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Laboratory biosecurity in the United States: evolution and regulation

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Chapter Outline

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Introduction

The term “biosecurity” is used in a wide variety of contexts and carries with it an equally diverse set of meanings. For example, veterinarians traditionally view biosecurity as the set of management practices to protect animals – livestock or others of economic value – against microbial threat, some of which may be inadvertently introduced by humans. Preventing influenza in pig farming and tuberculosis (Mycobacterium tuberculosis) among elephants in zoological parks are two illustrations [1]. “Biosecurity” takes on an entirely different meaning in international political agreements such as the Biological and Toxin Weapons Convention of 1975, where it refers to measures to prevent the research and development of microorganisms or their products for hostile purposes [2]. And it is not too far a reach to think of biosecurity as the prevention of infectious disease – and specifically communicable infectious disease – in humans [3].
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For the purposes of this chapter and those that comprise the balance of this text we will employ the definition promulgated by the US Department of Health and Human Services [4]:

"The term biosecurity refers to the protection, control of, and accountability for high-consequence biological agents and toxins and critical relevant biological materials and information within laboratories to prevent unauthorized possession, loss, theft, misuse, diversion, or intentional release. Biosecurity is achieved through an aggregate of practices including the education and training of laboratory personnel, security risk assessments, Biological Select Agent and Toxin (BSAT) access controls, physical security (facility) safeguards, and the regulated transport of BSAT. Achieving effective comprehensive biosecurity for BSAT is a shared responsibility between the Federal Government and facilities/individuals that possess, use or transfer BSAT.

Complementary to, but distinct from, biosecurity is biosafety based on principles of containment and risk assessment in the laboratory. Containment includes: “the microbiological practices, safety equipment, and facility safeguards that protect laboratory workers, the environment and the public from exposure to infectious microorganisms that are handled and stored in the laboratory,” whereas risk assessment is “the process that enables the appropriate selection of microbiological practices, safety equipment, and facility safeguards that can prevent laboratory-associated infections” [5].

A helpful means of distinguishing “biosecurity” and “biosafety” is to note that they commonly differ on intent, that is, biosecurity is implemented to obviate the intentional diversion or release of biological materials, whereas biosafety measures limit their unintentional dissemination in order to protect laboratory workers and the surrounding community and environment from accidental exposure to pathogens [6,7]. The functional components of biosecurity architecture will be described below.

The purpose of this chapter is to review the evolution of biosecurity and modern tenets of its implementation as it applies to high-containment laboratories or those working with “select agents” as defined by statute. Many (if not most) laboratorians are unaware of the historical origins of biosecurity. Perhaps of greater importance is that laboratory officials and researchers working with dangerous pathogens may be naïve to the origins in the law of the now lengthy list of operational biosecurity requirements, obviously of practical relevance in the day-to-day functions of research facilities. The key pieces of legislation that have mandated these requirements were responses to events such as bioterrorism threats in the late 1990s and the downing of the World Trade Center buildings in 2001 as we shall see in more detail shortly.

Biosecurity laws passed by the Congress vest considerable authority in government departments such as Health and Human Services (HHS) and Agriculture (USDA) to formulate and then implement regulations (frequently referred to by officials as “rules”) with which laboratory workers, researchers, staff and security personnel must comply. These rules are revised at intervals, sometimes on a regular basis and also

1 Select agents and toxins will be described in detail below.
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when new laws are passed. We will summarize the processes by which agencies with HHS and USDA – typically the Centers for Disease Control and Prevention (CDC) and the Animal and Plant Health Inspection Service (APHIS) – interpret the will of Congress (via laws that have been proposed, debated and passed), formulate proposed regulations, solicit comments from individuals and entities likely to be affected, and then disseminate final rules. Beyond the legislation itself, the president may issue directives: these include executive orders or “EO”s, which have the full force of the law and must be published in the Federal Register (FR); and administrative orders such as memorandums, determinations, notices, which have the same legal effect but do not have a publication requirement in the FR and may therefore be “born classified.” All of these may prompt executive agencies (such as HHS and USDA) to craft new rules as well. Several biosecurity-relevant EOs will also be reviewed.

But neither Congress nor the Executive Office of the President act without also taking into account the advice – sometimes directly solicited, sometimes not – of subject matter experts in academia and professional practice. Thus, over the past few decades there have also been several key reports from professional organizations, ad hoc groups and government-sponsored panels that have had a dramatic influence on biosecurity practice. Their importance goes beyond mere operational standards for laboratories. Rather, documents such as those produced at the ground-breaking Asilomar Conference in 1975 [8] through the recent publications of National Science Advisory Board for Biosecurity (NSABB) and the Federal Experts Security Advisory Panel have set in motion an inclusive process for scientists in and outside of government to recommend revision of biosecurity requirements that reflect research priorities involving naturally occurring organisms and (regrettably) those which might be used in bioterrorism. Because of their importance to laboratorians these reports will also be summarized.

In the end, the detailed regulations now extant in laboratories where certain pathogens and toxins – those dangerous to humans, animals or plants if released either inadvertently or intentionally – are kept for research purposes came about as a result of the complex interaction of public apprehension expressed in Congressional legislation and EOs, technical analysis from scientists and expert groups, and practical concerns from researchers who seek to carry out noble work in disease prevention and treatment. The now famous “Select Agent and Toxin List” (SATL) is perhaps the most visible result of the regulatory framework that applies to many biological laboratories and we will show its development over the past decade-and-a-half in detail. In so doing, we hope to foster involvement of thoughtful scientists in formulating policy. After all, bench scientists often have far more familiarity with cutting-edge research and experience with laboratory practices than most officials in the executive branch of government tasked with enacting far-reaching legislation.

