countermeasures available, infectivity, contagiousness, etc. Although the exact criteria are not part of the public domain, the public comment sections of the Code are a source of rich discussion of these matters.[12]

The status of the current SATL has been challenged in a number of venues since 2002, including scientific publications and U.S. government advisory bodies such as the NSABB.[13] For example, in a 2010 *Perspectives* piece in Nature Reviews Microbiology by Casadevall and Relman, the authors question the utility of the SATL and highlight the following paradox: if an agent lacks countermeasures, it is more likely to be included on the SATL; yet the increased regulatory burden placed on research with the agent might in turn prevent the discovery and development of effective countermeasures.[14] Similarly, while a mechanism is available to request the removal of an agent from the SATL, the regulatory burden associated with the experimental evidence required to support such an application may hinder initiation of the request.[15]

[9] HHS (Department of Health and Human Services). 2005. "42 CFR 72 and 73 and 42 CFR Part 1003: Possession, Use, and Transfer of Select Agents and Toxins; Final Rule" (FR Doc. 05-5216). *Federal Register* 70(52, March 18), pp. 12294-13325.
[10] OSHA Act of 1970 Section 5, The General Duty Clause Under the Clean Air Act Section 112(r)(1)
[11] U.S. National Institutes of Health and the Centers for Disease Control and Prevention, 2007. Biosafety in Microbiological and Biomedical Laboratories, 5th ed. L.C. Chosewood and D. E. Wilson, eds. Washington D.C. U.S. Government Printing Office; online version http://www.cdc.gov/od/ohs/biosfty/bmbl5/bmbl5toc.htm.
[12] 42 CFR Part 73. Possession, Use, and Transfer of Select Agents and Toxins; Biennial Review; Proposed Rule Federal Register / Vol. 76 , No. 191 / Monday, October 3, 2011/ Proposed Rules
[13] NSABB (National Science Advisory Board for Biosecurity). 2007. *Proposed Framework for the Oversight of Dual Use Life Sciences Research: Strategies for Minimizing the Potential Misuse of Research Information.* Available at <http://oba.od.nih.gov/biosecurity/pdf/Framework%20for%20transmittal%200807_Sept07.pdf>
[14] Casadevall, A and Relman, D.A. Microbial threat lists: obstacles in the quest for biosecurity? 2010. Nat Rev Microbiol Feb;8(2):149-54
[15] Ibid.

If an agent lacks countermeasures, it is more likely to be included on the Select Agent and Toxin List, yet the increased regulatory burden placed on research with the agent might in turn prevent the discovery and development of countermeasures.

More recently, a Federal Experts Security Advisory Panel (FESAP) released its Recommendations Concerning the Select Agent Program (finalized June 2011) in response to Executive Order 13546.[16]

In the report, the following issues were addressed:

1. the designation of Tier 1 Biological Select Agents and Toxins (BSAT);
2. reduction in the number of BSAT on the Select Agent List;
3. the establishment of appropriate practices to ensure reliability of personnel with access to Tier 1 BSAT at registered facilities;
4. the establishment of appropriate practices for physical and cyber security for facilities that possess Tier 1 BSAT; and
5. other emerging policy issues relevant to the security of BSAT.

A set of proposed changes to every section of the Select Agent Rule was under consideration and posted by the CDC for public comment until December 2, 2011.[17] For example, several viruses, fungi and toxins are targeted for removal from the list, while two viruses are slated for addition.[18] Further, the proposed changes designate eleven agents ("Tier 1 agents") for increased oversight. The select agents and toxins in this subset are considered the greatest risks of deliberate misuse with the "most significant potential for mass casualties or devastating effects to the economy, critical infrastructure or public confidence." The proposed regulations contain options for "graded protection" for these Tier 1 agents and toxins to permit "tailored risk management practices based upon relevant contextual factors."[19] Entities with Tier 1 Agents[20] will be subject to additional requirements in personnel reliability, occupational health programs, and minimum security requirements.

LABORATORY SECURITY

In December 2002, a set of guidelines was prepared and released, addressing laboratory management and oversight, entitled "Laboratory Security and Emergency Response Guidance for Laboratories working with Select Agents."[21] These guidelines were built upon the 1999 guidelines ("BMBL") released by the NIH and CDC.[22] The following topics were addressed: risk and threat assessment, facility security plans, physical security, data and electronic technology systems, security policies for personnel, policies regarding accessing the laboratory and animal areas, specimen accountability, receipt of agents into the laboratory, transfer or shipping of select agents from the laboratory, emergency response plans and reporting of incidents, unintentional injuries, and security breaches. The complexity involved in launching a select agent reseach program is clear from this list of requirements, and highlights the enormous commitment of infrastucture and support personnel demanded of sponsoring institutions.

