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**NAVAL  
POSTGRADUATE  
SCHOOL**

**MONTEREY, CALIFORNIA**

**THESIS**

**BIOSECURITY OF SELECT AGENTS AND TOXINS**

by

Thomas E. Engells

March 2005

Thesis Advisor:  
Second Reader:

Maria Rasmussen  
Robert Emery

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REPORT DOCUMENTATION PAGE			Form Approved OMB No. 0704-0188	
Public reporting burden for this collection of information is estimated to average 1 hour per response, including the time for reviewing instruction, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden, to Washington headquarters Services, Directorate for Information Operations and Reports, 1215 Jefferson Davis Highway, Suite 1204, Arlington, VA 22202-4302, and to the Office of Management and Budget, Paperwork Reduction Project (0704-0188) Washington DC 20503.				
1. AGENCY USE ONLY (Leave blank)		2. REPORT DATE March 2005	3. REPORT TYPE AND DATES COVERED Master's Thesis	
4. TITLE AND SUBTITLE: Biosecurity of Select Agents and Toxins			5. FUNDING NUMBERS	
6. AUTHOR(S) Thomas E. Engells				
7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES) Naval Postgraduate School Monterey, CA 93943-5000			8. PERFORMING ORGANIZATION REPORT NUMBER	
9. SPONSORING /MONITORING AGENCY NAME(S) AND ADDRESS(ES) N/A			10. SPONSORING/MONITORING AGENCY REPORT NUMBER	
11. SUPPLEMENTARY NOTES The views expressed in this thesis are those of the author and do not reflect the official policy or position of the Department of Defense or the U.S. Government.				
12a. DISTRIBUTION / AVAILABILITY STATEMENT Approved for public release; distribution is unlimited.			12b. DISTRIBUTION CODE	
13. ABSTRACT (maximum 200 words) The concept of biosecurity as it pertains to Biological Select Agents and Toxins in American biomedical research institutions is explored in some depth. Posing the research question "How can specific public biomedical research universities securely use and store biological select agents?" the thesis outlines the dynamics of the select agent and toxin list, the relevant history of the control of biological agents both in the international and domestic settings, including federal regulations pertaining to biosecurity (42CFR73). Two specific case studies are presented in the thesis. The biosecurity strategies and tactics at these two distinct biomedical research are compared. An answer to the research question is proposed and additional areas for research are outlined.				
14. SUBJECT TERMS Select Agents, Select Biological Agents and Toxins, Biosecurity			15. NUMBER OF PAGES 89	
			16. PRICE CODE	
17. SECURITY CLASSIFICATION OF REPORT Unclassified	18. SECURITY CLASSIFICATION OF THIS PAGE Unclassified	19. SECURITY CLASSIFICATION OF ABSTRACT Unclassified	20. LIMITATION OF ABSTRACT UL	

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**BIOSECURITY OF SELECT AGENTS AND TOXINS**

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**MASTER OF ARTS IN SECURITY STUDIES  
(HOMELAND SECURITY AND DEFENSE)**

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## **ABSTRACT**

The concept of biosecurity as it pertains to Biological Select Agents and Toxins in American biomedical research institutions is explored in some depth. Posing the research question “How can specific public biomedical research universities securely use and store biological select agents?” the thesis outlines the dynamics of the select agent and toxin list, the relevant history of the control of biological agents both in the international and domestic settings, including federal regulations pertaining to biosecurity (42CFR73). Two specific case studies are presented in the thesis. The biosecurity strategies and tactics at these two distinct biomedical research are compared. An answer to the research question is proposed and additional areas for research are outlined.



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## LIST OF ACRONYMS AND ABBREVIATIONS

The following acronyms are used with some regularity in this thesis and the definitions are provided to aid and assist the reader.

AEDPA	Anti-Terrorism and Effective Death Penalty Act, PL 104-132
APHIS	US Department of Agriculture, Animal and Plant Health Inspection Service
ASM	American Society of Microbiology
BMBL	<u>Biosafety in Biomedical and Microbiological Laboratories Handbook</u>
BPARA	Public Health Security and Bioterrorism Preparedness and Response Act, PL 107-188
BTWC	Biological and Toxin Weapons Convention
CDC	US Department of Health and Human Services, Centers for Disease Control
CFR	Code of Federal Regulations
HHS	US Department of Health and Human Services
MSI	Mass Sociogenic Illness
NAS	National Academy of Sciences
SEB	Staphylococcal Entertoxin B
USA PATRIOT Act	The Uniting and Strengthening of America by Providing Appropriate Tools Required to Intercept and Obstruct Terrorism, PL 107-56

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## **ACKNOWLEDGMENTS**

I wish to acknowledge the support of the administration of The University of Texas M.D. Anderson Cancer Center during this effort. As important, the encouragement and support provided my wife, Peggy, and my daughter, Laura, enabled me to accomplish this personal and professional goal. Finally, the faculty, staff and my fellow students made this a worthwhile experience that I will treasure for many years to come.



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## I. INTRODUCTION

Today, in the post 9/11 environment, biomedical research universities have the unique and timely opportunity to contribute to the national defense and the “global war on terrorism”. At the same time because of the very nature of the work conducted, many biomedical research laboratories are effectively warehouses for biological source material which can be used as primary ingredients in biological weapons. As a societal institution, the research university’s fundamental quandary is that of striking an acceptable balance between a progressive biomedical research agenda and the continuing verifiable compliance with recent federal biosecurity requirements.

A focused biosecurity effort is important for both private and public biomedical research universities, but it is also important for private biotechnology concerns and governmental research laboratories. The risk inherent from a single unauthorized release of a biological select agent or toxin could be serious and, some would argue, frightening.<sup>1</sup> However, the physical security necessary to protect these select agents and toxins within the laboratory should not inhibit a biomedical research university’s fundamental mission, that of research and scientific discovery. Implementation of progressive security practices coupled with a heightened vigilance at biomedical research university laboratories may substantially contribute to the prevention of the theft and the diversion of select agents and toxins and thus reduce the likelihood of a biological weapons attack from occurring within the United States.

American biologists and biomedical researchers have attained a professional fluency with modern biosafety practices. The standard reference for laboratory biosafety practices is the federal publication Biosafety in Biomedical and Microbiological Laboratories (BMBL)<sup>2</sup>. That written reference document establishes a comprehensive series of safety standards that govern the safety practices within biomedical research

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<sup>1</sup> A recent Hart-Teeter Research Study, based on a national survey sample of 1,600 citizens and 250 frontline emergency response personnel, reported that 77 percent of respondents believe the United States will be the target for another major terrorist attack in the next few months. The poll further indicated that 48 percent of all respondents selected bioterrorism as the most feared of all types of attacks, “Nation a Mix of Emotions on Homeland Security” PA Times, Vol. 27, No. 4, April 2004.

<sup>2</sup> The BMBL Handbook is updated every five years; the fifth edition revision is underway and will include substantive discussion and guidance on biosecurity. The Federal Register, March 23, 2004, Vol 69, No.56, pp. 13527-13529.

laboratories. These standards of practice were adopted as safety measure for researchers and their staffs due to the deadly infection rates biomedical researchers had encountered for decades. The strict adherence to these safety practices “. . . does contribute to a healthier and safer work environment for laboratorians, their co-workers, and the surrounding community. They must be customized for each individual laboratory and can be used in conjunction with other available scientific information.”<sup>3</sup> Biological Safety Officers<sup>4</sup>, who are frequently found within the universities’ Environmental Health and Safety Departments, educate staff as to the specifics of BMBL biosafety standards. They also critically assess and carefully inspect the affected laboratories to achieve ongoing compliance with those standards.

In contrast to the now near universal acceptance of these biosafety practices within the biomedical research community, biosecurity is a relatively new and a generally suspect concept. Biosecurity can be defined as the art and science of applying modern physical security principles to specified research endeavors and facilities. Its purpose is to ensure the positive control of certain substances of interest in order to reduce unauthorized access or use of those substances.<sup>5</sup> As distinct from biosafety, biosecurity has a limited number of advocates and is often found to be an active and unnecessary impediment to the open and vigorous research practices that spark the necessary innovation and progress in the biological sciences.<sup>6</sup>

The general public’s interest in and awareness of biological weapons has surged during the last decade. The ease of access to the elements necessary for biological

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<sup>3</sup> National Institutes for Health. (1999). “Laboratory Security and Emergency response for Microbiological and Biomedical Laboratories, BMBL Appendix F”. Accessed on 18 April 2004 at <http://bmbf.od.nih.gov/appendf.htm>

<sup>4</sup> Biological Safety Officers are safety professionals who are trained and educated on the unique demands and dangers encountered in research involving biological substances in laboratory and manufacturing settings.

<sup>5</sup> The CDC at the [Biosafety in Microbiological and Biomedical Laboratories, 4th Edition, Appendix F](#) defines biosecurity as “Preventing unauthorized entry into laboratory areas and preventing unauthorized removal of dangerous biological agents from the laboratory”. A similar but distinct definition is offered by R. Salerno and J. Koelm in “Biological Laboratory and Transportation Security and the Biological Weapons Convention” SAND No. 2002-1067B. “the objective of biosecurity is to protect facilities against the theft or diversion of high-consequence microbial agents, which could be used by someone who maliciously intends to conduct bioterrorism or pursue biological weapons proliferation”.

<sup>6</sup> T. Agres (2003) “Researchers Bemoan Bioterror Bureaucracy” [The Scientist](#), September 23, 2003. Accessed on 21 April 2004. <http://www.biomedcentral.com/news/20030924/02/>

weapon production in a civilian setting is alarming. Biological agents and toxins can be acquired by a variety of means that range from theft to self-manufacture. The National Strategy for Homeland Security notes that “the expertise, technology and material needed to build the most deadly weapons known to mankind – including chemical, biological, and radiological and nuclear weapons – are spreading inexorably.”<sup>7</sup>

Certain biological materials are integral to the manufacture of biological weapons of mass destruction. Such biological weapons are potentially the most dangerous within a terrorist’s arsenal. A biological weapon, unlike a chemical or nuclear weapon, strikes silently and has a delayed presentation. Days or weeks may elapse between exposure and the actual presentation of disease. Yet these same biological select agents are necessary for progressive biomedical research. For example, to effectively research the attributes of cutaneous anthrax disease, a biomedical researcher must have ready access to a stock of anthrax bacterial spores, *Bacillus anthracis*.

More than 11,000 universities and private organizations engage in biomedical research within the United States, and of these more than 230 universities routinely use one or more select agents and toxins<sup>8</sup> in research. Universities are the primary recipients of federal biomedical research funding; the National Institutes of Health awarded more than \$22 billion in grants to universities in 2002. Yet research universities were not designed with security as a goal, and they remain easy to obtain access to, easy to infiltrate, readily visible to the news media, and as organizations go among the least able to defend themselves.<sup>9</sup>

Media focus on biological weapons has also increased during the last twenty years. During that time a less than successful attempt at introducing salmonella in Oregon occurred in 1984. A series of nation wide best-sellers published in the mid-1990s focused on exotic biological attacks. Finally the anthrax attacks of the autumn of 2001

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<sup>7</sup> G.W. Bush (2002) National Strategy for Homeland Security. Accessed on 21 April 2004 <http://www.whitehouse.gov/homeland/book/>.

<sup>8</sup> Select Agents and Toxins are specified substances established by federal regulation by the Secretaries of Health and Human Services and Agriculture pursuant to their statutory authority, see Chapter II, Appendix I and <http://www.cdc.gov/od/sap/docs/salist.pdf>.

<sup>9</sup> Attorney General of the United States. (1993). Report to Congress on the Extent and Effects of Domestic and International Terrorism on Animal Enterprises. September 2, 1993 - Report Transmitted to the Vice President and the Speaker of the House. Accessed on 12 December 2004 at [http://www.responsiblewildlifemanagement.org/congress\\_on\\_animal\\_rights\\_terrorism.htm](http://www.responsiblewildlifemanagement.org/congress_on_animal_rights_terrorism.htm).

profoundly changed the public's perception of security measures at the nation's biomedical research laboratories.<sup>10</sup> The anthrax attacks were geographically dispersed. These unsolved criminal attacks occurred at locations as diverse as Connecticut and Florida and required the evacuation of the offices of the United States Senate as well as regional postal processing centers. They also highlighted the weaknesses of several of our public health and biosecurity systems, and in 2002 the United States Congress adopted statutory law to address many of those systemic weaknesses. This thesis discusses the implementation of biosecurity practices required by the 2002 statute.

State of the art laboratory facilities staffed with skilled scientists are found throughout the United States at research universities. The modern research university, be it public or private, is an intellectual resource for the people of the United States and to the world at large. The research university is cosmopolitan by nature. Graduate students and post-doctoral fellows from across the globe routinely relocate to the United States to engage in biomedical research. The large numbers of international scientists employed or associated with these laboratories presents very unique challenges. Yet biomedical research acts as the dynamo from which change and progress in the life sciences are realized.

The research conducted in the university setting can be divided into two general categories – basic and applied. Basic research grapples with fundamental intellectual questions which may have no direct link to practical application, while applied research focuses on the practical application of research on a problem of significance. Biomedical research at the research university includes both. The importance of such research was assessed by Broad and Glanz (2003)

Clearly science has mattered a lot, for a long time. Advances in food, public health and medicine helped raise life expectancy in the United States in the past century from roughly 50 to 80 years. So too, world population between 1950 and 1990 more than doubled, now exceeding six billion. Biology discovered the structure of DNA, made test-tube babies and cured diseases. And the decoding of the human genome is leading

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<sup>10</sup> Those books included Richard Preston's The Hot Zone (1996) and Cobra Event (1998). The anthrax attack is now referred to as 5/11 as five of the eleven individuals exposed to anthrax died from that exposure in the autumn of 2001.

scientists toward a detailed understanding of how the body works, offering the hope of new treatments for cancer and other diseases.<sup>11</sup>

During the last decade, public awareness of the janus-faced nature of biological research has increased with the understanding that the same research that has led to vaccines and pharmaceuticals which have enabled mankind to conquer diseases and counter weaponized biological agents can also be used to develop and refine the lethal biological weapons themselves.<sup>12</sup> Biotechnology's dual use was considered in depth by a National Academy of Sciences Panel (NAS) in January 2003. While university based biomedical research has customarily been conducted without security restraints, in the current geopolitical climate that past practice is subject to serious debate and active reconsideration.<sup>13</sup> To address the concerns that research may be misused by non-state actors or others, the NAS has recommended a solution, specifically that a system composed of both locally based review committees and a single national committee – the National Science Advisory Board for Biodefense – to include both security experts and recognized biologists be formed, activated, and tasked to assess biomedical research and devise ways to keep these materials safe<sup>14</sup>.

The university-based academic community wrestles with finding an acceptable balance between intellectual freedom for their faculty and graduate students and the university's civic responsibilities to the society at large. Difficult choices concerning traditional academic freedom are being made in an age of heightened concern about

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<sup>11</sup> W. Broad and J. Glanz. (2003). "Does Science Matter". The New York Times. November 11, 2003.

<sup>12</sup> L. Ember (2002). "Biotechnology: A Two Edged Sword". Chemical & Engineering News., June 17, 2002.

<sup>13</sup> S. Block (2001). "The Growing Threat of Biological Weapons". The American Scientist. Vol. 89, Number 1. Block a prominent Stanford biologist, became very engaged in this topic early in the discussions of the national security impact of biological weapons.