Finally, since the turn of the century there have been a few high-profile “near misses” where the breakdown of biosecurity in containment laboratories could have resulted in infections among personnel or the public. Investigations directed at root-cause analysis often result in additional regulatory restrictions with both direct and indirect costs. We will attempt to weigh their benefits against perceived and real costs.
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In the mid-nineteenth century a series of “International Sanitary Conferences” were held in Paris, Vienna, Constantinople, Washington, Rome and Dresden with the goal of interrupting recurring epidemics of three diseases recently arrived or reappearing in Europe and North America: cholera, plague and yellow fever (each disease entity had a clinical pedigree and its epidemiologic characteristics roughly described, though all were without known cause). Over the course of 14 meetings starting in 1851 and ending in 1938, participants from the medical and diplomatic communities debated the origins of these diseases and the preventive actions that could be taken to “protect [people] and control” biological agents. This was the naissance of biosecurity in its most straightforward sense, and in retrospect is surprising given that the germ theory of disease was, at that moment in history, barely being formulated and understood. Absent that theory, early on in the Sanity Conferences, physicians and diplomats representing about a dozen countries from the United States to Russia argued over the effectiveness of quarantine and the very nature of what is now recognized as infectious disease. Anthony Perrier of Great Britain declared at the first gathering that cholera was not “communicable” and that “contagion is not a fact, but a hypothesis invented to explain a number of facts that without this hypothesis would be inexplicable” [9]. Offering no better explanation himself, Perrier went on to note that his colleagues “persisted in the routine path of practices that are outmoded, useless and ruinous to commerce and harmful to public health in that instead of enlightening the peoples on the true means of guaranteeing themselves against epidemics, they inspire on the contrary a false sense of security that prevents them from taking the only sanitary precautions that can offer real guarantees.” Perrier did not at this juncture specify what might constitute those “guarantees.”

This is perhaps the first association of the words “security” and “public health” in the setting of (then unknown) infectious diseases. Remarkably enough, less than 80 years after Perrier’s confusing admonitions, the origin and routes of transmission for all three diseases had been identified and effective preventive practices put into routine use – “biosecurity” by any other name. As the Sanitary Conferences continued to meet, in December 1907 representatives decided to formalize the forum into the “Office International d’Hygiène Publique” (OIHP), ultimately subsumed into the League of Nations at the end of World War I. It became known as the League’s “Health Organization” and produced an astonishing body of work including outbreak control and mitigation (with locales that ranged from Europe to ports in the Far East), nutrition (across the age spectrum from infants to adults), standards for medications, vitamins, antitoxins and vaccines, epidemiology of cancer (of a variety of organs) and even building construction guidelines to name but a small portion of their work [10]. The OIHP continued to operate until 1946 when the nascent World Health Organization (WHO), today’s premier international health security institution, subsumed its functions [11].

Though more than seven decades would pass from the inception of the OIHP, in 1983 the WHO published the Laboratory Biosafety Manual establishing standards
for worker safety and laboratory practices. By the time of the third edition in 2004 the Manual evolved to include succinct definitions of biosafety and biosecurity. “‘Laboratory biosafety’ is the term used to describe the containment principles, technologies, and practices that are implemented to prevent unintentional exposure to pathogens and toxins or their accidental release. ‘Laboratory biosecurity’ refers to institutional and personal security measures designed to prevent the loss, theft, misuse, diversion or intentional release of pathogens and toxins” [12]. The WHO Manual further describes biocontainment (including biocontainment levels) and risk assessment as the foundations of biosecurity, which in turn have informed US biosecurity strategies in legislation and laboratory practice.

**Elements of modern laboratory biosecurity**

In its common application and also as enshrined in various US laws, biosecurity is generally taken to be comprised of five or six main components (depending somewhat on definitions), all designed to limit access to pathogens and toxins to prevent their loss, theft or misuse [5,13]:

- Risk assessment that is a detailed listing of the hazardous characteristics of an organism or toxin, the probable consequences of unwanted exposure and associated occupational health plans.
- Access control equipment and barriers, perhaps including perimeter and internal monitoring.
- Personnel reliability, which may include background investigations, medical screening and assessment of expertise and experience.
- Control and accountability of materials (with associated documentation of archived materials).
- Training and emergency planning.
- Program management and supervision.

As noted earlier, none of these constituents is completely unique to biosecurity. Successful biosafety programs also depend to one extent or another on the same processes and physical constructs.

**Key legislation in biosecurity (or how Congressional intent defines biosecurity)**

While most laboratory managers and scientists working with pathogens and toxins are aware of the numerous regulations that govern access to and use of those materials, fewer understand the legal processes by which these come into effect. It is useful to understand the source of legislative action that lead directly to many of the current laboratory biosecurity/biosafety rules and procedures because scientists have the opportunity to influence the rule-making process even (and some would say “especially”) after US Congress passes new laws. We begin with a brief review of the
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Legislation and its implementation through “rule-making”

The Constitution of the United States vests “all legislative Powers” in “a Congress of the United States”. Any member of Congress may introduce legislation, and such proposals are usually referred to as “bills.” Bills originating in the House are designated as “House Resolutions,” and carry the abbreviation “HR” before the unique number assigned to it. Similarly in the Senate one finds “S,” that is “Senate” (with “Resolution” omitted) for bills proposed by one or more its members. Thus, when tracking the course of a bill through Congress, it is convenient to specify the “HR” or “S” number. Both HR and S require approval by the other body and the signature of the president to become law.

After a bill is introduced, Congressional committees almost always hold formal hearings designed to gather information about the impact of the bill on already existing laws and any new requirements it imposes, and costs (if money has to be appropriated to fund the bill). Committee chairmen invite both private and government experts to testify (especially from departments or agencies that will help write the regulations that implement the bill if it passes), and in the process the bill is typically changed (or “marked up”) before the committee takes a vote to either move the bill forward or not. It is not unusual for a full committee to refer a bill for discussion to a subcommittee.

Should a bill be “reported out of Committee” – meaning it is referred to the full body of the House or Senate – it is then debated “on the floor” where any member can request time to speak. Generally, after debate has completed, amendments can be offered, and then the bill is voted upon. A similar version of the bill goes through the same process in the other body, and if passed by a majority of both houses in the same form, is then sent to the president for signature.