INVENTORY: ACCOUNTING vs. ACCOUNTABILITY

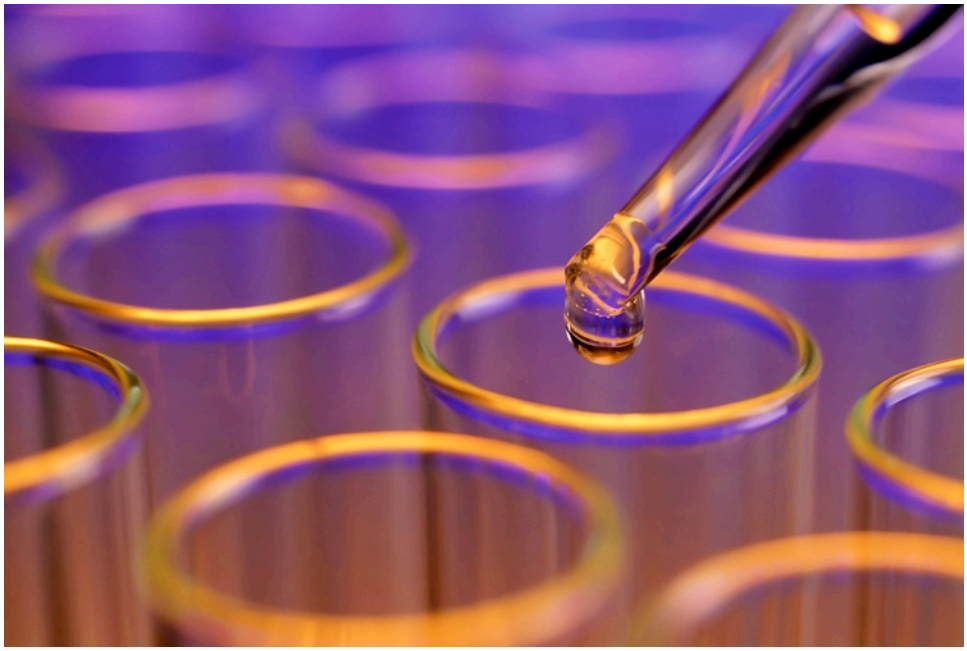
The current requirement for record keeping is found in 42 CFR part 73.17: "Accurate, current inventory for each select agent (including viral genetic elements, recombinant nucleic acids, and recombinant organisms) held in long-term storage (placement in a system designed to ensure viability for future use, such as in a freezer or lyophilized materials). Specific instructions are provided to ensure that adequate information (date, time, location and personnel involved) is available describing the agent, its use and purpose of use, its source, any transfers out, storage site, removal from or return to storage (and for what purpose). The

[16] Federal Experts Security Advisory Panel Recommendations Concerning the Select Agent Program. Nov 2, 2010, revised Dec 2, 2010 and Jan 10, 2011. http://www.phe.gov/Preparedness/legal/boards/fesap/Documents/fesap-recommendations-101102.pdf. Accessed Oct 30, 2011.
[17] 42 CFR Part 73. Possession, Use, and Transfer of Select Agents and Toxins; Biennial Review; Proposed Rule Federal Register / Vol. 76 , No. 191 / Monday, October 3, 2011/ Proposed Rules
[18] Ibid.
[19] Ibid.
[20] Proposed Tier 1 agents: Ebola, *Francisella tularensis,* Marburg virus, Variola major, Variola minor, *Yersinia pestis*, botulinum neurotoxins, toxin producing strains of Clostridium botulinum, *Bacillus anthracis*, *Burkholderia mallei, Burkholderia pseudomallei.*
[21] Richmond JY, Nesby-O'Dell SL. 2002. Laboratory security and emergency response guidance for laboratories working with select agents. Centers for Disease Control and Prevention. MMWR Recomm Rep. Dec 6;51(RR-19):1-6
[22] U.S. Department of Health and Human Services/CDC and National Institutes of Health. Biosafety in microbiological and biomedical laboratories [BMBL]. Richmond JY, McKinney RW, eds. 4th ed. Washington, DC: US Department of Health and Human Services, 1999.
[23] 42 CFR Part 73. Possession, Use, and Transfer of Select Agents and Toxins; Biennial Review; Proposed Rule Federal Register / Vol. 76 , No. 191 /

frequency of inventory review is not mandated by the Select Agent Rule, but is tailored to each program in consultation with the CDC.

The proposed changes to the Select Agent Rule do not include any modification of existing requirements, despite the fact that many commenters have pointed out that "requirement to account for individual vials of each pathogen is inappropriate for replicating biological agents" and "that this is a costly and burdensome responsibility for laboratories and their staff and that this requirement should be abolished except for Tier 1 agents."[23] The National Academies' Report entitled "Responsible Research with Biological Select Agents and Toxins," released in 2009, argues that while accurate accounting and inventory maintenance is essential for both safety and security, the current "requirements for counting the number of vials or other unreliable measures of the quantity of biological select agents are counter-productive, and lead to a false sense of security." The report suggests that the focus of inventory should be on controlling access while maintaining accurate records of the identity of all agents and toxins, who uses them and for what purpose.