<sup>14</sup> The suggested board has been formed, yet not staffed as of December 2004. The board, the National Science Advisory Board for Biosecurity (NSABB), is to provide technical oversight on a variety of biosecurity issues. At the FAQ website, the Board notes, "The NSABB will advise all federal departments and agencies that conduct or support life science research. The new board will recommend specific strategies for the efficient and effective oversight of dual use biological research, including the development of guidelines for the case-by-case review and approval by Institutional Biosafety Committees (IBCs). The NSABB will take into consideration both national security concerns and the needs of the research community. This includes strategies for fostering continued rapid progress in public health research (e.g., new diagnostics, treatments, vaccines and other prophylactic measures, and detection methods), as well as in food and agriculture research while being mindful of national security concerns." Accessed on 26 December 2004 at <http://www.biosecurityboard.gov/faq.htm> .

terrorism. Widespread and deeply entrenched resistance is still encountered at the university to any limitation on perceived intellectual freedom. The federal government, a major source of funding for much of biomedical research<sup>15</sup>, has defined the primary principle of research as:

1. Ensure Academic Freedom and Publication

Academic research freedom based upon collaboration, and the scrutiny of research findings within the scientific community, are at the heart of the scientific enterprise. Institutions that receive NIH research funding through grants or contracts ("Recipients") have an obligation to preserve research freedom and ensure timely disclosure of their scientists' research findings through, for example, publications and presentations at scientific meetings. Recipients are expected to avoid signing agreements that unduly limit the freedom of investigators to collaborate and publish.<sup>16</sup>

The very nature of modern scholarship in the life sciences may unintentionally aid terrorists in targeting a specific scholar or university. Scholars, as a matter of practice, publish their work in peer-reviewed professional journals and present those research findings at symposia and conferences throughout the world. In pursuit of quality science, scholars try to conduct and publish transparent research thereby enabling colleagues to confirm their findings through the exacting replication of the scientific experiments. A scholar's ongoing work and research interests are well known within their academic discipline, and publication practices continue to include listing the specific addresses and affiliations of the scholars involved. Visitors, scholars and other interested persons are commonplace on campus and cause neither alarm nor concern within that unique community.

The risk of unintentionally aiding terrorists was directly considered in the January 2003 National Academy of Sciences conference by both senior academic scientists and government security specialists. "While some scientists contend that the best defense against biological weapons is robust research that is widely accessible, security

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15 SHARING BIOMEDICAL RESEARCH RESOURCES: Principles and Guidelines for Recipients of NIH Research Grants and Contracts. Federal Register Notice. Tuesday, May 25, 1999. 64 FR 28205. Accessed on 18 April 2004 at <http://ott.od.nih.gov/NewPages/RTguide.htm>.

16 "Developing Sponsored Research Agreements: Considerations for Recipients of NIH Research Grants and Contracts". Federal Register. Vol.59, No.215, Tuesday, November 8, 1994. p.55676.

specialists maintain that scientists are being naïve at best and reckless at worst.”<sup>17</sup> The initiation or continuation of research involving biological select agents and previously accepted practices within academia poses a risk to the scholar, the university and the community as a whole.

The nation must balance this historic, and many would say essential, academic freedom of inquiry with the people’s reasonable expectation of responsible scientific conduct and the acknowledgement of national security concerns by biomedical research scientists. The task of balancing academic rights and civic responsibilities is not a new problem. During the last sixty years much nuclear physics research has been significantly regulated by a similar national review body, ensuring both the freedom of academic inquiry and the security of the nation’s defense by regulating the publication and open discussion of certain research within the nation’s universities.<sup>18</sup>

Universities by tradition and practice are decentralized and somewhat loosely knit organizations. Generally members of the biomedical research faculty consider themselves less as employees of a large organization and more as skilled partners within a group of scientists committed to research excellence. Command and control practices which may succeed in many large organizations, such as manufacturing and the military, may not be as effective in the context of a university, especially a renowned research university with tenured faculty members. World class research scientists are sought after by other organizations and are generally a mobile group of professionals who often have few or no qualms about changing their affiliation to another major research university, even one located outside the United States, if it would further their individual research agendas and eliminate obstacles to their research.<sup>19</sup>

The creation of a list of select agents and toxins developed within the United States during the last six years has been perceived as an obstacle to biomedical research by some prominent scientists. The designation of such select agents provoked some

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<sup>17</sup> D. Schemo. (2003). “Threats and Responses: Bioterrorism”. The New York Times. January 10, 2003.

<sup>18</sup> National Academy of Sciences (1982) *Scientific Communication and National Security*.. Accessed on 12 June 2004 at <http://www.nap.edu/openbook/0309033322/html/>.

<sup>19</sup> This generalization is supported by the author’s twenty four years of professional experience at a major biomedical research university.



controversy within the biomedical research community. The federal government at the 42 Code of Federal Regulations (CFR) 73, defines a select agent as:

. . . any microorganism (including, but not limited to, bacteria, viruses, fungi, rickettsiae, or protozoa), or infectious substance, or any naturally occurring, bioengineered, or synthesized component of any such microorganism or infectious substance, capable of causing death, disease, or other biological malfunction in a human, an animal, plant, or another living organism,; deterioration of food, water, equipment supplies or material of any kind; or deleterious alteration of the environment.

The Secretary of Health and Human Services (HHS) designated forty-three substances as select agents or toxins at 42 CFR 73. These substances are listed in Appendix A. This list was finalized after significant controversy within the scientific community, including among them biomedical researchers, microbiologists, biological weapons experts, and public health officials. The current list of select agents is based upon work initially done at the Centers for Disease Control in partnership with subject-matter experts in 1996 to 1997, to fulfill the statutory requirements of the Antiterrorism and Effective Death Penalty Act of 1996 (AEDPA), Public Law 104-132, Section 511. Under the provisions of that law the Department of Health and Human Services was to prepare a list of select agents that are capable of causing substantial harm to human health. That task was fraught with disagreement and controversy. Hundreds of candidates were reviewed and culled to make a list that became the basis for the 2002 Select Agent List.<sup>20</sup>

While there has been some focus on issues of biosafety for several decades, biosecurity is a new concept and one which was of generally little interest to university administrators and researchers prior to 2002. Auditors from the General Accounting Office noted in their November 2002 report that the “CDC can improve its management of the Select Agent Program . . . to reasonably ensure that appropriate security and safety precautions are in place for select agents.”<sup>21</sup> While the Inspector General of the

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<sup>20</sup> M. Enserink and D. Malakoff. (2001). “Congress Weighs Select Agent Update.” Science. November 16, 2001, and Centers for Disease Control and Prevention. (2003). “Select Agent Program”. Accessed on 30 April 2004 at <http://www.cdc.gov/od/sap>.

<sup>21</sup> General Accounting Office (2002) Homeland Security: CDC’s Oversight of the Select Agent Program, GAO-03-315R. Accessed on 12 June 2004 at <http://www.gao.gov/new.items/d03315r.pdf>.

Department of Agriculture noted in a September 2003 report that “. . . there were no consolidated standards either federal or institutional that provided guidance on security to the laboratories.”<sup>22</sup>

The research question explored in this work is how can specific public biomedical research universities securely use and store biological select agents. The answer(s) proposed to this question will be of value to university presidents, facility officers, law enforcement executives, and research directors. This research may also translate both to use in private industry as well as other organizations engaged in biotechnology research involving select biological agents and toxins.

While most university environmental health and safety functional staff are prepared by technical training and professional education to ensure the ongoing compliance with modern biosafety practices within the laboratory, there remains a general ignorance within many research universities as to fundamental biosecurity practices. Such practices are critical to the positive control of biological select agents and toxins in laboratory settings. Enhancement of security at biomedical research laboratories using biological select agents and toxins is the civically responsible thing to do.

This thesis includes a policy analysis with a primary focus on the implementation of the specific federal regulations governing biosecurity for select agents and toxins. The analysis will center on two specific settings during the period 2001 to 2003, one an academic health science center and the other a state supported comprehensive cancer center. The goal is to assess compliance efforts and to explore the specific implementation challenges encountered during an abbreviated compliance time frame. The three criteria used in that analysis are efficiency (essentially costs - labor and capital equipment/sunk costs), effectiveness (the ability to demonstrate acceptable compliance to federal regulators within an established time frame) and equity (willing compliance with statutory and regulatory mandates, as well as the demonstrable impact the compliance choices have had on institutional/research agendas).

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<sup>22</sup> Office of the Inspector General, Southeast Region, US Department of Agriculture, Audit Report: Controls Over Biological, Chemical and Radioactive Materials at Institutions Funded by the United States Department of Agriculture, 50099-14-AT September 2003. Accessed on 15 May 2004 at <http://www.usda.gov/oig/webdocs/50099-14-At.pdf>.

The documented biosecurity compliance efforts will be supplemented by a meta-textual review to establish context, including the spectrum of public media and professional journals, and a series of interviews with affected primary investigators, institutional safety officers and the program officers at the Centers for Disease Control, Department of Health and Human Services.

This thesis is organized into five chapters. Chapter II will discuss the select agent list-making process within the United States. The specific substances included on the list, as well as subsequent prioritization of the approved list is discussed. The future viability of the list of select agents and toxins is explored, with significant current and potential problems highlighted. In Chapter III the current statutory laws and applicable federal regulations are discussed as they pertain to the biosecurity for select agents and toxins. The performance of the responsible regulatory agency, Centers for Disease Control, in this specialized area is assessed as well as the tension created within the organization as a result of this statutorily assigned regulatory role. The controversy caused by the adoption and implementation of these new regulations on an institutional and national level is also be covered. In Chapter IV the experiences of two biomedical research universities in establishing compliance to the federally-mandated biosecurity regulations is explored. Through a series of principal actor interviews and archived document reviews, the challenges encountered and the compliance achieved with the federal biosecurity regulations is discussed and institutional conformance with those regulations assessed. Chapter V presents the significant findings relevant to the research question. A credible answer to the basic research question, effective security for select biological agents and toxins, is proposed. Effective biosecurity is found to be the result of a coordinated, multi-disciplinary and collegial effort by three professional groups (primary investigators, environmental health and safety specialists and law enforcement). The thesis closes with a discussion of the future opportunities for research in this important, but often neglected area of homeland security.

## II. LIST MAKING

We will undertake a concerted effort to prevent the spread and use of biological weapons and to protect our people in the event these terrible weapons are ever unleashed by a rogue state, a terrorist group, or an international criminal organization.

President William Jefferson Clinton<sup>23</sup>

On September the 11th, the world learned how evil men can use airplanes as weapons of terror. Shortly thereafter, we learned how evil people can use microscopic spores as weapons of terror. Bioterrorism is a real threat to our country. It's a threat to every nation that loves freedom. Terrorist groups seek biological weapons; we know some rogue states already have them.

President George W. Bush<sup>24</sup>

This chapter considers one of the most important issues underlying the topic of biosecurity for select biological agents and toxins, the scope of the issue as defined by the list promulgated by the federal government. That list of the substances defined as select agents and toxins, establishes the parameters of all subsequent legal and administrative requirements. The practice of list making is reviewed, some of the notable responses to the list-making in this specific context are considered, and the relevancy of the sub categorization of risk within the list is assessed. To assist the reader, Appendix A: Acronyms is provided as a ready reference for the several common and somewhat arcane acronyms used throughout this thesis.

Psychologists have found list making to be an activity of some interest, but not within the specific context in which that task is examined in this paper.<sup>25</sup> List making in

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<sup>23</sup> Remarks of the President at the United States Naval Academy Commencement. May 22, 1998. Accessed on 20 August 2004 at <http://cns.miis.edu/research/cbw/naval.htm>.

<sup>24</sup> Remarks of the President of the United States at Signing of H.R. 3448, the Public Health Security and Bioterrorism Response Act of 2002. The Rose Garden. June 12, 2002. Accessed on 14 September 2004 at <http://www.whitehouse.gov/news/releases/2002/06/20020612-1.html>.

this context is actually the artifact produced from the human interaction of various individuals and members of small groups who endeavor to meet a specific policy objective. Within the Anti-Terrorism and Effective Death Penalty Act (AEDPA)<sup>26</sup>, the Secretary of Health and Human Services is required to promulgate a list and necessary regulations for select biological agents. It is of particular interest that within the AEDPA the Secretary was provided with very specific guidance as to the criteria to be used in making this list as follows:

(d) REGULATORY CONTROL OF BIOLOGICAL AGENTS-  
(1) LIST OF BIOLOGICAL AGENTS-

(A) IN GENERAL- The Secretary shall, through regulations promulgated under subsection (f), establish and maintain a list of each biological agent that has the potential to pose a severe threat to public health and safety.

(B) CRITERIA- In determining whether to include an agent on the list under subparagraph (A), the Secretary shall--

(i) consider--

(I) the effect on human health of exposure to the agent;

(II) the degree of contagiousness of the agent and the methods by which the agent is transferred to humans;

(III) the availability and effectiveness of immunizations to prevent and treatments for any illness resulting from infection by the agent; and

(IV) any other criteria that the Secretary considers appropriate;

and

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<sup>25</sup>The psychological literature is replete with references to the practice of list making as both a disease symptom (Obsessive Compulsive Disorder) and also a therapeutic technique in effectively countering the effects of chronic depression and anxiety. For example: S. Lepore & J. Smyth. (2002). The writing cure: How expressive writing promotes health and well-being. Washington, D.C.: American Psychological Association and M. Jenike (1994). "Managing the patient with treatment-resistant obsessive compulsive disorder". Journal of Clinical Psychiatry 55:3 (suppl):11-17, 1994.

<sup>26</sup> Anti-terrorism and Effective Death Penalty Act of 1996. Accessed on 15 September 2004 at <http://www.stimson.org/cbw/?sn=CB20011221147>

(ii) consult with scientific experts representing appropriate professional groups.<sup>27</sup>

The AEDPA was enacted on April 24, 1996, and the Secretary was directed to promulgate proposed rules within 60 days and final rules within 120 days of the enactment of the legislation. Thus, the federal Secretary of Health and Human Services had both a regulatory task and specific guidelines as to list criteria and parties to be included in the production of that list.

This legislation was in large part a response to the episodes of shipment of biological agents to unauthorized individuals who had links to criminal activities and domestic terrorist organizations in 1995.<sup>28</sup> This situation was a near classic application of small group dynamics in a specific task oriented environment.<sup>29</sup> When examining list making in this context, we have a variety of factors to consider including power (formal, informal and expert), time constraints<sup>30</sup> and formal and informal communication patterns. Absent detailed interviews of principals and a critical review of the group's working papers (documentary evidence), the actual group dynamics in play can only be inferred; but these inferences can be generally accurate if compared carefully to the official records and the open source media on the topic. Some of those inferences on list making during 1996-1997 include that the representatives of the Department of Health and Human Services (specifically the Centers for Disease Control – CDC) were in the position of greatest influence. These civil servants, many possessing formal training as biologists, microbiologists or biomedical researchers, had formal power anchored in both statutory law and federal regulations. The CDC representatives did exercise control over the agenda, for they convened the meetings and established the participant list.

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<sup>27</sup> Guidance is found at Public Law 104-132, Title V, Subtitle B, Biological Weapons Restrictions, Section 511 Enhanced penalties and control of biological agents.

<sup>28</sup> S. Leader (1997) "The Rise of Terrorism" Security Management. Accessed on 17 September 2004 at <http://www.securitymanagement.com/library/000339.html>.