There are, of course, complications that frequently derail the more-or-less straightforward description above, often deriving from the complex committee structure in the Congress. There are currently 26 committees in the House and 24 in the Senate. With rare exception, each committee has several subcommittees (as of this writing a total of 94 subcommittees in the House and about 70 in the Senate), and subcommittees often have overlapping jurisdiction, so several may hold hearings on a given bill simultaneously. Thus, only a minority (around 15%) of introduced bills are reported out of committee for vote on the floor of House and Senate, and few bills escape the

2 Constitution of the United States, Article 1 Section 1.
3 One website for following the progress of bills through introduction, committee deliberations, floor debate and voting is: https://www.govtrack.us/congress/bills/
4 http://www.house.gov/committees/
5 http://www.senate.gov/pagelayout/committees/d_three_sections_with_teasers/committees_home.htm
committee process without substantial rewriting of the original proposed text based on the decisions of committee members after listening to witnesses at hearings, or taking into account the views of their constituents. And even after surviving this process, the senior leadership of the House and Senate each decide whether or not they will, in fact, allow a bill to come up for floor debate at all. Should a bill pass both houses in something other than identical form – as often occurs when one house makes amendments to a bill originating in the other body – a “conference committee” must reconcile the differences. If (as is not unusual) a dozen or more subcommittees from each house have been involved in discussing the bill, more than a hundred members may appear at the conference committee (or “conference” for short) meetings.

After the conference negotiates the differences in House and Senate versions of the Bill, it is sent back to both bodies for a final vote; usually the bill is passed after all effort described above is completed. Before printing of the bill, it receives a numerical designation of the session of Congress and the number of the bill for that session. For example, the “Antiterrorism and Effective Death Penalty Act of 1996” (the “popular name” of the original bill) was originally introduced in the Senate of the 104th Congress and (in session from 1995 to 1996) as S735, and was the 132nd piece of legislation considered, so when passed it received the numerical indicator 104-132, in addition to its popular name, which is then abbreviated as “Public Law 104-132” or “PL 104-132”.

The president may sign the bill or choose to veto it, and Congress may override that veto with a two-thirds vote in both houses. Upon the president’s signature, or in the case of a veto followed by a Congressional override, a “bill” becomes a “law” and the various provisions of the law “statutes.” The vast majority of laws are denoted as “Public Laws” which means that they apply to individuals and their relationship with government or society. (There are also “Private Laws” applying to the relationships between individuals, such as contracts).

Laws are, in essence, codes of conduct, and Public Laws (also called “Acts”) often impose new rules for behavior of individuals, companies or institutions. Public Laws almost always also make modifications to existing laws that comprise the United States Code (formally abbreviated as “USC”), currently arranged in 51 “Titles,” really sections of law covering familiar aspects of life such as commerce and trade, crimes and criminal procedure, copyrights, food and drugs, taxes, foreign relations, alcohol and firearms, banks and transportation to name but a few. Of particular interest in biosecurity law is Title 42 – “The Public Health and Welfare” also denoted as “42 USC” – that is comprised of many hundreds of sections. So, perhaps unsurprisingly PL 104-132 made more than a dozen changes to Title 42 since laboratory safety and security naturally impact the public’s health. But it also made changes to 18 USC (“Crimes and Criminal Procedure”).

New Public Laws routinely mandate actions to be taken by cabinet departments in the executive branch of government, such as HHS. It is then the responsibility of the cabinet secretary to implement those actions. As we will see shortly, with recent biosecurity-related legislation, the secretaries of both HHS and USDA are now

6 http://www.law.cornell.edu/uscode/text
required to formulate and update a list of organisms and toxins that may be of particular importance to public health if inadvertently released or misused (for example in a biological weapon).

How does this implementation happen in practice? In order to execute new laws, the Secretary (one or more are always specified in the law) designates an agency within her department to publish an initial proposal indicating the intent of the executive branch to carry out the will of Congress, and it appears in the FR as a “notice of proposed rule-making” (NPRM), often within days of the president’s signature on the original Act. It is worth noting that the Secretary is granted latitude in interpreting Congressional intent, and as we shall see exercises considerable judgment in publishing the NPRM.

The FR is closely read by administrators in business, government, law, and law enforcement, along with individuals who may be affected by the new PL. Via the announcement in the FR, any interested party may submit comments or critiques of the agency’s proposed means of implementing the law. Comment periods typically last 30–60 days (and may even be supplemented by public meetings if the new regulations that result from the rule-making procedure are sweeping enough), after which the agency assembles the suggestions and testimonies. A “Final Rule” is published in the FR as soon as the agency adjudicates the (frequently disparate) collection of views, which then becomes new regulation. The agency and cabinet secretary are under no obligation to accept any particular individual or individual entity’s views, and by no means is the decision on the structure and requirements of the new regulation a matter of simply tallying the net opinion of commenters. Rather, the agency uses its own experts – including attorneys who interpret the oft-subtle intention of the Congress – in formulating the regulation. It may take many months for the cabinet department to publish the Final Rule.

Shortly after the Final Rule appears in the FR, the new regulation is enshrined in the Code of Federal Regulations (the CFR, not to be confused with the United States Code) where it remains in force until a review is ordered by Congress, or if a new legislation includes provisions for updating the regulation; agencies may also publish proposed updates in the FR and solicit additional comments from individuals or organizations likely to be affected. The CFR is, like the USC, organized by “Title” whose names mostly parallel the Titles in the US Code (unfortunately, this is not always the case).

In summary, after a bill is introduced into Congress, debated and then enacted into law by signature of the president, executive agencies (e.g. HHS or Department of Agriculture) are then mandated to implement the detailed requirements by a “rule-making” process that is initiated with a NPRM published in the FR. Individuals, organizations, businesses or other entities are invited to comment on the agency’s initial plans. These comments are considered by the agency tasked with crafting the new rule, and then published as a “Final Rule” that is, in practice, the set of regulations that carry out the will of Congress which are then recorded in the CFR.