The exact nature of inventory requirements going forward remains a contested issue within the research community. Indeed, the American Society for Microbiology has submitted several eloquent arguments during public comment periods, and Victoria Sutten of the Texas Tech School of Law's Center for Biodefense, Law and Public Policy argued that "the regulatory agency attempted to use a regulatory model that fit neither the target nor the outcome."[24] However, the CDC remains steadfast in its commitment to requiring certain kinds of quantification methods in maintaining current, accurate inventory,



stating "we are not proposing any changes to the select agent regulations based on these comments." [25]

PERSONNEL RELIABILITY

Personnel reliability remains a critical aspect of the U.S. Select Agent oversight program, especially in view of the FBI's conclusion that the bacterial strain used in the anthrax mailings likely originated in a government research laboratory.[26] The current screening process for employees to work with select agents involves an FBI background check for disqualifying behaviors and activites, relying on a wide range of databases.[27] Clearance, once obtained, lasts for five years. The terms in the 2002 Bioterrorism Response Act that related to the identification of restricted persons are the following, modeled on the Bureau of Alcohol, Tobacco, Firearms, and Explosives (ATF) when enforcing the Gun Control Act of 1968:permanent residence, mental institution, and unlawful user of any controlled substance."[28]

The proposed changes to the Select Agent Rule further clarify these terms, including, for example, how to interpret foreign criminal convictions and extending the conviction terms to include misdemeanors accompanied by imprisonment. In the proposed rules, institutional responsibility for personnel will be further increased by requiring (1) self and peer reporting of incidents or conditions that could affect a person's ability to safely access/ work with SA/ toxins; (2) procedures that ensure that those accessing Tier 1 agents are trustworthy and behaving in a manner that upholds public health and safety, security and the integrity of the scientific enterprise; and (3) "ongoing suitability assessments" of personnel with access, including shorter times between FBI clearance (i.e. at three year rather than at five year intervals). It can be argued that during a five or even three year period, an individual might experience significant personal changes, including those that might render him or her a security risk.[29]

[25] See 42 CFR Part 73. Possession, Use, and Transfer of Select Agents and Toxins; Biennial Review; Proposed Rule Federal Register / Vol. 76 , No. 191 / Monday, October 3, 2011/ Proposed Rules, p. 61213, paragraph 6.
[26] FBI (Federal Bureau of Investigation). 2008. Science Briefing on the Anthrax Investigation: Opening Statement by Dr. Vahid Majidi. Available at <http://www.fbi.gov/page2/august08/anthraxscience_081808.html>.
[27] A "restricted person" is identified as an individual under section 817 of the *USA PATRIOT Act* (18 U.S.C. 175b).
[28] 42 CFR Part 73. Possession, Use, and Transfer of Select Agents and Toxins; Biennial Review; Proposed Rule Federal Register / Vol. 76 , No. 191 / Monday, October 3, 2011/ Proposed Rules.
[29] Ibid.

Various approaches have been explored to ensure that laboratory workers do not engage in malfeasance while simultaneously guaranteeing safety and experimental standards. There are two approaches in use: one is to require that two people be present during all Select Agent work ("the two-person rule") and the second is the use of video monitoring. In 2009, the directors of all of the BSL4 laboratories in the United States met to discuss these and other options.[30] The consensus view was that video monitoring provided a marginal increase in safety and security over the two-person rule. The latter may decrease compliance with both safety and security requirement by placing undue pressure on the worker to finish quickly, and by exposing the observer unnecessarily to the containment environment. Again, the issue of the two-person rule and video monitoring remains under discussion within and between the research and regulatory communities.

Taken together, these proposed changes underscore the role of "laboratory culture" in the safe execution of Select Agent Research. Indeed, the National Academies' 2009 report on Responsible Research states that in order "to support active monitoring and management, laboratory leadership and the Select Agent Program should encourage and support the implementation of programs and practices aimed at fostering a culture of trust and responsibility," including "training in scientific ethics and dual-use research to foster community responsibility and raise awareness of available institutional support and resources."[31]

The NAS report provides the final word in this brief analysis of some of the regulatory issues involved in Select Agent research: "to provide continued engagement of stakeholders in oversight of the Select Agent Program, a federal Biological Select Agents and Toxins Advisory Committee should be established."[32] Such a committee would provide a mechanism to increase communication among all the stakeholders: funding and regulatory agencies and research communities, including, importantly, institutional management, safety and response personnel.

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[30] LeDuc JW, Anderson K, Bloom ME, Carrion R Jr, Feldmann H, Fitch JP, et al. Potential impact of a 2-person security rule on BioSafety Level 4 laboratory workers [online report]. Emerg Infect Dis [serial on the Internet]. 2009 Jul [date cited]. Available from http://wwwnc.cdc.gov/eid/article/15/7/08-1523.htm (http://wwwnc.cdc.gov/eid/article/15/7/08-1523.htm)

[31] NRC 2009. *Responsible Research with Biological Select Agents and Toxins*. Washington, D.C.: The National Academies Press.

[32] Ibid.

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