<sup>29</sup> Small group dynamics is an area rich in research, primarily applied research, published in either industrial psychology or administrative sciences journals. A seminal recent work in the field is R. Tindale, et. al. (1998) Theory and Research on Small Groups. New York: Plenum Press.

<sup>30</sup> Some critically incisive work was recently completed on the effect of time urgency on actual performance E. J. Kempf. (2003). "Time's Up: The Effects of Time Urgency on Dyadic Performance". Missouri Western University Clearinghouse. Accessed on 16 September 2004 at <http://clearinghouse.mwsc.edu/manuscripts/436.asp>.

Such regulatory work does not take place in a vacuum, and orderly compliance to externally imposed regulations could neither be expected nor realized. The process was rife with negotiations with the other groups that had identifiable stakeholder interests. A primary stakeholder in this issue was the microbiologists. The American Society of Microbiology (ASM), representing the professional interests of the nation's microbiologists, played a critical role in the development of the federal regulations.<sup>31</sup> The society reported that in drafting the regulations that took effect on April 15, 1997, they had surveyed the 11,000 members of the society by e-mail soliciting their advice as to the organisms that should be subject to regulation and the protocols pertaining to their safe transfer and shipment. While the opinions provided by the ASM members polled were far from unanimous, when integrated with the goal of reducing the threat of terrorism by focusing on those substances that have the greatest potential for use in biological weapons an acceptable list was crafted. The ASM noted in their 1997 report that:

As with other issues related to the potential misuse of microorganisms as biological weapons, the ASM offered advice in the development of these regulations that was consistent with ensuring continuance of essential biomedical research and diagnostic activities. In the final regulations, the list of restricted agents is limited so as not to unduly restrict legitimate biomedical research. Clinical laboratories certified under the Clinical Laboratory Improvement Amendments of 1988 (CLIA) that intend to use and transfer select agents only for diagnostic, reference, verification, or proficiency testing purposes are exempt from the requirements of the regulations. Thus, essential medical diagnostic practices can proceed unimpaired. <sup>32</sup>

The list of select biological agents and toxins circa 1997 was finalized after significant controversy within the scientific community, including biomedical researchers, microbiologists, biological weapons experts and public health officials. The difficulty of list making was exacerbated by the vested self-interests of several individuals and organizations in keeping substances outside the scope of the list, to avoid the significant restrictions on research incurred when a substance is labeled as a select

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<sup>31</sup> R. Atlas (1997) Preventing the Misuse of Microorganisms: The Role of the ASM in Protecting Against Biological Weapons. Accessed on 17 September 2004 at <http://www.asm.org/Policy/index.asp?bid=3009>.

<sup>32</sup> Ibid, p. 3.

agent. Additionally, primary investigators, who have a comprehensive knowledge of the attributes and risk potential for each of the several select biological agents and toxins, could reach consensus on some, but not unanimity on all, substances and organisms that are included on the list.

In the autumn of 2001 anthrax spores were mailed throughout the United States. Attacks occurred at the United States Senate, United States Postal Service mail sorting facilities and media corporate headquarters. Anthrax spores were also mailed to an elderly woman in rural Connecticut. Taken together these incidents increased the national awareness of the threat of bioterrorism and the acknowledgment of the nation's vulnerability to such an attack. The Public Health Security and Bioterrorism Preparedness and Response Act of 2002 (BPARA), Public Law 107-188 was adopted as law on June 12, 2002, as a legislative response to the surge of anthrax attacks within the United States. The statute has three overarching goals:

- assessing and improving infrastructure integrity;
- increasing pathogen security;
- and augmenting public health capabilities.

This statute changed the scope of the Secretary of Health and Human Services list making responsibilities as previously outlined in the AEDPA. The BPARA mandated the review and biennial publication of the list of select agents and toxins or more often as needed. The criteria used to create the Select Agent List and the subsequent federal regulations are critical to the question examined in this thesis, specifically the physical security practices at biomedical research facilities using select agents. The substances that are included or excluded from the biennial list will drive the actions required of the institutions and facilities that use, possess, transmit and store the materials.

That list making exercise in 2002 was fraught with disagreement and controversy<sup>33</sup> Professional groups and academic scientists expressed critical concerns on

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<sup>33</sup> The controversy raged not only in professional journals and publications, but also in the major media outlets in 2002; see S. Davis. (2002). "Government tightens controls on lab agents". *DVM*, October; J. Fierer and T. Kirkland. (2002). "Questioning the CDC's 'select agent' criteria". *Science*, January 4, 2002; D. Schemo (2002). "Threats and Responses: Laboratories". *The New York Times*, December 17, 2002 and R. Mestel (2002). "In the Lab: Suspicion Spreads". *The Los Angeles Times*, August 28, 2002 and Centers for Disease Control and Prevention. (2003). "Public Comments on New Regulation" 03-SAR-013. Accessed on 15 December 2003 at <http://www.cdc.gov/od/sap/comments/03sar013.htm>.



several topics. First, there was significant disagreement about the inclusion of some agents and toxins on the Select Agent List, much of it carried over from the 1997 discussions. “Although such legislation is probably appropriate, the CDC’s ‘watch list’ contains many organisms, such as fungus *Coccidioides immitis*, that are unlikely candidates for biological weapons”<sup>34</sup>. Second, many scientists accused university administrators of overreaction to the anthrax events of the autumn of 2001 and the subsequent gross misapplication of the provisions of the BPARA in 2002, “Biologists understand that times, and laws, have changed. . .the response by university administrators and authorities – who are not, after all, microbiologists – have been driven by an inflated fear of the bacterium itself. The reaction...has been far out of proportion to the actual risk...”<sup>35</sup> The cost of compliance with the new law and regulations was deemed quite significant. “After 11 September; however, convenience and efficiency gave way to security . . . Across the country, in hundreds of ways both large and small, US academic researchers are feeling the effects of that catastrophic day on their ability to carry out science . . . eager to plug security gaps. Congress and agency officials have set tight deadlines for complying with the new regulations...the incentive to get it right is very high because universities and researchers who don’t comply face stiff, potentially criminal penalties”<sup>36</sup>

Unlike the 1997 version of the list, the 2002 version would require certain facilities and primary investigators to significantly change both laboratory practices and area security measures to achieve compliance with the new regulations. During this iteration of the list making exercise, the CDC again included such major stakeholders as the ASM and several universities in the crafting of the list. A federal interagency work group was formed to finalize the list.<sup>37</sup> That interagency work group included representatives from 21 separate federal agencies. They reviewed hundreds of candidates

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<sup>34</sup> J. Fierer and T. Kirkland. (2002). “Questioning the CDC’s ‘select agent’ criteria”. Science. January 4, 2002

<sup>35</sup> R. Mestel (2002). “In the Lab: Suspicion Spreads”. The Los Angeles Times. August 28, 2002.

<sup>36</sup> D. Malakoff (2003). “Tighter security reshapes research”. Science. September 6, 2003.

<sup>37</sup> Department of Health and Human Services (2002) Public Meeting on the Interim Final Rule for Select Agents, December 16, 2002. Accessed on 17 September 2004 at <http://www.cdc.gov/od/sap/docs/cdc-05at.txt>.

for the notional list. That notional list was culled to form the 2002 Select Biological Agent and Toxins list, see Appendix 2.

The list is unique because it includes both select biological agents and toxins applicable to man and animals. The CDC, whose primary jurisdiction includes the agents with impact on humans, reported that 21 agents were their sole regulatory responsibility and 20 substances were to be found on an overlap list. That overlap list was jointly regulated by the Department of Health and Human Services (CDC) and the Department of Agriculture Animal and Plant Health Inspection Service (APHIS). The two departments worked closely to ensure that their regulations in this area worked in tandem. A unique aspect of the 2002 version of the Select Agent List, which will be an ongoing factor in all subsequent lists, is the inclusion of materials that contain genetically altered substances. The life sciences continue to evolve at a rapid rate and the Select Agent List must be dynamic to remain relevant. Between 1997 and 2002 great strides were made in recombinant DNA scientific work. This progress prompted regulators to include such substances within the 2002 version of the Select Agent List. At the December 16, 2002, public meeting co-hosted by the Departments of Agriculture and Health and Human Services, Dr. Stephen Ostroff, the deputy director of the National Center for Infectious Diseases at CDC and the acting director of the Select Agent Program noted regarding this element of the list making that:

. . . we reassessed what essentially we were trying to focus on, and that is the ability to create, through the genome of one of the viruses, the ability to replicate more of it through some sort of recombinant technique. And we believe in number 1, where we've specified nucleic acids that are either synthetic or naturally derived, that are either contiguous or have been fragmented and then reassembled, that if they encode for an infectious or replicative competent form of any of the select agents viruses listed is what we're intent on regulating here.

Thus viral nucleic acid extracted in and of itself would not be subject to the requirements of the select agent rule. Its inclusion would be dependent upon it to be put into a system, as noted here, where there is the potential to produce replicative forms of the virus.<sup>38</sup>

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<sup>38</sup>Department of Health and Human Services (2002). page 25.

The regulators and those subject to these regulations were able to agree that some of these substances on the list presented a substantially greater danger to the public health people of the United States and the world. Those substances (viruses, bacteria and toxins) were accorded a higher classification in a public health matrix. A cursory review of some of these biological agents may serve to illustrate the danger posed to humans by exposure to these agents, see Table 1.

Table 1. Select Biological Agents and their Impact on Humans

Agent Type	Name of Agent	Rate of Action	Effective Dosage	Symptoms/Effects	Prophylaxis/Treatment
<b>Bacteria</b>	<i>Bacillus anthracis</i>  ● Causes anthrax	<i>Incubation:</i> 1 to 6 days  <i>Length of illness:</i> 1 to 2 days  Extremely high mortality rate	8,000 to 50,000 spores	Fever and fatigue; often followed by a slight improvement, then abrupt onset of severe respiratory problems; shock; pneumonia and death within 2 to 3 days	Treatable, if antibiotics administered prior to onset of symptoms  Vaccine available
	<i>Pasturella tularensis</i>  ● Causes tularemia  ● Also known as rabbit fever and deer fly fever	<i>Incubation:</i> 1 to 10 days  <i>Length of illness:</i> 1 to 3 weeks  30% mortality rate	10 to 50 organisms	Fever, headache, malaise, general discomfort, irritating cough, weight loss	Treatable, if antibiotics administered early  Vaccine available
<b>Viruses</b>	Variola virus  ● Causes smallpox	<i>Incubation:</i> average 12 days  <i>Length of illness:</i> several weeks  35% mortality rate in unvaccinated individuals	10 to 100 organisms	Malaise, fever, vomiting, headache appear first, followed 2 to 3 days later by lesions  Highly infectious	Treatable if vaccine administered early  Limited amounts of vaccine available  <u>Note:</u> World Health Organization conducted a vaccination campaign from 1967 to 1977 to eradicate smallpox.

<b>Toxins</b>	Botulinum toxin ● Causes botulism ● Produced by <i>Clostridium botulinum</i> bacterium	<i>Time to effect:</i> 24 to 36 hours  <i>Length of illness:</i> 24 to 72 hours  65% mortality rate	.001 microgram per kilogram of body weight	Weakness, dizziness, dry throat and mouth, blurred vision, progressive weakness of muscles  Interruption of neurotransmission leading to paralysis  Abrupt respiratory failure may result in death	Treatable with antitoxin, if administered early  Vaccine available
	Ricin ● Derived from castor beans	<i>Time to effect:</i> few hours  <i>Length of illness:</i> 3 days  High mortality rate	3 to 5 micrograms per kilogram of body weight	Rapid onset of weakness, fever, cough, fluid build-up in lungs, respiratory distress	No antitoxin or vaccine available

Source: Adapted from the chart “Characteristics and Symptoms of Some Anti-Human Biological Agents” at the Henry Stimson Center. Accessed on 17 September 2004  
<http://www.stimson.org/cbw/?sn=cb2001112953#human>.

The Centers for Disease Control further classifies the Select Agents into three categories. These three categories enable government officials, scientists, public health workers and first responders to quickly assess the risk of specified select agents. At Category A, high-priority agents include organisms that pose a risk to national security because they:

- can be easily disseminated or transmitted from person to person;
- result in high mortality rates and have the potential for major public health impact;
- might cause public panic and social disruption
- require special action for public health preparedness.

At Category B, the second highest priority agents include those that:

- are moderately easy to disseminate;
- result in moderate morbidity rates and low mortality rates
- require specific enhancements of CDC's diagnostic capacity and enhanced disease surveillance

Finally at Category C, the third highest priority agents include emerging pathogens that could be engineered for mass dissemination in the future because of:

- availability;
- ease of production and dissemination; and
- potential for high morbidity and mortality rates and major health

As shown in Table 2, the categories contain agents that range from toxins to viruses and many are very well known threats to public health and national security.

Table 2. CDC Categorization of Select Agents

**Category A**

- » [Anthrax](#) (*Bacillus anthracis*)
- » [Botulism](#) (*Clostridium botulinum* toxin)
- » [Plague](#) (*Yersinia pestis*)
- » [Smallpox](#) (variola major)
- » [Tularemia](#) (*Francisella tularensis*)
- » [Viral hemorrhagic fevers](#) (filoviruses [e.g., Ebola, Marburg] and arenaviruses [e.g., Lassa, Machupo])

**Category B**

- » [Brucellosis](#) (*Brucella* species)
- » Epsilon toxin of *Clostridium perfringens*
- » [Food safety threats](#) (e.g., *Salmonella* species, *Escherichia coli* O157:H7, *Shigella*)
- » Glanders (*Burkholderia mallei*)
- » Melioidosis (*Burkholderia pseudomallei*)

- » Psittacosis (*Chlamydia psittaci*)
- » [Q fever](#) (*Coxiella burnetii*)
- » [Ricin toxin](#) from *Ricinus communis* (castor beans)
- » Staphylococcal enterotoxin B
- » Typhus fever (*Rickettsia prowazekii*)
- » Viral encephalitis (alphaviruses [e.g., Venezuelan equine encephalitis, eastern equine encephalitis, western equine encephalitis])
- » Water safety threats (e.g., *Vibrio cholerae*, *Cryptosporidium parvum*)

**Category C)**

- » Emerging infectious diseases such as Nipah virus and hantavirus

Source: Centers for Disease Control

<http://www.bt.cdc.gov/agent/agentlist-category.asp>.

While such categorization aids in understanding and is generally defensible, a caveat should be made that this categorization is not comprehensive and the absence of an agent placement in Category A does not diminish its potential danger to the nation as a bio-weapon.

The list making in both 1997 and 2002 were major achievements by the federal government, indicating responsiveness to the desires of the Congress and the ability to successfully partner with several disparate groups to craft robust and flexible regulations in an area that has direct and enduring impact on the national security and modern biomedical research. We now turn from the dynamics of the list making exercise to a detailed discussion of the statutory law and administrative regulations that are foundational to the biosecurity effort within the United States.

### III. STATUTORY LAW AND ADMINISTRATIVE REGULATIONS

In this chapter the legal and administrative context in which regulation of biological agents and toxins occurs is examined in some detail. The efforts to regulate select biological agents and toxins within American biomedical research takes place within a context that has been greatly influenced by western history as well as international and statutory laws. While we face continuing threats from chemical, radiological, incendiary, and explosive weapons of mass destruction, this thesis focuses on biological weapons and their precursors for these substances are available within the university laboratory and are the most economical of all potential weapons of mass destruction to construct. The chapter opens with a short history of the use of biological weapons including a vignette of the physical effects of exposure to anthrax, followed by a review of the applicable international law, statutory law and federal regulations. To fully understand the importance of select biological agents and toxins as a policy issue, it is crucial that the intricacies of the applicable law and federal regulations be outlined.