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7 Announcements in the Federal Register are designated by volume number and the first page of the announcement. For example, “61 FR 29327” starts at page 29,237 of the 61st volume of the Federal Register. In general, any announcement may be found online at: https://www.federalregister.gov/
Historical origins of current biosecurity regulations

On April 19, 1995 the Alfred P. Murrah Federal Building in Oklahoma City was destroyed by a truck bomb planted by Timothy McVeigh, a former soldier and militia movement sympathizer. This event, which resulted in 169 deaths and hundreds of injuries and property damage in excess of a half-billion dollars, stood as the deadliest terrorist attack on US soil until the downing of the World Trade Center 6 years later.

With the memory of yet another terrorist attack – the 1993 World Trade Center bombing – still fresh, President Bill Clinton had already introduced antiterrorism legislation in early 1995 (called “the Omnibus Counterterrorism Act”), but within days of the Oklahoma City event Senate Majority Leader Robert Dole was motivated to propose a similar but more sweeping bill, “The Comprehensive Terrorism Prevention Act,” S735 [14]. When initially introduced, the most prominent component of the Act was a limitation on habeas corpus actions brought to federal court by prisoners suspected of an act of terror. When finally passed by the Congress as The Antiterrorism and Effective Death Penalty Act (ATEDPA) of 1996 exactly 1 year to the day after the Oklahoma tragedy, the new law (PL 104-132) included requirements for the Secretary of HSS to:

- “Establish and maintain a list of each biological agent that has the potential to pose a severe threat to public health and safety,” based on specific criteria including effect on human health, degree of contagiousness, availability and effectiveness of immunization and treatments for illness caused by the agent, and “any other criteria that the Secretary considers appropriate in consultation with scientific experts.”
- Regulate transfers of listed biological agents including establishing and enforcing safety procedures, safeguards to prevent access to listed agents for use in terrorism or other criminal purposes while maintaining “appropriate availability of biological agents for research, education, and other legitimate purposes” [16].

The Act was signed into law by President Clinton on April 27, 1996. On June 10th of the same year, the CDC, acting on behalf of the Secretary of HHS published in the FR a “NPRM” soliciting comment on implementing the new requirements of PL104-132 to ensure public safety, strengthen public–private sector accountability and collect information concerning the location of potentially hazardous infectious agents while tracking the acquisition of those agents. The SATL was born. The CDC also

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8 By 1996 there were at least two other factors motivating the Congress. In May of that year Larry Wayne Harris a member of Aryan Nation and a self-styled biological weapons expert purchased several vials of Yersinia pestis, the causative organism of plague from the American Type Tissue Collection a microbiologic supply house in Maryland. Harris was arrested but at the time there was no US law prohibiting individuals from purchasing disease-causing organisms so officials charged him with mail fraud because he misrepresented himself as the operator of a legitimate medical laboratory. Also a few weeks before Mr Harris’ arrest on March 20, 1995 members of Aum Shinrikyo, an apocalyptic cult in Japan, released an unknown quantity of sarin gas in the Tokyo subway system. Thirteen people were killed and more than 6000 individuals with varying symptoms (some of which were surely related to panic alone) were seen in hospital emergency rooms [15].

9 http://www.gpo.gov/fdsys/pkg/FR-1996-06-10/pdf/96-14707.pdf
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proposed procedures for alerting law enforcement of unauthorized attempts to acquire select agents. A 30-day comment period permitted interested parties to address:

- the content of the “Select Infectious Agents List” initially comprised of 26 organisms (viruses, bacteria, Rickettsiae species and fungi) and 14 toxins,
- registration and inspection of facilities transferring Select Infectious Agents,
- transfer requirements (including transfer forms),
- verification procedures including requiring facilities to have a “Responsible Official” (RO),
- agent disposal requirements,
- exemptions for biosafety level 2 and clinical laboratories.

The final rule took into account over 200 written comments and was published in the FR on October 24, 1996. The SATL (changed from “Select Infectious Agents List”) was comprised of 13 viruses or virus groups, seven bacteria species, three Rickettsiae species, Coccidioides immitis as the sole fungal species and 12 toxins. At the same time, the CDC also informed entities owning select agents that it would provide application forms for facility registration with the possibility of facility inspection depending on documentation provided and agent transfer forms. The Federal Bureau of Investigations (FBI) (and perhaps other federal agencies) would have access to records and databases for law enforcement purposes.

The final rule took effect on April 15, 1997 and was placed in the CFR Title 42 Part 72 (later moved to Part 73, see below).

Thus, the history of creating the initial SATL and its associated reporting and implementation requirements was:

- Introduction of “The Comprehensive Terrorism Prevention Act” to Congress as a result of terrorist attacks on US soil.
- Passage of a markedly revised bill renamed as “The Antiterrorism and Death Penalty Act” of 1996 and signed into law as PL 104-132 by President Clinton.
- Changes are made to the US Code and in particular Title 42 of the US Code, “Public Health and Welfare”. Because the Secretary of HHS was required by PL 104-132 to regulate transfer of certain dangerous pathogens and toxins, the CDC, an agency within HHS and acting on its behalf, publishes a proposed Rule Making for implementation in the FR.
- The CDC accepts comments from any interested party, since the proposed rule was only a proposal – written by technical experts in the department.
- After comments were received the CDC made decisions for implementation of the PL (it did not have to accept any particular suggestion, nor did it accept most) and published a Final Rule. The “Final Rule” included the date when the new regulations will go into effect.

10 http://www.gpo.gov/fdsys/pkg/FR-1996-06-10/pdf/96-14707.pdf
11 As a starting point, the CDC adopted the list of organisms and toxin on the “Australia list”, a pre-existing export control regulation limiting the shipment of potentially dangerous biological materials to only selected states (initially comprised of 15 countries). See http://www.australiagroup.net/en/origins.html
12 http://www.gpo.gov/fdsys/pkg/FR-1996-10-24/pdf/96-27082.pdf
13 The entire Code of Federal Regulations is available electronically at: http://www.ecfr.gov/. The most recent version of the Select Agents List may be seen at: http://www.ecfr.gov/cgi-bin/text-idx?SID=08582cfb436f670fc3796e016a114198&node=42:1.0.1.6.61&rgn=div5
14 http://www.law.cornell.edu/uscode/text/42
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- The rule was added to US CFR. In this case Title 42 of the CFR part 73 (abbreviated in legal parlance as “42 CFR 73” now entitled as the “Select Agents and Toxins” section of the CFR) specifically part 73.3.\(^{15}\)

A very similar series of legislative and regulatory events took place after the terror attacks of September 11, 2001. Less than 2 months after that horrific day, the Congress passed the *Uniting and Strengthening America by Providing Appropriate Tools Required to Intercept and Obstruct Terrorism* \[^{17}\] (abbreviated as the USA PATRIOT Act in a rather tortured acronym). While not directly impacting laboratory biosecurity, the Act defines possessing a biological weapon as a crime and also defined a “restricted person” as one who may not ship or transport any biological agent or toxin that is listed as a select agent (adding to Title 18 of the US Code “Crimes and Criminal Procedures” an entirely new section in “Biological Weapons” chapter called “Possession by restricted persons”).

But 9/11 led to yet another milestone in biosecurity law in the following year. The *Public Health Security and Bioterrorism Preparedness and Response Act of 2002* (PHSBRA) \[^{18}\] was passed in Congress and signed by the president in June. From the standpoint of biological laboratory management and work the Act required the following:

- The Secretaries of both HHS and USDA must undertake a biennial review of select agents and are instructed to consider agents that should be added or removed from the SATL. The purpose of including the Department of Agriculture was so that biological materials dangerous to animals or plants could be included in the SATL. This would thus enlist the expertise of specialists in the USDA not necessarily available at CDC.
- Required all persons in possession of a Select Agent notify the Secretary of HHS by September 2002.
- Required security risk assessments to be conducted by the FBI of the Department of Justice, in effect security clearances for all individuals who might work with select agents in any laboratory possessing them.
- Required all facilities in possession of select agents to designate an RO who “will need to inventory its facility and consult with others (e.g. principal investigators) as necessary to obtain the information required for this application”.\(^{16}\)

The scope of PL 107-188 was enormous and several iterations of proposed rules for implementing the law were published in the FR. Briefly the official publications (date and FR volume and page) bringing the terms of the law into effect were:

- 7/2/02 (67 FR 44464): Proposed data collection requirements for public comment issued by the CDC.
- 7/12/02 (67 FR 46364): Preliminary Guidance for Notification of Possession of Select Agents issued by the CDC.
- 8/12/02 (67 FR 52383): Interim rule and request for comments, APHIS.
- 12/13/02 (67 FR 76886): Interim final rule (“interim” rules are published as rules that are enforced but which may be changed by subsequent public comment).

\(^{15}\) [http://www.ecfr.gov/cgi-bin/text-idx?SID=ad0987e5119d0bce7cf252d00f17de1&node=42:1.0.1.6.61&rgn=div5](http://www.ecfr.gov/cgi-bin/text-idx?SID=ad0987e5119d0bce7cf252d00f17de1&node=42:1.0.1.6.61&rgn=div5)

\(^{16}\) [Federal Register Vol. 67 (127) July 2, 2002: http://www.gpo.gov/fdsys/pkg/FR-2002-07-02/pdf/02-16674.pdf](http://www.gpo.gov/fdsys/pkg/FR-2002-07-02/pdf/02-16674.pdf)
12/3/03 (68 FR 62245): Second interim final rule.
3/18/2005: Final rule regarding possession use and transfer of select agents and toxins.

Throughout the 2½-year period – which also included a public meeting in late 2002 – about 150 written comments were received by officials at the CDC and many more at APHIS (the agency within and designated by USDA to implement the requirements of the legislation). Although most of the suggestions submitted by commenters were rejected by the agencies, some clarifications and changes were made to the proposed rules as a result. An additional outcome was a re-organization of 42 CFR 73 to make its structure similar to analogous rules promulgated by the USDA that appeared in 9 CFR 121.17

Thus, there are three legislative milestones that have largely defined biosecurity as practiced in laboratories in the United States: The Anti-terrorism and Effective Death Penalty Act of 1996 establishing the first SATL and reporting and archiving requirements for transfer of those agents (later put into effect by the CDC acting on behalf of the Secretary of HHS); the US PATRIOT Act of 2001, defining possession of a biological weapon as a crime, and also “restricted persons” who may not possess or transfer any biological agent – that is, not merely “Select Agents” that can cause disease; and PHSBRA that required a biennial review of the SATL by both the Secretary of HHS and the Secretary of Agriculture, and also mandated security requirements for access to listed agents, including background checks (a “Security Risk Assessment”) of laboratory researchers and designated RO, performed by the FBI and ultimately approved by the Attorney General.

Recent Executive Orders (EOs) affecting laboratory biosecurity

Presidents may issue EOs in order to “take Care that the Laws [of the United States] be faithfully executed”18 even though there is no explicit provision for these declarations in the US Constitution. Since the time of George Washington through the administration of Barack Obama more than 13,000 EOs of various types – some proclamations, others directives for implementing laws or establishing policy – have been issued.19 It is solely at the discretion of the president to determine whether a policy matter or resolution of ambiguities in the administration of laws warrant an EO. So it has been with biosecurity. Shortly before the end of his term in office on January 9, 2009, President George W. Bush issued EO 13486 entitled “Strengthening the Biosecurity of the United States” establishing a formal Working Group of the same name comprised of cabinet secretaries, the Attorney General, the Director of

17 In addition, 7 CFR 331 contains the rules promulgated by USDA for the select agent list for organisms that can damage important food crops. As should now be unsurprising, Title 9 of the Code of Federal Regulations is “Animals and Animal Products”; with part 121 addressing “possession, use and transfer of select agents”. Title 7 of the Code is “Agriculture” with part 331 also referring to select agents.
18 US Constitution Article II Section 3.
19 http://www.presidency.ucsb.edu/data/orders.php
National Intelligence and the Director of the National Science Foundation [19]. Three tasks were assigned to the Working Group:

1. Review and evaluate the efficiency and effectiveness of existing laws, regulations, guidance and practices relating to select agents and toxins, physical, facility, and personnel security and assurance at Federal and non-Federal facilities that function as described above.
2. Obtain information or advice from heads of executive departments and agencies, elements of foreign governments and international organizations with responsibility for biological matters.
3. Prepare a written report to the president, including recommendations for new legislation, regulations, guidance, or practices in laboratories including new oversight mechanisms [4].