#### A. HISTORICAL BACKGROUND TO THE ISSUE

Biological weapons of war are reported to be as old as war itself. In a recent book on the history of early man, Greek Fire, Poison Arrows & Scorpion Bombs: Biological and Chemical Warfare in the Ancient World, the folklorist Adrienne Mayor<sup>39</sup> makes the innovative argument that bacteria, viruses and toxins have been deployed on the battlefield stretching back to the earliest history of western man and are referenced in classical myths of western civilization. However, in a generally more accepted historical

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<sup>39</sup> In this work Mayor traces back the earliest reference to biological warfare to a legend of poisoned arrows in which the Greek God Hercules had a quiver of missiles tipped with the hydra's venom (probably snake venom). Greek Fire, Poison Arrows & Scorpion Bombs: Biological and Chemical Warfare in the Ancient World (2003). Van Wees notes in his cogent book review "Germs of Truth" American Scientist, May-June 2004. Accessed on 15 June 2004 at <http://www.americanscientist.org/template/BookReviewTypeDetail/assetid/32687>, that her central message that "a warning that biological and chemical weapons, once created, are almost impossible to contain and are liable to backfire against those who design and deploy them." is unassailable, but her research methods are non-standard and her conclusions are often broad.



chronology of biological warfare in the west<sup>40</sup>, three events are notable. First, in 1346 at the siege of Kaffa (now known as Feodosia, Ukraine) bodies of Tartar soldiers who succumbed to the plague were thrown over the city's walls. It is hypothesized, and widely accepted, that this was the precipitating event for the infamous plague pandemic that spread over the entire continent of Europe from Genoa via the Mediterranean seaports in the fourteenth century.

Second, in 1710 during a war between Russia and Sweden, Russian Imperial troops used the cadavers of plague victims to provoke an epidemic among their Swedish enemies. The third notable event occurred in North America in 1767 during the French and Indian War, 1754-1767. During that colonial war both English and French field armies relied heavily on the support of Native American allies. The English attacked Fort Carillon twice and were repulsed each time with heavy losses. Sir Jeffery Amherst, an English general, then surreptitiously provided the Native Americans allied with the French forces with blankets contaminated with smallpox virus. The resulting epidemic decimated the Native American population. Shortly thereafter, General Amherst successfully attacked Fort Carillon and renamed it Fort Ticonderoga. By deduction, the small pox epidemic played a significant role in the victory.

Even as late as World War One armies have attempted to utilize disease as a force multiplier in battle although the recorded German attempts to infect allied war horses with glanders during that war were deemed complete failures. In the 1920s the civilized world, recoiling from the terrors and horrors experienced in the First World War, sought to regulate and control the proliferation of chemical and biological weapons. A Geneva Protocol sought to regulate both chemical and biological agents in warfare.

However, the actual efficacy of the Protocol was seriously suspect. This protocol had no discernible impact on the Japanese Empire as it pursued the use of biological weapons against the people of China in the 1930s to 1940s. The infamous Dr. Shiro Ishii, a Japanese army surgeon affiliated with Japanese Army Units 731 and 100,

<sup>40</sup> Several sources agree upon these pivotal events in western biological warfare. See "The United States Army Medical Research Institute for Infectious Diseases' Short History of Biowarfare." Accessed on 15 June 2004 <http://www.au.af.mil/au/awc/awcgate/usamriid/bw-hist.htm>. and M. Wheelis (2002). "A Short History of Biological Warfare and Weapons" in M. Chevier et. al. (2002) The Implementation of Legally Binding Measures to Strengthen the Biological and Toxin Weapons Convention. Amsterdam: ISO Press.

conducted field tests of both offensive and defensive biological weapons on military and civilian targets from 1939-1942 in Manchuria, China. It is estimated that “. . . more than 10,000 people were killed or allowed to die after deliberate infection.”<sup>41</sup>

As Table 3 shows, in the post-war period, the major powers continued biological weapons research as an element of their national defense.

Table 3. Declared and Suspected Biological Weapons by States

<b>Declared Current Possession</b>	<b>Suspected Possession</b>	<b>Suspected Attempted Acquisition</b>	<b>Abandoned Biological Warfare Program</b>
None	China	Libya	Canada
	Egypt		France
	Iran		South Africa
	Iraq		United Kingdom
	Israel		United States
	North Korea		
	Russia		
	South Korea		
	Syria		
	Taiwan		
	Vietnam		

Source: Falkenrath, Newman and Thayer (2001). *America's Achilles' Heel*. Cambridge: MIT Press.

These powers included the United States who fielded major research and weapons programs centered primarily at Fort Detrick, Maryland. President Nixon ordered the cessation of such weapons programs in 1969. However, the Union of Soviet Socialist Republics did not relent in their research and weapons acquisition efforts. The former Soviet Union was reported to have intentionally flaunted the provisions of relevant international treaties, especially during the period 1972 to 1992. Biopreparat, the Soviet state pharmaceutical agency, actively engaged in significant research and production of weaponized biological agents. Professor Ken Alibek, formerly known as Colonel Kanatjan Alibekov, has fully reported on the scope of these treaty transgressions during

<sup>41</sup> M. Wheelis (2002). p. 4.

his intelligence debriefings, television appearances and subsequent publications as a scholar. Block assessed the impact of those activities:

Alibek supervised as many as 32,000 people (out of 60,000 in the program) at nearly 40 facilities spread throughout the Soviet Union, effectively a toxic archipelago. Here the Soviets worked not only on perfecting 'conventional' biological weapons based on anthrax, glanders and plague, but also on weaponizing deadly (and highly contagious) viruses, such as smallpox, Marburg and Ebola. In contrast to American bioweapons effort, the Soviets considered the best bioweapons agents to be those for which there are no prevention and no cure . . . the current economic and political climate in the former Soviet Union raises the disturbing likelihood that their bioweapons experts will be forced to seek employment elsewhere, resulting in unwelcome proliferation.<sup>42</sup>

It is now widely reported that other nations may field these biological weapons of war for they have declared or have been suspected of the possession of biological weapons.

## **B. A MEDICAL EXAMPLE**

To understand the importance of the work in controlling these biological weapons of war, an example of the physical consequences to an exposure to *Bacillus anthrax* is illustrative. Anthrax, a widely publicized biological agent, is but one of the many biological select agents covered by the federal law governing select biological agents and toxins. In a recent work of popular fiction, anthrax was portrayed as follows:

Anthrax bacteria are as murderous as South American flesh-eating ants. An army of ants, traveling in the millions, can decimate an immobilized individual by devouring his flesh layer by layer. Death is gradual and agonizing. Anthrax bacilli do to the body from within what ants do from without. They attack everywhere, shutting down and destroying the body's functions from top to bottom. The organisms continue to multiply and swarm until there is nothing left to feed on. In 2 or 3 days a few thousand bacilli may become trillions. At the time of death, as much as 30 percent of a person's blood weight may be live bacilli. A microscopic cross section of a blood vessel looks as though it is teeming with worms.<sup>43</sup>

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<sup>42</sup> S. Block (2001). "The Growing Threat of Biological Weapons". The American Scientist. Vol. 89, Number 1.

<sup>43</sup> L. Cole (2003) The Anthrax Letters: A Medical Detective Story. Washington: John Henry Press. Page vii.

Anthrax, unlike so many other biological weapons of war, can be successfully treated if diagnosed early. However, the public response (panic) to such a weapon's use, or reported use, can far exceed the actual risk that such an agent poses to the public health. The collapse of a modern society's medical infrastructure, on both a local and regional basis, becomes a real possibility when encountering such widespread public panic.<sup>44</sup> An illustrative example of such a threat to medical infrastructures occurred in June, 2001, in Akron, Ohio, where a suspected meningitis case caused the "worried well" to overwhelm the local medical system. This fear of disease at a mass scale contributes to what is referred to as Mass Sociogenic Illness (MSI).

In an intriguing literature review<sup>45</sup>, Bartholomew and Wessley maintain that Mass Sociogenic Illness (MSI) is underreported in the literature in English and that MSI mirrors prominent social concerns, changing in relation to context and circumstance. Prior to 1900, MSI reports were dominated by episodes of motor symptoms marked by dissociation, histrionics, and psychomotor agitation. A limited number of twentieth-century reports feature anxiety symptoms that are triggered by exposure to an anxiety-generating agent such as an innocuous odor or food poisoning rumors. From the early 1980s until present there has been an increasing presence of chemical and biological terrorism themes within the study of MSI.

## **C: THE TREATIES**

The League of Nations convened a Conference on the Control of the International Trade in Arms, Munitions, and War Materials in 1924. That generally ineffective conference did achieve an enduring contribution to world peace, for the conference crafted a chemical agent of war treaty which included provisions addressing bacteriological or biological methods of war. The 1925 Geneva Protocol, properly known as the Protocol Prohibiting the Use in War of Asphyxiating, Poisonous, or Other Gases,

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<sup>44</sup> This case was incorporated into the prepared testimony of P. Quinlist, MD, MPH in her testimony of June 21, 2001 on Combating Terrorism: Federal Response to Biological Weapons Attack before the Committee on Government Reform of the US House of Representatives. Accessed on 13 August 2004 at <http://www.bioterrorism.slu.edu/bt/official/congress/quinlist072301.pdf>.

<sup>45</sup> R.E. Bartholomew and S. Wessley (2002) "Protean Nature of Mass Sociogenic Illness: From Possessed Nuns to Chemical and Biological Terrorism Fears" *British Journal of Psychiatry* 180: 300-306.

and of Bacteriological Methods of Warfare is now accepted as international customary law. More than forty nation-states were involved in crafting the treaty that came into force in 1928. The Protocol states:

Whereas the use in war of asphyxiating, poisonous or other gases, and of all analogous liquids, materials or devices, has been justly condemned by the general opinion of the civilized world; and Whereas the prohibition of such use has been declared in Treaties to which the majority of Powers of the world are Parties; and To the end that this prohibition shall be universally accepted as a part of International Law, binding alike the conscience and the practice of nations;

DECLARE:

That the High Contracting Parties, so far as they are not already Parties to Treaties prohibiting such use, accept this prohibition, agree to extend this prohibition to the use of bacteriological methods of warfare and agree to be bound as between themselves according to the terms of this declaration.<sup>46</sup>

The other major international treaty relevant to the issue of biological weapons is the 1972 Biological and Toxin Weapons Convention (BTWC). President Nixon declared in 1969 that the United States would end its biological weapons program. That prompted an international movement that culminated in the 1972 Biological and Toxin Weapons Convention. This convention, with 18 signatory nations and 146 state parties, provided significantly improved detailed guidance as compared to the 1925 Geneva Convention. The convention's signatories and interested parties now meet every five years at review conferences to discuss compliance and consider amending the base treaty. Since its initial adoption in Washington, London, and Moscow in 1972, the treaty signatories have pledged to realize the goals outlined in Article I:

Each State Party to this Convention undertakes never in any circumstances to develop, produce, stockpile or otherwise acquire or retain:

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<sup>46</sup> Protocol for the Prohibition of the Use in War of Asphyxiating, Poisonous or Other Gases, and of Bacteriological Methods of War (June 17, 1925). Accessed 16 June 2004 <http://64.177.207.201/cbw/resources/index.htm>.

(1) Microbial or other biological agents, or toxins whatever their origin or method of production, of types and in quantities that have no justification for prophylactic, protective or other peaceful purposes;

(2) Weapons, equipment or means of delivery designed to use such agents or toxins for hostile purposes or in armed conflict.

Supplementing the ongoing work of the BTWC has been the Australia Group.<sup>47</sup> This voluntary group of 30 nations began their work in 1984 as a result of chemical weapons use in the Iran-Iraq war. The Australia Group seeks common export controls for chemical and biological weapon nonproliferation. The group occasionally issues warnings seeking to alert the international community of chemical and biological weapon proliferation, shares warning lists of suspicious transactions, and alerts others of the risk of inadvertently aiding in biological weapons (BW) proliferation. It is critical to note that the Australia Group has no charter or constitution and its work is achieved through consensus of the participant members. While without formal status, the work of this non-governmental organization has been recognized<sup>48</sup> as a valuable international resource and an authority in the ongoing work to prevent biological weapon proliferation.

The United States has sought to achieve ongoing compliance with treaty obligations as well as progressive control of biological weapons through a series of statutory laws, executive activities, and federal regulations. President Nixon announced on November 25, 1969, the unilateral and unconditional renouncement of biological weapons. As President he terminated the biological warfare program and directed the Department of Defense to destroy all stockpiles of biological agents. Yet, a loophole in that declaration required a clarification and specific termination of the toxin agent weapon research program and directed the Defense Department's destruction of toxin agents and weapon stockpiles, with the provision that "The United States will confine its

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<sup>47</sup> The Australia Group has been actively engaged in the informal monitoring of biological and chemical weapons and is considered an interested party and active Non Governmental Organization in the global non-proliferation effort, accessed on 10 July 2004 <http://www.australiagroup.net/>.

<sup>48</sup> The Australia Group has been recognized by groups as diverse as the United Nations, the Carnegie Endowment for International Peace and The Arms Control Association. An informative overview of their work is found at a Fact Sheet published by the Arms Control Association. Accessed 13 December 2004 at <http://www.armscontrol.org/factsheets/australiagroup.asp>.

military programs for toxins, whether produced by bacteriological or any other biological method or by chemical synthesis, to research for defensive purposes only, such as to improve techniques of immunization and medical therapy.”<sup>49</sup> The United States completed the destruction of all stockpiles and weapons during the period May 1971 to May 1972.

#### **D. AMERICAN STATUTORY LAW**

The Anti-Terrorism and Effective Death Penalty Act (AEDPA), Public Law 104-132 was adopted on April 24, 1996, and criminalized the threatened use of a biological weapon. Previously only the attempted use of such a weapon constituted a crime. AEDPA directs the Secretary of Health and Human Services to “establish and maintain a list of each biological agent that has the potential to pose a severe threat to public health and safety.”<sup>50</sup> The Secretary was provided with criteria for that task to include:

- The effect on human health of exposure to the agent;
- the degree of contagiousness of the agent and the methods by which the agent is transferred to humans;
- the availability and effectiveness of immunizations to prevent and treatments for any illness resulting from infection by the agent; and
- any other criteria that the Secretary considers appropriate; and
- consult with scientific experts representing appropriate professional groups.

The General Accounting Office in November 2002 presented a clear summary of the AEDPA objectives as follows:

- provide safeguards to prevent access to such agents for use in domestic or international terrorism or for other criminal purposes;
- provide for the establishment and enforcement of safety procedures for the transfer of the listed biological agents, including measures to ensure

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<sup>49</sup> Although the extant literature refers to an Executive Order, this is a factual error for there is no February 14, 1970, Executive Order by President Richard Nixon on Biological Warfare. The directive to renounce biological warfare was found within National Security Decision Memorandum (NSDM) 35. That declassified NSDM is found at the National Security Archive at George Washington University, accessed on 8 August 2004 at <http://www.gwu.edu/~nsarchiv/NSAEBB/NSAEBB58/#doc8>.

<sup>50</sup> Anti-Terrorism and Effective Death Penalty Act, Public Law 104-132, Enhanced Penalties and Control of Biological Agents, Section 511 (d) (1) A, 110 STAT. 1284.