In its report in May 2009 the Working Group recommended:

- With respect to Select Agents and Toxins, that the US government perform a risk assessment for each listed item and develop a “stratification scheme that includes biodefense and biosecurity criteria as well as risk to public health.”
- With regard to personnel security enhancements to the “Security Risk Assessment … to allow for improved vetting of US citizens and foreign nationals” with access to select agents and toxins.
- To improve physical security, the development of a “a set of minimum prescriptive security standards.”
- A review of existing risk assessment of transportation of select agents and toxins.

Professional societies were quick to respond to the Working Group’s recommendations. For example, the American Biological Safety Association (ABSA) commented that: “Select Agent Regulations are [already] sufficiently rigorous” and “should not be made more prescriptive;” that the “Federal Government absolutely should not develop prescriptive physical security requirements;” and that inspections of laboratories with select agents would benefit from “careful selection and training of inspectors,” probably reflecting frustration on the part of laboratory managers with questionable results of inspections. There were also concerns that “additional restrictions on shipping will inhibit important research” citing the example of H1N1 samples from Mexico that had to be shipped to Canada because of restricting US import and transfer regulations.20

The ABSA also objected to components of enhanced personnel security requirements that would include the “two person rule” in all circumstances and recommended instead that federal funds “be used to develop or enhance existing biosafety and biosecurity training programs.” Finally ABSA objected to licensure of individual researchers as “unnecessary and undesirable.”

Notwithstanding the criticism of the Working Group’s recommendations, EO 13486 was followed about 18 months later by EO 13456 in July 2010. This directive required the Secretaries of HHS and Agriculture to review the SATL in order to:

- designate a subset of the List called “Tier 1 agents” that present “the greatest risk of deliberate misuse with most significant potential for mass casualties” or other severely adverse effects on the economy or public confidence.

20 http://www.absa.org/pdf/090530ABSAcommentsBWG.pdf
• identify options for graded protection of these Tier 1 agents with “tailored risk management practices” and
• consider reducing the number of agents on the SATL.

Thus, since the attacks of September 2001, US presidents have shown increasing interest in biosecurity reflected in two key EOs, the most recent of which directed subject matter experts at CDC and USDA/APHIS to review the SATL, to further stratify the agents based on risk (for greatest potential harm if released), and to make changes in security arrangements at facilities to minimize those risks. We will see shortly how these EOs melded with existing law to generate the most recent modifications to the SATL and other security and procedural requirements in laboratories.

Some important documents from professional and ad hoc groups

In addition to the report of the Working Group summarized above, several other reports from biological scientists stand out as key documents providing guidance to the Congress and the executive branch on measures that might be taken to enhance biosecurity in the United States.

The National Research Council in 2003 released “Biotechnology Research in an Age of Terrorism” [20]. This document focused mainly on Dual Use Research of Concern, but also recommended the creation of a National Science Advisory Board for Biodefense (NSABB) that, inter alia would periodically review existing federal government legislation to “provide protection of biological materials and supervision of personnel working with these materials.” In addition the Council opined “it is crucial to avoid well-meaning but counter-productive regulations on pathogens. Rules for containment and registration of potentially dangerous materials must be based on scientific risk assessment and informed by a realistic appraisal of scientific implications.” The Council suggested that the NSABB could “provide advice … about revising regulations in response to new developments” and that “rules governing transfer of materials between laboratories… might also be regularly reviewed by NSABB” in light of new threats.

Shortly thereafter, the NSABB was chartered by the Secretary of HHS [21].

In 2008, the Commission on the Prevention of Weapons of Mass Destruction, Proliferation, and Terrorism (C-WMD) tasked by the Congress in PL 110-53 (Implementing Recommendations of the 9/11 Commission Act of 2007) produced a comprehensive report entitled “World at Risk” [22]. The Commission regarded as “likely” that there would be a terrorist attack somewhere on the globe utilizing a weapon of mass destruction (WMD) within 5 years, and further believed that terrorists were more likely to use a biological than a nuclear weapon. The Commission’s prediction has fortunately not come to pass. Nonetheless, few would regard the risk of WMD use as receding. Among the recommendations of the Commission of importance to biological scientists were that the United States should: “conduct a comprehensive review of the domestic program to secure dangerous pathogens, … tighten
government oversight of high-containment laboratories, … [and] promote a culture of security awareness in the life sciences community.” These measures closely align with the biosecurity principles of access control to disease-causing organisms and toxins, accounting of those agents and personnel reliability programs.

The last of the Commission’s recommendations was explored in detail by the NSABB in 2009. In a report entitled “Enhancing Personnel Reliability Among Individuals with Access to Select Agents” [23], board members recognized that research programs involving nuclear materials often involved sensitive national security issues and might serve as a model for addressing the “insider threat” problem in biological laboratories, but at the same time realized that there are significant differences between pathogens and nuclear materials (including nuclear materials that might be part of weapons systems). Noting that local institutions were already successfully screening individuals who might work with select agents (and based on the very few applications rejected by the Department of Justice in the Security Risk Assessment Program), the Board counseled against a “formal, national Personnel Reliability Program” as it might have “unintended and detrimental consequences” for scientific research. Instead the Board suggested that individual institutions should work to enhance a “culture of responsibility and accountability” in combination with education on biosecurity issues within professional societies. The Board also recommended reducing the list of select agents or stratifying them further by risk, which was in fact taken up by EO 13546 in 2010. Thus, we can see the careful considerations of the C-WMD and NSABB finding their way into US government policy.