- proper training and appropriate skills to handle agents and proper laboratory facilities to contain and dispose of agents;
- establish and maintain a list of biological agents that have the potential to pose a severe threat to public health and safety; and
- provide for the establishment of procedures to protect the public safety in the event of an actual or potential illegal transfer of a biological agent.<sup>51</sup>

The Uniting and Strengthening America by Providing Appropriate Tools Required to Intercept and Obstruct Terrorism (USA PATRIOT Act), Public Law 107-56 was adopted in response to the September 11, 2001, attacks on the United States. That law includes sections that strengthened the capabilities of intelligence agencies to detect terrorist activities and restricted foreign access to potentially dangerous materials and knowledge. At section 175b, the term *select agent* is clarified as to not include any biological agent in its naturally occurring environment if the biological agent or toxin has not been cultivated, collected or otherwise extracted from its natural source. At section 416, foreign student access is clarified and regulated, and at section 817 the biological weapons statute is expanded to include the criminalization of the act of possession of a biological agent, toxin, or delivery system if not reasonably justified by a prophylactic, protective, bona fide research or other peaceful purpose.

The Public Health Security and Bioterrorism Preparedness and Response Act of 2002 (BPARA), Public Law 107-188 was adopted on June 12, 2002. This law modified the Secretary of Health and Human Services' scope of responsibilities to include the review and publication of the list of select agents and toxins biennially, or more often as needed. This legislation and its subsequent federal regulations address specifically the physical security practices at university biomedical research facilities using select agents.

#### **E. FEDERAL ADMINISTRATIVE REGULATIONS**

Within the American system, statutory objectives and goals are translated into action through the bureaucratic construction, adoption, and implementation of federal regulations. Four specific sections within the Code of Federal Regulations (CFR) structure that regulatory implementation of these statutory laws. 42 CFR 73 Department of Health and Human Services specifically addresses the possession, use and transfer of

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<sup>51</sup> General Accounting Office (GAO-03-315R). November 2002.



select agents and toxins, while 9 CFR 121 and 7 CFR 331 Department of Agriculture address the possession, use, and transfer of biological agents within agriculture. Finally, 49 CFR 171-180 Department of Transportation specifies the shipping and packaging practices to be used with these select agents and toxins. Within these voluminous federal regulations are the mandated reports and activities levied upon affected businesses, institutions, and individual scientists. Included within the regulations are provisions for inspections, both announced and unannounced, and thorough self-reports of stolen or missing biological material.

The initial regulations governing the Select Agent Program took effect on April 15, 1997. Those regulations include six components:

1. Preparation of a list of select agents that pose a severe threat to public health and safety.
2. Registration of facilities prior to the domestic transfer of select agents.
3. Construction of a process to document successful transfer of agents.
4. Implementation of audit, quality control and accountability mechanisms.
5. Designation of select agent disposal requirements.
6. Specification of research and clinical exceptions to the regulations.

The Department of Health and Human Services (HHS), Centers for Disease Control (CDC) designated primary responsibility for the Select Agent Program to the Office of External Activities within the Office of Health and Safety. However, auditors from the General Accounting Office have discovered serious deficiencies in program administration in a study that reviewed program activities between November 2001 and September 2002. Specifically the GAO found that CDC and HHS could strengthen the inspection and approval of facilities, the monitoring the shipment and transfer of select agents, and the accuracy of the CDC databases of registered facilities and select agent transfers. Their report of November 2002 noted “CDC can improve its management of the Select Agent Program to reduce the likelihood of unauthorized access to biological agents. . . To better position CDC to reasonably ensure that appropriate security and safety precautions are in place for select agents, we made recommendations aimed at establishing proper internal control...”<sup>52</sup>

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<sup>52</sup> General Accounting Office. (2002) Homeland Security: CDC’s Oversight of the Select Agent Program. GAO -03-315R.

The Public Health Security and Bioterrorism Preparedness and Response Act of 2002 (BPARA) significantly expanded the scope and responsibilities of the Select Agent Program. The General Accounting Office in November 2002 (GAO-03-315R) included a clear summary of the impact of BPARA which:

- requires all facilities possessing select agents to register with the Secretary of HHS, not just those facilities sending or receiving select agents;
- restricts access to biological agents and toxins by persons who do not have a legitimate need and who are considered a risk by federal law enforcement and intelligence officials;
- requires transfer registrations to include information regarding the characterization of agents and toxins to facilitate their identification, including their source;
- requires the creation of a national database with information on all facilities and persons possessing, using, or transferring select agents;
- directs the Secretary of HHS to review and publish the select agent list biennially, making revisions as appropriate to protect the public; and
- requires the Secretary to impose more detailed and different levels of security for different select agents based on their assessed level of threat to the public.

The challenge is clear. If the CDC failed to successfully fulfill the regulatory tasks outlined in the 1996 legislation, as noted in the GAO report, then the expanded tasking found in these more recent regulations may well prove to be overwhelming.<sup>53</sup> The CDC has acknowledged its Select Agent Program deficiencies<sup>54</sup> and has set a very demanding compliance schedule for the estimated 11,000 regulated institutions under the scope of the 2002 law.

## **F. THE REGULATORY PROCESS**

The regulation of human behavior has been the quest of government since the very earliest periods of organized behavior. While the subject and nature of the

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<sup>53</sup> General Accounting Office. (2002) Homeland Security: CDC's Oversight of the Select Agent Program. GAO -03-315R. p.5. This report includes the telling statement that the Select Agent Program staff estimates that BPARA could result in “. . . a tenfold expansion of their responsibilities because many more facilities possess select agents than those registered to transfer them so far.”

<sup>54</sup> Ibid, p.3. The GAO report which was transmitted to HHS Secretary Thompson on November 22, 2002, that “In discussing these recommendations with CDC officials, they concurred and noted improvements planned or already in progress.”

regulation may be intrinsically political, the actual practice of regulation within the United States is often an attempt to be free of political overtones.

In the national context, the first federal rule-making agency was the Interstate Commerce Commission established in 1887. At first the growth of federal regulatory activity was slow, with significant focus on preventing monopoly abuse.<sup>55</sup> The Anti-Trust Division of the Department of Justice was not established until 1903, and was followed over the next three decades with slow expansion of regulatory bodies, Federal Reserve System (1913), Federal Trade Commission (1914) and the Federal Power Commission (1920).

With the onset of the Great Depression, the federal government's regulatory activities bloomed. A plethora of "alphabet agencies" were formed to regulate specific areas within and activities of the economy, e.g. Federal Maritime Commission. The enduring and real change of this era of regulation was the sizable expansion of the established governmental agencies' regulatory powers. For instance the Interstate Commerce Commission regulatory authority expanded in the 1930s from a primary focus on railroad regulation to include the regulation of intercity bus and the trucking industries.

In the postwar era the very nature of federal regulation changed profoundly. Rather than focusing on a single industry or family of industries, the new regulatory agencies focused on specific problems rather than industries. These agencies' charters enabled their regulation of many varied industries and enterprises, e.g. the Environmental Protection Agency.

The underlying concept in governmental regulation is the determination by the people, via congressional statutory authority and/or executive interest, to intervene in the private or public sectors to enhance the safety or security of the people as a whole. Such regulatory activity can take one of several forms, largely dependent upon the nature of the problem, the skills of the regulators, and the organizational traditions of the regulatory agency as well as a cornucopia of external pressures ranging from politically

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<sup>55</sup> A superb introduction to the federal regulatory process is found in chapter four of C.F. Bonser, et al (2000) American Public Policy Problems – Second Edition. Upper Saddle River: Prentice Hall.

inclined interest groups to investigative media attention. Sparrow<sup>56</sup> outlines a dichotomy of regulatory styles; one consists of formal precise rules coupled with an adversarial or punitive relationship with the group being regulated while the other is softer in approach, more results oriented, with less attachment to formal rules and a distinct bias towards responsiveness using tools of negotiation, dialogue, and tradeoffs with the group being regulated. The regulatory cycle is found to follow certain distinct patterns, identified as “the pendulum of regulation”, a cycle in which regulations and regulatory practices follow the organizational maturation of the groups being subjected to such regulation.

In the 1970s and 1980s scholars and practitioners sought to break free of this dichotomy. Again, according to Sparrow, “Developing regulatory versatility, and learning to manage it, appears a more constructive notion than continuing to merely push or pull the regulatory pendulum.”<sup>57</sup> In this new era, a variety of tools was applied to the regulatory craft as alternatives to mere rule enforcement. Among them were:

- Tripartism: An approach which breaks the dyad between regulators and regulated by involving various third parties with practical interest in the regulated activity and the regulatory agencies.<sup>58</sup>
- Information Strategies: An approach which communicates the risks and risk factors to affected actors and others to encourage socially responsible behavior.<sup>59</sup>
- Self-Regulation: An approach in which regulated activities are deemed trustworthy to conduct self-inspections and audits subject to external verification.<sup>60</sup>

The regulation of the biological select agent and toxin program during the period 1997-2002 is especially interesting. There was no singular regulatory approach used during this period, but rather the regulatory scheme was an effective admixture of tripartism, self-regulation and a focused information strategy. There are several explanations for this success. First, a non-traditional enforcement agency, CDC, was

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<sup>56</sup> M. Sparrow, The Regulatory Craft. (2000). Washington: Brookings Institute, pp. 34-43.

<sup>57</sup> M. Sparrow, The Regulatory Craft. (2000). Washington: Brookings Institute, p. 39.

<sup>58</sup> I. Ayres and J. Braithwaite, Responsive Regulation: Transcending the Deregulation Debate (1992) New York: Oxford University Press, p. 20.

<sup>59</sup> M. O’Hare, “Informational Strategies as Regulatory Surrogates” in Eugene Bardach (1982) Social Regulation: Strategies for Reform San Francisco: Institute for Contemporary Studies, p. 221.

<sup>60</sup> The United States Environmental Protection Agency has piloted a number of field tests involving self-regulation.

unexpectedly tasked with regulation of both public and private entities involved in research involving select biological agents and toxins; with no history as an enforcement agency, CDC was not confined in the regulatory strategies it chose to use. Second, the regulatory scheme that was used with select agents was a visible attempt to blend the strengths of several regulatory strategies. The applicable regulations, 42 CFR 73, included both extremely precise and detailed rules (i.e., an extensive list of select agents and microscopic quantities subject to regulation) as well as significant elements of self-regulation (the biosecurity section includes self-assessment and locally prepared compliance reports).

**G. FAST TRACK IMPLEMENTATION OF REGULATIONS**

The federal regulations, 42 CFR 73, are built upon the authority of the BPARA and set a very vigorous and demanding compliance schedule for the both the individual scientists and the public, private and not for profit organizations at which they worked, as described in Table 4.

Table 4. Time Line for Implementation of Provisions of 42 CFR 73

February 7, 2003	March 12, 2003	April 12, 2003	June 12, 2003	September 12, 2003	November 12, 2003
Rules Effective	Application Due	DOJ Review	DOJ Review/ Security Plan	Security/Training Plan	Full Compliance
<i>Publication of 42 CFR 73.1-73.21</i>	<i>Certifies compliance with all effective sections</i>	<i>Applications for Foreign Workers/Students submitted to DOJ</i>	<i>DOJ Review completed and Security Plan is developed</i>	<i>Security Plan is implemented and staff training on security provisions initiated.</i>	<i>Entity must be in full compliance with all provisions of 42 CFR 73</i>

Source: Federal Register, Vol. 240, No.67/Friday, December 13, 2002/Rules and Regulations, p. 76896.

The term “fast track” can be better understood by placing it into the current regulatory context. Recently, a national newspaper outlined a typical timeline for the adoption of a rule and found that adoption usually takes a year, but one rule in ten takes

more than four years for adoption. Typically regulations require six steps from passage of legislation until adoption of the final rule (see Table 5).

Table 5. Six Stages of Federal Regulation Formulation and Adoption

Process Stage	Activity	Typical Time Period
Stage 1	Congress passes legislation that requires a new rule or rule change; or a federal Judge orders revision to a rule by lawsuit; or a federal agency initiates routine rule revisions.	Small or routine rules can be written quickly, while large complex rules can take years.
Stage 2	Proposed Rules are published in the Federal Register; important rules require prior approval of the Office of Management and Budget (OMB).	Proposed rules, once approved by OMB as required, are immediately published to the Federal Register.
Stage 3	Agencies collect comments from the public, interest groups, other government agencies and members of Congress.	The comment period typically lasts 30-90 days. Redrafting of proposed rules may take years.
Stage 4	Agencies publish final regulation in the Federal Register; agencies may be required to obtain approval by OMB.	Final regulations take effect upon publication or after a specified waiting period designated within the regulation.
Stage 5	Agencies notify the Congress of major regulations. Congress may exercise authority to overturn a rule with a resolution of disapproval.	Congress has sixty days to overturn a regulation via resolution of disapproval.
Stage 6	A rule is implemented.	To overturn a rule, the process begins again at Stage 1.

Source: Goldstein and Cohen (2004) "The Rules That Apply" The Washington Post National Weekly Edition, August 23-29, 2004, Page 6.

As might be anticipated, the groups, scientists, and scholars subject to this regulation were far from unanimous in their support of these regulations. The biomedical academic community is robustly diverse and far from a unified whole. The community

differs along many lines including academic discipline, physical research capabilities and priorities, as well as the perception of the threat posed by biological agents in terrorism. On the issue of bioterrorism, Steven Block, a prominent biologist and physicist on faculty at Stanford University wrote in 2001:

The community of biologists in the United States has maintained a kind of hand wringing silence on the ethics of creating bioweapons, a reluctance to talk about it with the public, even a disbelief that it's happening. Biological weapons are a disgrace to biology. The time has come for top biologists to assert their leadership and speak out, to take responsibility on behalf of their profession for the existence of these weapons and the means of protecting the populations against them, just as leading physicists did a generation ago when nuclear weapons came along. Moral pressure costs nothing and can help; silence is unacceptable now.<sup>61</sup>

In contrast to that view, Richard H. Ebright, a molecular biologist on faculty at Rutgers's Waksman Institute noted in a recent interview:

The labs [Biosafety Level 4 laboratories] are a perilous overreaction to an inflated threat and will do more harm than good. Although the threat of biological warfare is real, the weapons used by terrorists are unlikely to be the next-generation agents that the high-security labs are intended to study. . .by increasing the availability of such pathogens...the labs will bring that threat to fruition...It's arming our opponents. . .It's [the acquisition of Biosafety Level 4 laboratories] the easiest way to bring \$100 million to your university.<sup>62</sup>

The biomedical academic community was not actively writing about bioterrorism to any significant extent prior to 1997. Saint Louis University's Center for the Study of Bioterrorism<sup>63</sup> has prepared select bibliographies on the scholarly work in the field of bioterrorism. Those bibliographies clearly indicate the trends in academic interest in biological weapons. During the period of 1980-1989, 92 articles on the subject were cited with that number rising to 109 for the 1990-1997 period. By dramatic contrast in 1998 alone 67 articles were cited with the number rising to 131 in 1999, 110 in 2000, and 108 in 2001 respectively.

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<sup>61</sup> Block, p. 11.

<sup>62</sup> W. Broad. (2004) "In a Lonely Stand, A Scientist Takes On National Security Dogma" The New York Times. June 29, 2004. D 1.

<sup>63</sup> The Saint Louis University's Center is an internationally recognized research source on this arcane, but important, aspect of national defense. Their work on compiling bibliographical resources was accessed on 10 August 2003 at <http://www.slu.edu/colleges/sph/csbei/bioterrorism/bibliography.htm>.

With the onset of demanding federal regulations both in 1996 and in 2002, the academic community was stirred to vigorous response to the proposed federal regulations. The Secretary of Health and Human Services, Donna Shalala, consulted with professional associations when she prepared the initial list of select agents in 1996-1997 as directed by the AEDPA. List making was very controversial, even with the inclusion of the recognized professional associations in the process.

A draft list generated nearly 70 letters, and the CDC responded by dropping agents such as *Western equine encephalitis virus* and a bacterium called *Chlamydia psittaci* and adding *equine morbillivirous* and a fungus called *Coccidioides immitis*.<sup>64</sup>

Active participation in relevant rule-making and federal regulation by affected parties is not uncommon, but the vigor and the total number of responses from the academic community and related professional organizations to the select biological agents and toxins list certainly indicates the gravity of the issue of such regulation of science.

The enforcement of the biosecurity regulations, including criminal sanctions was not long in coming. In July 2002, a University of Connecticut graduate student, Tomas Foral, was the first person charged under the USA PATRIOT Act with possessing a biological agent without a “reasonably justified purpose”<sup>65</sup>. Foral recovered five vials of anthrax (wet form) during the inventory process, yet instead of autoclaving all the vials as instructed, Foral retained two vials of anthrax in his freezer in the university’s pathobiology laboratory. Federal authorities received an anonymous tip from a student but delayed their investigation until after the inhalational anthrax death of an elderly Connecticut woman in November 2001<sup>66</sup>. Authorities found the marked vials in a pathobiology building with broken door locks, stored within an unattended freezer equipped with a lock but the key left in the lock.

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<sup>64</sup> M. Enserink and D. Malakoff (2001). “Congress Weighs Select Agent Update.” Science. November 16, 2001.

<sup>65</sup> D. Altimari. (2002). “Student Who Kept Anthrax Charged”. Hartford Courant. July, 23, 2002. Accessed on 24 December 2004 at <http://www.ctnow.com/about/hc-archives.htmlstory>. and <http://www.ph.ucla.edu/epi/bioter/studentkeptanthrax.html>.

<sup>66</sup>University of California at Los Angeles, Department of Epidemiology, School of Public Health. (2001). American Anthrax Outbreak of 2001, Case 23. Accessed on 24 December 2004 at [http://www.ph.ucla.edu/epi/bioter/detect/antdetect\\_case23.html](http://www.ph.ucla.edu/epi/bioter/detect/antdetect_case23.html).



Foral accepted pre-trial diversion, for the federal Grand Jury failed to issue an indictment to the US Attorney. On November 20, 2002, Foral was placed on pre-trial diversion and received six months probation and 96 hours of community service. As the Foral case indicates, microbiologists were moving to the forefront of interest to federal law enforcement authorities, as they sought assistance with the investigation of the Anthrax attacks of the autumn of 2001. Ronald Atlas, then president of the American Society of Microbiology, remarked that “The scientific community has been put on notice that we have to watch what we do.”<sup>67</sup>

On December 10, 2002, the CDC posted the Interim Final Rule to comply with the provisions of the BPARA. The proposed rule was eighty-four pages in length and broadened the scope of affected institutions from an initial estimate of 200 to 250 institutions to a revised estimate of 1,653 institutions. A detailed critique of the rule was submitted under the aegis of the Howard Hughes Medical Institute in January 2003 and was more than eleven pages in length. This group of researchers identified primary flaws in the definitions of Responsible Official and Access as well as significant disagreement with the scope, purpose and utility of the required security plans.<sup>68</sup> Professional groups and academic scientists expressed concern in 2002 on several topics.

First, there was significant disagreement about the inclusion of some agents and toxins on the Select Agent List, much of it lingering from the 1997 discussions. “Although such legislation is probably appropriate, the CDC’s ‘watch list’ contains many organisms, such as fungus *Coccidioides immitis*, that are unlikely candidates for biological weapons”<sup>69</sup>. Second, many scientists accused university administrators of overreaction to the anthrax events of the autumn of 2001 and the subsequent gross misapplication of the provisions of the BPARA in 2002. As Mestel wrote:

Biologists understand that times, and laws, have changed. . .the response by university administrators and authorities – who are not, after all,

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<sup>67</sup> R. Mestel. (2002). “In the Lab: Suspicion Spreads”. The Los Angeles Times. August 28, 2002.

<sup>68</sup> CDC. (2003). Public Comments on New Regulation, 03-SAR-013.

<sup>69</sup> J. Fierer and T. Kirkland (2002). “Questioning the CDC’s ‘select agent’ criteria”. Science. January 4, 2002.

microbiologists – have been driven by an inflated fear of the bacterium itself. The reaction...has been far out of proportion to the actual risk...<sup>70</sup>

The cost of compliance with new law and regulations was deemed quite significant by several academic administrators. Malakoff observes:

After 11 September; however, convenience and efficiency gave way to security. Across the country, in hundreds of ways both large and small, US academic researchers are feeling the effects of that catastrophic day on their ability to carry out science . . . eager to plug security gaps, Congress and agency officials have set tight deadlines for complying with the new regulations...the incentive to get it right is very high because universities and researchers who don't comply face stiff, potentially criminal penalties."<sup>71</sup>

That observation was echoed by a near panicked researcher who commented that “No one is sure what will constitute a satisfactory security plan...at many institutions, budget plans for new laboratory security systems run into hundreds of thousands of dollars.” <sup>72</sup>

The Code of Federal Regulations, 42 CFR 73.11 requires that an entity, for example a university with a biomedical research laboratory, “must develop and implement a security plan establishing policy and procedures that ensure the security of areas containing select agents and toxins.” The regulations require that the security plan be the result of the definition of threats, examination of vulnerabilities and the mitigation of those vulnerabilities through a security systems approach. The security plan must address each of these eight points:

- (1) Describe inventory control procedures, minimal education and experience criteria for those individuals with access to select agents or toxins, physical security, and cyber security;
- (2) Contain provisions for routine cleaning, maintenance and repairs; provisions for training personnel in security procedures; provisions for securing the area (e.g. card access, key pads, locks) and protocols for changing access numbers or locks following staff changes;
- (3) Describe procedures for loss or compromise of keys, passwords, combinations, etc;

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<sup>70</sup> Mestel, page 3.

<sup>71</sup> D. Malakoff (2002). “Congress adopts tough rules for labs.” *Science*. May 31, 2002.

<sup>72</sup> P. Reinhart (2003). “New Select Agent Rules Will be Costly for Research Universities”. *NCURA Newsletter*. Vol. XXXV. No.1.

- (4) Contain procedure for reporting suspicious persons or activities, loss or theft of listed agents or toxins, release of listed agents or toxins, or alteration of inventory records;
- (5) Contain provisions for the control of access to containers where listed agents and toxins are stored; and procedures for reporting and removing unauthorized persons;
- (6) Contain provisions for ensuring that all individuals with access, including workers and visitors, understand security requirements and are trained and equipped to follow established procedures;
- (7) Establish procedures for reporting and removing unauthorized persons; and
- (8) Establish procedures for securing the area when individuals approved under section 73.8 are not present (e.g. card access system, key pads locks) including protocols for changing access numbers or locks following staff changes.

The development and implementation of these specific security plans, especially in an age when violation of the regulations can result in both civil fines and criminal prosecution, has presented a true challenge to biomedical research scientists at various universities throughout the nation. The regulations controlling the use and storage of select biological agents and toxins were remarkable on several grounds. First, the communities subject to regulation, primarily microbiology and biomedical research institutions, were far from convinced that regulation was necessary or desirable. Second, in contrast to a standard federal regulation adoption timeline of one to four years, as described earlier at Tables 4 and 5, the select biological agent and toxins regulation was adopted and implemented within nine months. Third, the costs to achieve compliance with the security plans were a seriously underestimated burden to many universities. In the next chapter, the experiences of two separate biomedical research institutions will be examined in order to assess the challenges posed by these new federal regulations and the enduring impact of these regulations on American biomedical research.

## IV. THE CASE STUDIES

This chapter explores local compliance with BPARA as expressed in the regulatory requirements at 42 CFR 73. The analysis focuses on two geographically adjacent, but distinct biomedical research institutions during the period 2001-2003. The two institutions have different purposes and missions, yet both are subject to federal law and regulation, for both are engaged in research using biological select agents and toxins. Federal and state law and regulations pertaining to confidentiality presented a challenge in this research effort. That challenge was overcome, thus allowing the unrestricted distribution of this thesis, by referring to the institutions studied as “the school” and “the hospital” with no other identifying features included. Each institutional experience was explored using a case study format. That format includes a brief overview of each institution’s purpose, the specific instances of select agent use, the initial compliance strategies pursued, and the success of those strategies over the short term. The specific interview questions can be found at Appendix C. This overview will be followed by a comparison of the experiences of the two institutions with a preliminary discussion of the cost effectiveness as well as the marginal costs of meeting the federally mandated biosecurity requirements.

### A. CASE STUDY: THE SCHOOL

The school case study references a state supported medical school located at a graduate public university within a major urban center. That medical school was founded in 1969 and graduated its first class of physicians in 1971. The stated mission of the school is:

The mission of the Medical School is to provide the highest quality education and training of future physicians for the state, in harmony with the state’s diverse population; to conduct the highest caliber of research in the biomedical and health sciences; and to provide exemplary clinical services<sup>73</sup>

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<sup>73</sup> Factbook (2004).

The medical school, hereafter referred to as “the school”, is the major academic component of a state university that also includes a consortium of graduate schools including a School of Health Informatics, School of Nursing, Dental Branch, and Graduate School of Biomedical Sciences. The school has a faculty of 1,215, a student enrollment of 3,417, and receives operational and support services from the university. The school is a recipient of private, state, and federal grants, of which primary federal grants and contracts sources are the National Institutes of Health, US Department of Agriculture, National Science Foundation, and National Aeronautics and Space Administration.<sup>74</sup> The school received total funds in the amount of \$312,533,000 in FY 2004. Within that budget the school received \$57,465,000 (18 %) in grants and contracts. This is a significant increase over previous grant and contract funding for the school. For example in FY 2000 the total funds budget was \$240,000,000 which included \$36,423,000 (15 %) in grants and contracts.

The school hosts a variety of ongoing basic and applied research projects that include select agents and toxins. A current primary investigator whose work on *Bacillus anthracis* has been underway since 1983<sup>75</sup>, has been registered with the CDC since 1997 as a researcher who occasionally exchanged samples of *B. anthracis* with other microbiologists throughout the nation.

The school has an active environmental health and safety component, a functional unit tasked with the mission

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<sup>74</sup> The Factbook (2004) at Budget and Research sections include comparative information both over time (1995-2004) for the institution and with other major biomedical research grant recipients within the state.

<sup>75</sup> A detailed discussion of Koehler’s views and considerations of the general policy implications of recent federal law and biosecurity regulations from a civil libertarian viewpoint can be found at P. Thomas (2003) “From Saviors to Suspects: New Threats to Infectious Disease Research” in R. C. Leone and G. Anrig, Jr., eds. (2003) The War on Our Freedoms: Civil Liberties in an Age of Terrorism. New York: Century Foundation.

“ . . .to work in conjunction with the community and ensure that education, research, and health-care related activities take place in conditions that are optimally safe and healthy for students, faculty, staff, visitors, surrounding community, and general public.”<sup>76</sup>

The school receives direct support from that university unit and the Biological Safety Officer actively partnered with the primary researchers in establishing viable compliance with the federal regulations. It was noted during interviews, that the compliance challenge encountered with conformance to the new federal biosecurity regulations was three fold. First, primary investigators, the lead biomedical research scientists, were “less than enthused” about changing laboratory practices and even the physical environment to comply with the new regulations<sup>77</sup>. Second, the 2002 regulations required the inventory of all biological select agents and toxins as an early deliverable to the regulatory agency (CDC).<sup>78</sup> Third, the design and maintenance of an effective system to track ongoing compliance with these federal regulations was not a simple accomplishment. <sup>79</sup> That system required initial software engineering, data input, data quality control, system redundancy, system or cyber-security, and reliable and valid information acquisition methods within a dynamic and resistive environment of academic research scientists.

The school’s Environmental Health and Safety (EHS) function initially became aware of the proposed 2002 regulations through a variety of sources in the early summer

<sup>76</sup> The school’s EHS support is provided by the university, an institutional economy of scale is realized through a centralized EHS function at a biomedical research university. Tasked with responsibility for biological, chemical, radiation safety, environmental and fire safety as well as risk management, the HSC EHS is recognized for excellence throughout the university.

<sup>77</sup> Interview with the Biological Safety Officer at the School remarkably mirrored the comments made by Thomas (2003) who noted after interviewing leading biomedical researchers and microbiologists concerning federal biosecurity regulations that “Complaints about increased red tape and paperwork are universal among scientists who work with select agents”, p.200.

<sup>78</sup> This was a serious change in federal regulations, while previously regulations (in conformance with the 1996 Anti-Terrorism and Effective Death Penalty Act, Public Law 104-132) registration was required for those researchers who shipped select agents and toxins to other laboratories, the 2002 regulations required a comprehensive inventory of all select agents and toxins possessed for use in all research activities.

<sup>79</sup> Interviews with the Biological Safety Officer revealed that after massive investment of labor hours to achieve initial compliance (estimated at 1800 labor hours between 2002-2003 split among the primary investigator <researcher>, the Biological Safety Officer and the university police), he notes that ongoing maintenance of compliance requires near daily involvement with the laboratory staff and the university police. Interviews conducted on November 11, 2003 and October 4, 2004.

of 2002. Several staff members of the Environmental Health and Safety function are active members of numerous professional associations, including the American Society of Microbiologists (ASM) which was directly involved in the formulation of these federal regulations. The society regularly advised its membership regarding changes in pending regulations in advance of the release of the proposed rules. In addition, as a major recipient of federal biomedical research grants, the school regularly received information alerts from the CDC. The school's EHS staff pursued an aggressive information campaign to alert all researchers of the pending regulations and the forecasted impact on their laboratory activities. In addition, a series of executive briefings were conducted by the school to include executives both at the local and regional levels, including senior university executive staff.

The school was one of the first institutions within the United States subjected to a federal compliance audit which included an intensive on-site inspection of their facility to assess conformance with federal regulations found at 42 CFR 73. That on-site inspection was conducted in May 2003<sup>80</sup>. However, prior to that on-site, especially with the critical link between the specific select agent used in the ongoing biomedical research at the school, *Bacillus anthracis*, and the nation-wide concern with apparent criminal use of anthrax beginning in the autumn of 2001, increased attention had been focused on the security of that specific laboratory. To enhance physical security measures as well as to comply with the federal regulatory requirements the university installed and upgraded the electronic security devices used to control access to the lab suite.<sup>81</sup>

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<sup>80</sup> This multi-day on-site included interviews, observations, and records review by a team of inspectors from the CDC. All participants (the primary investigator, EHS and the university police) were tasked to prove their compliance with the regulations. The experiences gained during this on-site were shared with other similar institutions throughout the region and nation.

<sup>81</sup> The laboratory is located in the medical school, a facility that has both controlled perimeter access and on-site armed peace officers and unarmed guards assigned to the facility. The author increased the directed patrols of the lab suites in October 2001 and those patrols continue to this date. The university police scoped, designed, installed, and continue to maintain several electronic security systems including closed circuit televisions, card access entry, and intrusion alarms in the winter-spring of 2003.