At about the same time and in response to a request from the Homeland Security Council at the White House, the National Academies of Sciences released its study “Responsible Research with Biological Select Agents and Toxins” that listed a series of recommendations similar to those from the NSABB and also suggested stratifying the list of select agents by risk [24]. The Academy group further advised that some baseline level of physical security be established for facilities holding select agents.

Also in 2009, a US government interagency “Working Group on Strengthening the Biosecurity of the United States” created under EO 13486 reviewed procedures at facilities possessing Select Agents and Toxins, specifically:

- Evaluating the efficiency and effectiveness of existing laws, regulations … and practices relating to physical, facility and personnel security and assurance at facilities.
- Obtaining advice from heads of US government executive agencies and departments and elements of foreign governments and international organizations that have similar responsibilities.

Like the C-WMD, the Working Group recommended a reduction or stratification of select agents so that security measures might be tailored to the level of risk; require at the local level that facility managers review the behavior and practices of individuals with access to select agents; and development of a set of minimum security standards with enhancements based on risk associated with select agents [4].

All of these reports ultimately contributed to the content of the 2010 EO 13546, “Optimizing the Security of Biological Select Agents and Toxins in the United States,” which as noted earlier called for a special designation for the highest-risk agents as “Tier 1 agents,” and graded protection of the items on the SATL.
Legislation, deliberation and executive exhortation become regulation

The timing of EO 13456, early July of 2010, coincided with the second Biennial Review of the SATL and an “Advanced NPRM and request for comments” appeared in the FR on 7/21/10 (75 FR 42363) that included the new “tiering” as directed by the president.

As a result of EO 13456 and acting on authorization already enshrined in law as a result of the PHSBPRA of 2002, over the next 2 years the CDC (acting on behalf of the Secretary of HSS) and the APHIS (acting on behalf of the Secretary of Agriculture) produced a final rule on October 5, 2012 that established “Tier 1” Agents as follows:

- **Human disease agents and toxins (CDC)**
  - Ebola virus,
  - *Francisella tularensis*,
  - Marburg virus,
  - Variola major virus,
  - Variola minor virus,
  - *Yersinia pestis*,
  - Botulinum neurotoxin,
  - Botulinum neurotoxin producing species of *Clostridium*.

- **Animal disease agents (APHIS)**
  - foot and mouth disease virus,
  - Rinderpest virus.

- **“Overlap” agents (CDC and APHIS)**
  - *Bacillus anthracis*,
  - *Burkholderia mallei*,
  - *Burkholderia pseudomallei*.

And, some agents and toxins were removed from the SATL. Specifically,

- at the recommendation of the CDC:
  - Herpesvirus 1 (Herpes B),
  - *Clostridium perfringers* toxin,
  - *Coccidioides* species,
  - Eastern equine encephalitis virus,
  - Flexal virus,
  - West African clade of Monkeypox,
  - *Rickettsia rickettsii*.

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21 77 FR 61084

22 As the SATL undergoes periodic revision, the list produced in the rule-making process of October 2012 is not necessarily the same as the current one that may be found at: [http://www.selectagents.gov/SelectAgentsandToxinsList.html](http://www.selectagents.gov/SelectAgentsandToxinsList.html) [last accessed 25.05.15]
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- all conotoxins except the short paralytic alpha conotoxins,
- Venezuelan Equine Encephalitis Virus (subtypes ID and IE) were also removed from the “overlap” select agent category.

- At the recommendation of APHIS:
  - Akabane virus,
  - bluetongue virus (exotic), bovine spongiform encephalopathy agent,
  - camel pox virus,
  - *Ehrlichia ruminantium* (heartwater),
  - Japanese encephalitis virus,
  - malignant catarrhal fever virus (*Alcelaphine herpes virus type 1*),
  - Menangle virus,
  - Vesicular stomatitis virus (exotic): Indiana subtypes VSV–IN2, VSV–IN3.

Finally, three viruses were added to the SATL with the publication of the new rule: SARS-CoV (the organism causing the severe acute respiratory syndrome first identified in 2003), Lujo virus (a hemorrhagic fever virus closely related to Old World arenaviruses) and Chapare virus (a New World arenavirus also causing hemorrhagic fever in humans).

For Tier 1 agents, new requirements emerged from the CDC and APHIS as follows (with their location in the CFR noted for ease of reference):

- Clinical laboratories must immediately report by telephone, facsimile or e-mail the identification of any of the HHS or overlap Tier 1 agents (42 CFR 73.5 and 73.6).
- Security plans for select agents must also include for Tier 1 agents (42 CFR 73.11):
  - A description of pre-access suitability assessment of persons who will have access to Tier 1 agents.
  - Procedures for how an RO will coordinate their efforts with the entity’s safety and security professionals.
  - Procedures for ongoing assessment of the suitability of personnel with access to Tier 1 agents.
- Additional security enhancements must be put in place to (42 CFR 73.11):
  - Limit access to Tier I agents only those individuals who are approved by the HHS Secretary after FBI security risk assessment.
  - Outside of normal laboratory hours, RO approval access to agents.
  - A minimum of three security barriers where each barrier adds to the delay in reaching secured areas where agents are stored.
- Facility biosafety plans must include an occupational health program for individuals with access to Tier 1 agents (42 CFR 73.12).
- Facility incidence response plans must describe an entity’s response in the case of failure to detect intrusion and procedures for notifying appropriate officials and law enforcement (42 CFR 73.14).

Hence, four related but distinct forces have resulted in current laboratory biosecurity practices and procedures: statutes, landmark studies from practicing professionals, EOs from the president, and recommendations from practitioners via professional organizations, academia and individual comment (see Figure 1.1). It is important to note that via the rule-making process subject matter experts in laboratory practices and management had the opportunity to influence the formulation of the SATL and
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some of the physical security and accounting practices now in force at facilities holding those potentially dangerous materials.