Nevertheless, physical security measures, while certainly a very visible manifestation of biosecurity, are but one of several elements of an effective biosecurity strategy.<sup>82</sup>

Essential regulatory compliance was achieved through a comprehensive education and information campaign waged by EHS, coupled with multi-disciplinary activities relentlessly pursued by the school. The Biological Safety Officer alerted the university community of the new regulations. He planned and conducted a comprehensive inventory of all select agents and toxins. This required in-person discussion with the primary investigators as all select agents and toxins were accounted for throughout all laboratories across a geographically disjointed campus. The Biological Safety Officer, in coordination with the primary investigator and the crime prevention staff of the university police planned and conducted laboratory training of staff on the new regulations which included an audit and revisions of laboratory procedures manuals. He maintains today an automated and password protected database on the location and amounts of select agents and toxins on campus. The plan to achieve regulatory compliance was multi-phased and took several months to achieve success in the 2002-2003 time frame.

## **B. CASE STUDY: THE HOSPITAL**

In this case study, the cancer center, referred to hereafter as “the hospital”, is a unique, university affiliated medical institution whose stated mission is:

. . .to eliminate cancer in Texas, the nation, and the world through outstanding programs that integrate patient care, research and prevention, and through education for undergraduate and graduate students, trainees, professionals, employees and the public.

The hospital was founded upon a philanthropic gift to the state from a successful businessman, which was further supported by the state legislature. The hospital has grown from a few rooms in a personal residence in 1943 to a multi-site, comprehensive

<sup>82</sup> A common and relevant aphorism within the crime prevention community is “Locks keep only the honest people out”. The deterrent effect of such electronic security systems is difficult if not impossible to quantify and measure. Additionally, the technical training of the users of such installed systems continues to be an issue; a high rate of false alarms (both intrusions and door held-open alarms) are experienced as new personnel are joined to the laboratory. The efficacy of the “guns, guards, and gates” approach to biosecurity was questioned in the American Biological Safety Association’s paper - ABSA Biosecurity Task Force White Paper: Understanding Biosecurity January 2003. Accessed on 23 October 2004 at <http://www.absa.org/0301bstf.html>.



cancer center with an annual budget that exceeds \$1.7 billion<sup>83</sup> The hospital takes pride in the quality of its research-driven patient care; in FY 2004 the physicians and surgeons performed 12,463 surgical procedures, had 20,608 patient admissions, and 605,848 outpatient visits. It has earned an international reputation for the world-class quality of its science. Applied biomedical research is a fundamental focus for this institution. The hospital received \$164,000,000 in federal grants in 2003 and notes that “Nearly 50% of our current research funding comes from NIH grants and contracts. . .”<sup>84</sup> This funding level has increased more than 143% during the last five years.

The hospital has an employee population of 14,250 and employs 663 physicians and research physicians (M.D./Ph.D.) and 368 (Ph.D.) basic scientists. These scientists engage in a remarkable number of biomedical research activities which include 12,332 patients enrolled in clinical trials. In addition it received 208 National Cancer Institute grants, nine Specialized Programs of Research Excellence (SPORES) grants, and 24 training grants<sup>85</sup>. The faculty has outlined seven research themes to guide an ongoing and diverse research agenda. Research theme seven was identified as “to continue to pursue research on cancer in each of the major organ sites and explore new diagnostic and therapeutic approaches to these cancers.”

The hospital became aware of pending federal biosecurity regulations through a variety of professional organizations sources including the American Biological Safety Organization and the American Society of Microbiology, as well as through communication from the Centers for Disease Control. The hospital’s Biological Safety Officer, during a period of major staff turnover, exercised due diligence and engaged the hospital research community, primarily basic research scientists, in an information exchange about the new regulations and the forecasted regulatory impact on the individual researchers and their laboratories. That information exchange was time sensitive and intensive in volume.

The hospital’s compliance officer, a senior executive who is by professional training an attorney, was involved in both the information exchange and the status of the

<sup>83</sup> Chief Financial Officer’s FY 2004 Hospital Quick Reference Data.

<sup>84</sup> President’s Annual Address of October 18, 2004, p. 21.

<sup>85</sup> Ibid, p. 8.

compliance efforts. The inventory of all biological agents and toxins was a critical first step for the hospital and was the most time intensive of all steps of regulatory compliance plan. Remarkably the hospital was actively involved in the inventory of biological agents and toxins as an element of the institution's general upgrade in safety practices prior to the adoption of the federal regulations in 2002<sup>86</sup>. The hospital's senior executive staff initiated that inventory to address the concern that while they had a comprehensive inventory of chemicals used and stored throughout the laboratories, an inventory verified through quarterly "zip rounds"<sup>87</sup>, they were less confident about their possession of biological agents and toxins.

However, as a major biomedical research facility whose primary focus is applied research in cancer treatment, compliance with the federal regulations concerning select biological agents and toxins was never an issue of substantive controversy at the hospital as it was at the school. The hospital has a single reportable biological select agent and toxin currently in possession - Staphylococcal Enterotoxin B (SEB)<sup>88</sup> which is a toxin used as a test marker in cancer research. The SEB is maintained in very limited amounts and securely stored in an industrial deep freezer within a research laboratory. The major compliance problem encountered at the hospital was the difficulty of securing the active cooperation from the various research scientists. These scientists apparently did not perceive the task of a biological agent and toxin inventory to be a significant priority.

In retrospect, this apathy has been attributed to the fact that such substances were rarely possessed or used by these biomedical researchers in their work with cancer. The preponderance of the non-compliant researchers<sup>89</sup> believed that the failure to submit a written response to the EHS constituted a negative response and they felt no pressure to

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<sup>86</sup> The hospital pursued and achieved ISO 14001 status in 2002. This was a voluntary accreditation effort of the Environmental Health and Safety function by external regulatory authorities.

<sup>87</sup> Zip rounds are conducted unannounced quarterly throughout the institution. These rounds involved safety specialists who assess ongoing compliance with institutional and professional standards of practice involving laboratory safety at the active research laboratories. Zip Rounds are reported to various institutional governance bodies.

<sup>88</sup> Staphylococcal Enterotoxin B is found to be "one of the best-studied and, therefore, best-understood toxins" and it is attributed to be one of the common causes of food poisoning by E Medicine Consumer Health's Bioterrorism and Warfare. Accessed on 26 October 2004 at <http://www.emedicinehealth.com/articles/15704-5.asp>.

<sup>89</sup> The Biological Safety Program Manager had estimated non-compliance to involve less than 100 of the more than 800 Primary Investigators at the hospital.

devote any further time to another set of inquiries from the university's support staff. The Biological Safety Officer and her staff overcame that apathy by making scheduled visits and conducting thorough inventories of the more than 800 active laboratories throughout the university<sup>90</sup>. It is interesting to note that the thorough and detailed inventories did uncover unexpected possession of some biological select agents in the laboratory freezers, attributed to legacy inventories that occurred as generations of research scientists occupied similar laboratory spaces within the institution. The biological agent and toxin inventory facilitated a long overlooked yet desirable laboratory clean out within the institution. Legacy biological agents and toxins, some decades old, were disposed of in conformance with professional standards by qualified biological safety professionals.

Regulatory compliance was not a significant issue for the hospital, for the nature of the research currently conducted does not include the routine use of select agents and toxins<sup>91</sup>. The hospital does undergo regular compliance audits from a series of public and private regulatory agencies each year. Due to the nature of some research, federal regulations permit specified entities, in this case a biomedical research institution, exemptions for specific toxins held in certain amounts<sup>92</sup>. The hospital's research activities made it eligible for these exemptions. As a result, the hospital incurred limited expenses in establishing compliance with these new biosecurity regulations. The major costs consisted of the creation of a secure automated database and the replacement of an industrial-grade laboratory deep-freezer.

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<sup>90</sup> These inventories were in fact challenging exercises. In contrast to chemicals that are stored on accessible shelves and cabinets in active research laboratories, the inventory of biological agents and toxins frequently required accessing storage trays within large industrial deep freezers and cross referencing marked specimen vials and containers with some idiosyncratic laboratory numbering systems designed by various Primary Investigators over the last forty years.

<sup>91</sup> Due to the nature and frequency of various governmental and professional compliance assessments and audits, the hospital has a separate official and support staff tasked as the institutional compliance officer.

<sup>92</sup> The applicable federal regulation, 42 CFR 73 at Section 73.5 at f Exclusions Subsection (4) notes that the regulations do not include "...the following toxins (in the purified form or in combination of pure and impure forms) if the aggregate amount under the control of a principal investigator does not, at any time, exceed the amount specified: 0.5 mg of Botulinum neurotoxins; 5 mg of Staphylococcal enterotoxins; 100 mg of *Clostridium perfringens* epsilon toxin; 100 mg of Shigatoxin; or 1,000 mg T-2 toxin.

### C. COMPARISON AND DISCUSSION

The two cases outlined above indicate two different but equally effective regulatory compliance strategies. Both cases evoke the significant concern regarding dual use in biomedical research. These diverse research entities pursued approaches to compliance that produced equal success while involving radically different substances. Their successes were not coincidental and can be largely attributed to both institutions' affiliation with a single umbrella organization, a university system. The university system staff methodically informed all member institutions from the outset of the new regulatory "fast track" approach to biological select agents and toxins. The system prepared a singular response to the federal regulations during the comment period<sup>93</sup>, outlining both academic and biomedical research community concerns about these regulations and the unintended consequences of biosecurity.

A comparison of the experiences of these two institutions, as outlined in Table 6, is illustrative of many of the critical similarities in their responses to the enhanced regulation of research involving select biological agents and toxins.

Table 6. Comparison of Institutional Responses to Federal Regulations of Biological Select Agents and Toxins at Selected Sites

Topical Area	School	Hospital
Major recipient of federal funding for biomedical research	Yes	Yes
Professional Environmental Health and Safety function	Yes	Yes
Advanced notice of regulatory intent	Yes	Yes
Response to the proposed rules filed with the CDC	Yes	Yes
Inventory completed in compliance with the regulations.	Yes	Yes
Inventory reduced total number of select agents and	Yes	Yes

<sup>93</sup> Discussions with EHS staff at both institutions revealed both had input into the consensus document submitted by university system. The system convened a study group that regularly met via teleconference and in person during the 2001-2003 timeframe preparing the system's terrorism response plans and a single comprehensive response to the proposed federal biosecurity regulations.

toxins held by the institution.		
Primary investigators resisted compliance activities	Yes	Yes
Security plans filed in conformance with regulatory timeline	Yes	Yes
Equipment purchased and Laboratory Procedures revised	Yes	Yes
Federal compliance audit	Yes	No

Source: Interviews with Principals conducted in October 2004

Cost is a critical factor in any discussion of programs or a comparison of responses to federal regulations, yet complete or total costs can be elusive to track, for they consist of both direct as well as indirect elements. For example, the purchase of a new deep freezer for SEB would be a direct cost while the maintenance of a software program that tracks the inventory of select biological agents and toxins would be an indirect cost, in that the software program also performs a series of other environmental health and safety tasks. Both the school and the hospital incurred unanticipated costs in establishing compliance with these federal regulations pertaining to biosecurity.

It would be naïve and generally irresponsible to limit the understanding of biosecurity costs solely to monetary expenditures. Responsible calculations of biosecurity costs must include as well opportunity costs. In both cases such opportunity costs are expressed within the context of public research universities, and those opportunity costs can be translated into other biomedical research activities or educational activities that were deferred or eliminated as a result of these funds and resources being allocated to the achievement of federal biosecurity mandates. Another consideration is the quantification and value of primary researchers' time. The time of these uniquely trained and educated basic research scientists spent on biosecurity compliance is arguably time lost and time never to be recovered. While we can capture

an estimated value of their time in monetary terms, such a calculation fails to fully capture the delays in research caused by these regulations.<sup>94</sup>

Based upon principal interviews and supporting documentation<sup>95</sup> the costs of compliance with biosecurity regulations can be estimated as listed in Table 7.

Table 7. Selected Costs of Biosecurity Compliance, 2002-2003

<b>Cost Center</b>	<b>School</b>	<b>Hospital</b>
Specialized Labor –EHS	600 hrs	2080 hrs
Specialized Labor - PD	600 hrs	200 hrs
Specialized Labor – Pis	600 hrs	1040 hrs
Equipment – Laboratory	Biosafety Cabinet New cleanable chairs and stools Specialized Rotors	Industrial Storage Freezer
Equipment – Security	Card Access Doors Closed Circuit Television system and recording devices Intrusion and Panic Alarms	None
Facilities Remodeling	Construction planning for a BSL 3 Lab	None

Source: Author Interviews and Documentation Review with Principals in October 2004.

By comparison, the school incurred substantially more costs due to the nature of the select agent used in its setting and the active research program executed by the primary investigator. In both cases the opportunity costs are difficult to quantify, for time devoted to compliance activities is time unavailable for active research and educational activities by the researcher. In summary, these costs were the result of choice made in order to continue active research using these agents.

Turning to another important aspect of the discussion of compliance with the biosecurity regulations, a question arises as to whether the funds that were expended in this effort can be assessed as to efficiency. The qualified answer is yes. Efficiency, as a

<sup>94</sup> This point was articulately made by the School’s Biological Safety Officer who remarked that the ongoing compliance efforts caused one Basic Research Scientist to state that her research productivity has markedly declined as she has implemented the mandated biosecurity measures at her laboratory.

<sup>95</sup> For the period 2002-2004, institutional biological safety staff provided the listed estimates of direct and selected indirect costs during interviews. While subject to some bias, both principals provided the information freely and without reservations. The specificity of the information provided meets the purpose of this work.

term often used in discussions of public agency performance, yet has a tendency to lend itself to partisanship, but efficiency can be defined as the relationship between the work performed and the resources required to perform that work.<sup>96</sup> An underlying concern is the value of efficiency as the best metric to use in evaluating the implementation of biosecurity as an element of the national defense strategy in a homeland security context. While our homeland security efforts should not be wasteful or exempt from the normal expectations of fiduciary responsibility, efficiency may not be the most appropriate performance metrics.

In the final analysis, at both the school and the hospital, full compliance with the federal regulations involving biosecurity was achieved. As noted in the earlier discussion, both the school and the hospital dedicated significant specialized labor efforts to achieving compliance with the biosecurity regulations. The variance between the school's 1800 hours and the hospital's 3320 hours in 2002-2003 can be explained by the variance in the scope of the task at the two institutions. For example, the hospital has more than 800 separate laboratories which were subject to the inventory for select agents and toxins.

Equity is the final element to be used for comparison in the two cases, and for the purposes of this discussion equity will be defined as fairness and impartiality<sup>97</sup>. The federal biosecurity regulations were imposed on all entities that possess biological agents and toxins. However, those same regulations are also steeped with a variety of inconsistencies, exceptions, and exemptions that call into question the fundamental equity of the regulatory attempts.

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<sup>96</sup> Efficiency was the goal of much of 20th century public and private enterprise. This definition is a meta-definition based largely upon the performance measurement work done by David Ammons and Harry Hatry as outlined at these two primary websites accessed on 15 September 2004 at

[http://www.ci.concord.nc.us/downloads/budget03/Performance\\_Measurement2nd.pdf](http://www.ci.concord.nc.us/downloads/budget03/Performance_Measurement2nd.pdf). and

<http://newark.rutgers.edu/~ncpp/cdgp/Manual.htm>.

<sup>97</sup> Equity has long been a topic of contentious discussion in philosophical, economic and legal circles. The discussion can be traced back to Aristotle, who discusses equity at length in Book V of Ethics. Aristotle noted that “. . . justice and equity coincide, and although both are good, equity is superior. . . the essential nature of equity; it is a rectification of law in so far as law is defective on account of its generality. This in fact is also the reason why everything is not regulated by law: it is because there are some cases that no law can be framed to cover. . .” J.A.K. Thomson (Trans) The Ethics of Aristotle – The Nicomachean Ethics. (1955) New York: Penguin Books. p. 199.

In this situation both the hospital and the school were required to establish conformance to federal biosecurity requirements found at 42 CFR 73. However, as noted earlier, the nature of that conformance varied. At the hospital, because the select agent held was the commonly researched toxin SEB, the degree of biosecurity imposed was much different from the school with active anthrax spores. The regulations exempt conformance if the select agents or toxins are contained in specimens or isolates of specimens presented for diagnosis, verification, or proficiency testing. They further provide exclusions for a variety of reasons including whether or not the select agent or toxin is in its naturally occurring environment<sup>98</sup>. Some attenuated strains of overlap select agents are determined by the HHS Secretary to “not pose a severe threat to the public health and safety”<sup>99</sup>

The regulations also provide a process whereby entities can apply to the HHS and have investigational products exempted from the regulations. Furthermore, the government retains the right to temporarily waive compliance with these regulations during responses to domestic or foreign public health emergencies as well as agricultural emergencies.<sup>100</sup> Therefore an answer to the question as to whether equity exists in the application of the regulations to the several public, private, academic, and commercial entities is difficult to craft, for many of the exceptions and exemptions granted are shielded from public review and consideration.<sup>101</sup> Equity does not exist as an independent factor, but rather exists within the interaction of forces within a specific context. Nonetheless it is undeniable that the federal biosecurity regulations created a disproportionate burden on some entities<sup>102</sup>.

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<sup>98</sup> For example the plague *Yersinia pestis* is commonly found naturally occurring in Prairie Dogs in the Southwestern United States.

<sup>99</sup> 42 CFR 73.5

<sup>100</sup> 42 CFR 73.6 (b) – (e).

<sup>101</sup> Interviews with Biological Safety Officers at the School and Hospital confirmed the author’s suspicions, in that during independent interviews principals noted that some institutions receive exemptions as a matter of routine, while other institutions seem subject to much more detailed regulatory review. As one principal noted “Politics occurs everywhere, including science.”

<sup>102</sup> It is noteworthy that the burden of biosecurity compliance was borne by even unexpected institutions. K. Carr, E. Henchal, C. Wilhelmsen and B. Carr (2004) “Implementation of Biosurety Systems in a Department of Defense Medical Research Laboratory” Biosecurity and Bioterrorism: Biodefense Strategy, Practice and Science. Volume 2, Number 1, 2004. Accessed 15 May 2004 at [http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list\\_uids=15068675](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15068675).



One entity that was especially and unexpectedly burdened by federal biosecurity regulations was The United States Army Medical Research Institute of Infectious Diseases (USAMRIID). This former center for military biological weapons research reported that the changes required to implement biosecurity have presented unique budgetary challenges for the institute. The costs of compliance are enormous, especially for an organization whose entire funding budget in FY 2004 was less than \$50 million. Installation of the closed circuit video system to monitor the 230 laboratories and 329 personnel with access to select agents and toxins at Fort Detrick is estimated at \$50 million with the related physical security upgrades (gates, key card access systems and advanced locks) at the laboratories estimated at \$12 million. The annual recurring costs of the program, once completed, will be approximately \$ 4 million. These capital and operational costs far exceed the program costs estimated by the federal government in 2002 at \$9,300 for a small lab and \$730,400 for a medium sized university for year one costs.

Still it must be noted the United States is actively engaged in a serious, multi-national conflict that includes a variety of non-state actors. The federal government, as it has expressed in these regulations, has attempted to balance the needs of ongoing biomedical research against the need for domestic defense against biological weapons of war. In the end, equity is not equivalent to convenience. While the school was subjected to more intense regulation and inspection than the larger hospital, the school is also the host to active research with a biological select agent that the nation has classified as falling within Category A, high-priority agents<sup>103</sup>.

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<sup>103</sup> The Centers for Disease Control attributes four characteristics to Category A high-priority agents – they can be easily disseminated or transmitted from person to person; result in high mortality rates and have the potential for major public health impact; might cause public panic and social disruption; and require special action for public health preparedness.

## V. CONCLUSIONS

In the concluding chapter of the thesis, a credible answer to the research question is proposed. The importance of biosecurity as a public policy issue is considered and further opportunities for research in Homeland Security studies are outlined.

The essential question posed within this thesis was how can specific public biomedical research universities securely use and store biological select agents. The question is critically relevant to the practice of Homeland Security within the United States in the early twenty-first century. In forming an answer to that question, the topics of list making dynamics, statutory law and administrative regulations were explored. Two case studies, both involving public biomedical research universities, were crafted and assessed focusing on biosecurity. Taken together this research leads to a durable and credible response to the research question.

Public biomedical universities are unique institutions. They exist to responsibly explore the frontiers of science while also fulfilling their core mission of public higher education. Public research universities are also major societal institutions which often serve as the engines of scientific progress, for university-based research fuels the continued growth of many sectors of the American economy. Biomedical research is an area of rapid expansion with revolutionary discoveries restructuring our fundamental understanding of biology and microbiology on a routine basis. These academicians and biomedical researchers continue to grapple with the challenge of dual use. Their biomedical research yields products that advance our understanding of disease and improves the human condition, yet those same biomedical products have the real potential for misuse in weapons of bioterrorism. The enduring solution to the conundrum has not been reached, and the dialogue continues among researchers, regulators, and security professionals. One critical element in the short-term response to the dual use conundrum has been the federal regulation of select biological agents and toxins.

Regulation of biological select agents and toxins is not a new practice, but such regulation has been evolutionary, and the modern lineage is anchored in the Geneva Protocol of 1925. An interesting, but necessary mix of international law, national

security decisions, statutory law, and federal regulations has methodically increased the control and regulation of these substances over time. The public policy issue of the regulation and control of biological select agents and toxins had generally lain dormant until the widespread increase in public awareness of the risk the nation faces in regards to bioterrorism starting in the late 1990s and peaking with the anthrax attacks of 2001 in several cities, broadcasting facilities, postal facilities, and even the offices of the United States Senate.

The dynamics which came into play with the preparation of the 2002 list of biological select agents and toxins can be seen as a microcosm of modern federal rule making under time constraints. A current list, a product of previous regulatory attempts of 1997, was the basis for the discussion. The federal regulatory agency used a variety of strategies during the formulation of the regulations including tripartism (involving the interested public, as well as regulators, and those regulated), effective information campaigns, and a bias towards self-regulation of the regulated entities with provisions for audits. While not all parties were completely satisfied with the final regulations, those regulations did include conscious and planned attempts at inclusiveness.

Still biosecurity remains a relatively new concept, and that novelty perplexes many microbiologists and biomedical researchers. The viable threat of civil fines and criminal penalties for failure to comply with the security provisions has sent shock waves through the biomedical research community. While the federal regulations outline some very basic requirements for security, the specific eight requirements flow from a security systems approach to the problem of biosecurity and require the renewed attention at the entity level to staff access control, physical space security features, and inventory practices. The answer to the question does not necessarily lie within the simplistic approach of more “guns, gates and guards”.

A proven successful answer to the question of how specific public biomedical research universities can securely use and store biological select agents is multi-disciplinary teamwork. A team composed of environmental health and safety professionals, primary investigators, and law enforcement officers formed at individual biomedical research entities can effectively realize the secure use and storage of

biological select agents and toxins. As was found at the two separate biomedical research institutions studied, such team work requires commitment from all participants, a willingness to communicate honestly, and a focus on the goal of biosecurity. Imposition of local biosecurity regulations based solely upon a single individual or a single profession's interpretation of the federal regulations is doomed to failure. The legitimate and contributory views of all three disciplines are required for an effective and durable response to the biosecurity challenge.

The field of biosecurity is new, and research challenges abound. The study of homeland security as well is still in its infancy, but with time and the judicious application of the skills and expertise from the several established disciplines substantive progress in current homeland security core studies should be realized for the benefit of the nation. Three areas that seem especially rich for further research include biosecurity strategy, policy implementation, and biosecurity tactics.

Security, in any of its many modern manifestations, requires tradeoffs. Schneier<sup>104</sup> eloquently outlines a five-step security analysis process which could be usefully applied to the biosecurity effort on a institutional or national basis. In the realm of biosecurity strategy, a review of the changes to the list of select biological agents and toxins over time may yield some very useful findings. That list is subject to biennial review, and those substances that are added and deleted from the list may be revealing both in terms of trends in microbiology and genetic engineering dual use. Additionally, over a period of time the 2002 list may come to be seen as an overreaction to the socio-political climate immediately after the 9/11 attacks. In biosecurity, the several stakeholders have taken definite positions concerning the utility of the list, and it will be very interesting to see if these positions endure the test of time and the inevitable changes to the list. It is probable that an attributable release of a biological select agent or toxin that is subsequently weaponized and ultimately traced back to a biomedical research facility will profoundly change the calculus used in designing biosecurity standards used

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<sup>104</sup> Schneier proposes a five step test that includes - What assets are you trying to protect; What are the risks to these assets; How well does the security solution mitigate those risks; What other risks does the security solution cause and finally What costs and tradeoffs does the security solution impose? B. Schneier (2003). Beyond Fear: Thinking Sensibly About Security in an Uncertain World. New York: Springer-Verlag. pp. 14-15.

within the United States. Moreover, in the face of a merciless public press, the patience and understanding of the regulatory authorities may radically change to the overall detriment to American biomedical research.

In the realm of policy implementation, a critical review of the use of the exemption and exception clauses to these federal regulations over a specific period of time may indicate some very interesting trends, for these are discretionary decisions by individual federal regulators initiated by the individual research entities and are thus shielded from public scrutiny. Moreover, the research in this thesis indicated there is a none too subtle application of institutional and political power in the design and implementation of the biosecurity policy at the federal level. The comprehensiveness and actual equity of the policy itself may be less than defensible in the light of the numerous exceptions and exemptions routinely granted to various large research institutions since adoption of the BPARA. The unanticipated biosecurity costs for laboratories using select agents and toxins, e.g. the physical redesign of laboratories and laboratory security practices, may have an unforeseen consequence of limiting critical biomedical research activity to those few institutions that can afford to comply with the federal biosecurity policy.

In the realm of biosecurity tactics, several issues will be of important research interest. First, will the commitment to biosecurity in both public and private settings continue into the future? Will the federal regulators, who have to date found gaping shortfalls in their biosecurity inspections of university affiliated research, find an increased level of voluntary compliance in the future? Will a viable solution to the precise inventory of living bacteria and viruses ever be achieved? Finally, will that specific technical solution translate to improved biosecurity for select agents? Much work is left to be done in biosecurity, but practitioners, academics, and interested public and professional groups each gain from their work in this area. Individually and together work in biosecurity directly contributes to both the defense and security of the homeland.

## APPENDIX A LIST OF SELECT BIOLOGICAL AGENTS AND TOXINS

The Secretary of Health and Human Services (HHS) designated the following as select agents or toxins at 42 CFR 73:

### Viruses

- Cercopithecine herpes virus 1 (Herpes B)
- Crimeran-Congo haemorrhagic fever virus
- Ebola viruses
- Lassa fever virus
- Marburg virus
- Monkeypox virus
- South American haemorrhagic fever viruses (Junin, Machupo, Sabia, Flexal, Guanarito)
- Tick borne encephalitis complex (falvi) viruses (Central European Tick-borne encephalitis, Far Eastern Tick-borne encephalitis, Russian spring and summer encephalitis, Kyasanur forest disease, Omsk hemorrhagic fever)
- Variola major virus (Smallpox virus)
- Variola minor (Alastrim)

### Toxins

- Abrin
- Conotoxins
- Diacetoxyscirpenol
- Ricin
- Saxitoxin
- Shiga-like ribosome inactivating proteins
- Tetrodotoxin

### Bacteria

- *Rickettsia prowazekii*
- *Rickettsia rickettsii*
- *Yersinia pestis*

### Fungi

- *Coccidioides posadasii*

### HHS-USDA OVERLAP AGENTS

#### Viruses

- Eastern equine encephalitis virus
- Nipah virus
- Hendra virus
- Rift Valley fever virus

- Venezuelan equine encephalitis virus

#### Bacteria

- Bacillus anthracis
- Botulinum neurotoxin producing strains of Clostridium
- Brucella abortus
- Brucella melitensis
- Brucella suis
- Burkholderia mallei
- Burkholderis pseudomallei
- Coxiella burnetii
- Francisella tularensis

#### Toxins

- Botulinum neurotoxins
- Clostridium perfringens epsilon toxin
- Shigatoxin
- Staphylococcal enterotoxins
- T-2 toxin

#### Fungi

- Coccidioides immitis

Source: The Centers for Disease Control List of Select Biological Agents and Toxins,  
<http://www.cdc.gov/od/sap/>.

## APPENDIX B CASE STUDY INTERVIEW QUESTIONS

Interview Subject: \_\_\_\_\_

Official Title: \_\_\_\_\_

Date/Time Began: \_\_\_\_\_

Date/Time Concluded: \_\_\_\_\_

Attribution: Anonymous                      Name                      Other

After brief introduction and restatement of the purpose of the interview, I will conduct the interview. I will offer them the opportunity to remain anonymous (a senior official at a biomedical university in the southwestern United States).

1. How significant is the threat of bioterrorism? Why?
2. Do you believe there is a threat of bioterrorism at the university? Why?
3. Have you heard of the term “biosecurity”? If yes, how do you define the term?
4. As the Biological Safety Officer, how were you made aware of the new biosecurity requirements of the BPARA in 2002?
5. How did you, in your official role as the Biological Safety Officer, address compliance with these new requirements?
6. Did you, or the university, exercise the right to respond to the proposed rule in the Federal Register?
7. Did the “fast track” compliance schedule present any issues?
8. Who was involved in designing the implementation planning for compliance with 42 CFR 73?
9. What challenges did you encounter, as the Biological Safety Officer in implementing the Select Biological Agents and Toxins at the university?
10. Did we achieve compliance with the new regulations on schedule? Were there any unforeseen challenges in compliance?
11. As a policy issue, how controversial is the Select Agent List in your opinion?
12. Did you encounter resistance from any segment of the university community in establishing compliance with these new regulations? If yes, who and to what degree?
13. Did you have any tailored outreach programs to the affected Primary Investigators to educate or achieve compliance with these new regulations? If yes, how would you assess the success of that effort?
14. Could you estimate some of the costs for achieving compliance with the Select Agent biosecurity regulations at this university:

Labor:

- How many hours did you devote to this project?
- During what time frame did you commit this labor?



- **Who assisted you during this period?**
- **How many hours did they devote to this project?**
- **To achieve compliance with 42 CFR 73 did you receive any specialized training? If so, what and when?**
- **Did your staff require any specialized training?**

Equipment:

- **Did compliance require the purchase of any new equipment?**
- **Do you know what equipment was purchased and installed?**

Facilities:

- **To achieve compliance did you have to refurbish/redesign/alter the physical plant within these laboratories?**

Other:

- **Were there other significant costs incurred not captured above? If yes, what were they?**

**15. Finally, in retrospect, do you think that planning was successful? Would you have changed any element of your planning strategy? Why?**

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