The formation of the SATL and its associated security measures is a good template for gaining insight into federal agency rule making after a new law is enacted. Since the comments received by an agency can be quite extensive, they may overwhelm the ability of individuals reviewing them to do so within the 30- or 60-day comment period. In addition, some comments may point to new information that was either overlooked or not available at the time of the original FR publication. Thus, the rule-making period may be extended; notification of such is made via the FR.

The evolution of the SATL – the centerpiece of much of the biosecurity apparatus in the hundreds of facilities across the United States that hold the agents – is summarized in the timeline from 1996 through 2012 when the “tiering” of select agents came into force as a result of EO 13546 (see Figure 1.1). It appears clear that biosecurity rule-making has, in the recent timeframe, become very complex and may extend over several years, involving as it does a wide variety of Congressional mandates and the need to solicit comments from researchers in academia and industry working with dangerous pathogens. Whether or not the plethora of regulations will result in actually strengthening biosecurity remains to be seen.

Figure 1.1 Biosecurity timeline. SATL, Select Agent/Toxin List; PL, Public Law; EO, Executive Order; NAS, National Academy of Sciences.

23 Professionals in the field are not always successful in changing the initial draft of an agency’s proposed rules. In this particular episode of rule-making, 30 comments were received “from researchers, scientific organizations, laboratories and universities” (see 77FR 61056, dated October 5, 2012, accessible at: http://www.gpo.gov/fdsys/pkg/FR-2012-10-05/pdf/2012-24434.pdf). Most of the recommendations for changes in the proposed rule were rejected by, in this case, the Department of Agriculture, but the rationale for each rejection was specifically addressed. In other cases, recommendations from comments are more frequently incorporated into the Final Rule.
What might the future bring?

As of the time of this writing, there have been two recent events that are likely to result in yet more oversight of biosecurity practices in the United States.

On June 6, 2014, CDC researchers working in the Bioterrorism Rapid Response and Advanced Technology (BRRAT) laboratory transferred samples of *B. anthracis* (Ames strain) from a Biosafety Level 3 (BSL-3) suite to a BSL-2 lab on the belief that neither viable vegetative cells nor spores were in the samples as they had been subjected to an inactivation process before being moved. However, at least some of the samples were not sterile, potentially risking infection in CDC personnel, although subsequent investigation revealed this possibility to be “highly unlikely” [25]. This breach of biosafety practice was announced on July 19, 2014 [26].

Further, on July 8, 2014 the CDC reported that several vials labeled “variola” (variola virus is the causative agent of smallpox) had been found at a cold storage facility operated by the Food and Drug Administration on the campus of the National Institutes of Health (NIH) in Bethesda, Maryland [27]. Subsequent testing performed at the CDC confirmed the presence of viable virus in two of six vials. By international agreement, all variola virus is to be kept in secure storage at two laboratories: at the CDC in Atlanta and at the State Research Center for Virologic Research in Koltsovo, Russia, and is technically “owned” by the WHO, which must approve all experiments involving its use. While such news was not wholly surprising – variola had turned up in at least two European laboratories since the WHO required destruction of the virus or transfer to the official WHO repositories – it did raise the question of accountability for extraordinarily dangerous pathogens in the United States.

Also, in January 2014 at the CDC’s Influenza Division laboratory in Atlanta, a sample of low-pathogenic avian influenza type A (subtype H9N2) was contaminated with a highly pathogenic avian influenza type A (subtype H5N1) with “subsequent shipment of the contaminated culture to an external high-containment laboratory.” Although there were no apparent adverse effects, the episode clearly posed a risk to individuals in the receiving laboratory (and perhaps others who handled the material before it was shipped). Many new review procedures and oversight processes were put into place (presumably at substantial cost) at the CDC [28].

These episodes were more than an embarrassment for the NIH and CDC. Since the CDC provides the staff to carry out inspections at facilities registered to hold Select Agents and Toxins, most researchers would probably assert that the CDC has a special responsibility to uphold all biosafety and biosecurity regulations. The head of the BRRAT resigned. Perhaps even worse, the United States was in violation of a critical international agreement intended to prevent the reintroduction of variola into the human population.

At the end of July, CDC Director Frieden announced the formation of an external advisory group comprised of leading researchers and biosecurity experts to “provide

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24 The vials labeled “variola” were co-located with a total of 327 vials in 12 boxes some of which were labeled as containing other possible SATL agents such as *Rickettsia* sp. See [http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm405434.htm](http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm405434.htm)
advice and guidance to the CDC Director and ... Director of Laboratory Safety” [29]. It remains to be seen whether the advisory group’s recommendations will lead to further revision of 42 CFR 73 and 9 CFR 121 biosecurity regulations. Many researchers have noted that well-intentioned regulations designed to protect public safety and limit the illicit use of select agents result in unintended consequences including significant costs to bring facilities into compliance with technical requirements [30] and decreased productivity as measured by publication count and even abandonment of research involving live agents [31].

**Summary**

Current-day biosecurity procedures and regulations are, in large measure, a result of several near-calamitous terrorist events in the United States, raising public awareness of the threat posed by a particular infectious agents and toxins that, if released by intent or accident, could have devastating effects on human or animal health, and even that of important food plants. Congress has responded by passing legislation that imposes formidable requirements on laboratories possessing “select agents and toxins,” and the executive branch of government has, as compelled by the Constitution, implemented those mandates with the assistance of technical experts inside and outside of government. Substantial but hard-to-quantify costs accrue to facilities that in turn may decrease research productivity.

It is probably impossible to know whether existing biosecurity legislation passed starting in 1996 actually reduces the chances of illicit use of biological materials or even accidents in their transfer or handling. Recent security breeches will likely result in additional Congressional action and EOs, some of which may prove costly. Laboratorians have opportunities to influence the process of rule-making by which laws are brought into effect, but only with a keen awareness of the process and review of proposed regulations in order to provide key federal agency administrators with critiques and suggestions to reduce the prospect of new biosecurity requirements that are either ineffective or onerous. While there is no guarantee that intervention from professionals will stem the tide of regulations, laboratory managers, biosafety officers and institutional oversight committee members must make an effort to remain current with proposed rules and to vigorously comment to regulatory agencies.

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