



***OLD PLAGUES, NEW THREATS:***  
**THE BIOTECH REVOLUTION AND ITS**  
**IMPACT ON US NATIONAL SECURITY**

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## ACRONYMS

BSL	Biosafety Level
BTTA	Botulinum Toxin Type A
BW	Biological Weapons
BWC	Biological and Toxin Weapons Convention
CAN	Counterfeit Alert Network
CBP	Customs and Border Protection
CBRN	Chemical, Biological, Radiological, and Nuclear
CBW	Chemical and Biological Weapons
CDC	Centers for Disease Control and Prevention
CPT	Current Procedural Terminology
CW	Chemical Weapons
CWC	Chemical Weapons Convention
DEA	Drug Enforcement Agency
DHHS	Department of Health and Human Services
DHS	Department of Homeland Security
DoJ	Department of Justice
EPA	Environmental Protection Agency
FBI	Federal Bureau of Investigations
FDA	Food and Drug Administration
FY	Fiscal Year
GAO	Government Accountability Office
HCPCS	Healthcare Common Procedure Coding System
ISU	Implementation Support Unit
LD50	Lethal Dose, 50 percent (Median Lethal Dose)
NDC	National Drug Code
NIAID	National Institute of Allergy and Infectious Diseases
NIH	National Institutes of Health
OSHA	Occupational Safety and Health Administration
PDMA	Prescription Drug Marketing Act
R&D	Research and Development
RFID	Radio-Frequency Identification
SARS	Severe Acute Respiratory Syndrome
TTX	Tetrodotoxin
USDA	Department of Agriculture
VA	Department of Veterans Affairs
WMD	Weapons of Mass Destruction

## PREFACE

Dear Reader,

I am pleased to present a new publication from the Stimson Center, *Old Plagues, New Threats: The Biotech Revolution and its Impact on US National Security*, written by Rita Grossman-Vermaas, Brian Finlay and Elizabeth Turpen. It is based on original, in-depth research into an evolving issue that demands immediate attention and a coherent and proactive policy response—namely, the impact of the biotechnological revolution on US national security.

For more than a decade, the confluence of global terrorism and biotechnology has been a major concern of the national security and policy-making communities. The October 2001 anthrax attacks, coming right after 9/11 and its aftershocks, led to rapid changes in budget priorities in our security and law enforcement agencies. Nonetheless, continued advances in biotechnology, combined with bureaucratic stovepipes across the US government, present new opportunities for would-be terrorists and a significant threat to public safety. This study focuses on toxins and virulent biological products and technologies that have been developed for beneficial therapeutic use, but have the potential for misuse if they fall in the wrong hands. Neither the public health community, nor the national security community, is being charged with planning a response in the event of an attack or accident involving these products and technologies. This project and its reports underscore how the national security field is changing as a result of globalization and stresses that a new, diverse set of actors must be involved in formulating creative solutions to emerging security challenges.

The collaboration among experts in the private sector, government agencies and think-tanks was a key factor in contributing to the completion of this study. While the analyses and recommendations are those of the authors alone, we want to acknowledge the important insights provided by these various sectors. We hope that this report will be useful to anyone who is concerned and wants to learn more about the rapid developments occurring in the biotechnology field and their potential impact on US and global security.

Sincerely,



Ellen Laipson, President/CEO  
The Henry L. Stimson Center

## FOREWORD

Beyond the obvious security challenge of terrorism itself, perhaps no other threat has approached the level of concern or complexity than the widespread recognition of emerging infectious diseases as a burgeoning transnational security threat. While concern about biological weapons (BW) proliferation among states existed during the Cold War, it was not until the early 1990s that fears about biological weapons in the hands of terrorists commanded the nation's attention.

As national security strategies dug deeper into the "bioterror" threat, it became clear that this new challenge lay at the doorstep of agencies and government departments that had never been part of the national security dialogue before. To combat a disease outbreak that might disrupt American society, federal and local departments responsible for public health and safety have begun to play a pivotal role in preserving the nation's security, alongside the traditional defense and security apparatus.

In addition to this more strategic justification, several incidents have provided added impetus for our research. Of particular relevance was the dissemination of anthrax through the US postal system in October 2001, which killed five people and infected eighteen others. There were also the 2004 and 2007 botulinum toxin poisoning cases in Florida and Las Vegas. While the motivations in the two latter cases involved financial gain rather than ill intent, the ease in which the biological agents were obtained and used raise serious questions about US capacities to keep track of bulk biological agents and toxins—particularly select agents.

Behind these cases is the looming knowledge that there are major gaps in biological agent control measures, importation practices, and supply chain security in the United States and around the world at a time when terrorist groups are showing increasing interest in pursuing a biological weapons capability. In 2007, the Stimson Center provided a baseline assessment of these cases and developed recommendations for improving US, private sector and international capacities to close any loopholes.

Now, this study considers new developments that have occurred in the past year and aims to assist Congress and industry stakeholders in navigating the complexity of old and new regulatory and security concerns. By doing so, we hope to assure that a more coordinated and proactive approach is developed to meet national security challenges today and in the future.

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## BACKGROUND

### THE THREAT OF BIOTERRORISM

*BY THEIR NATURE, TERRORIST EVENTS ARE UNEXPECTED...AND...  
EVOKE A SENSE OF FEAR AND UNCERTAINTY<sup>1</sup>*

For decades, national security and law enforcement communities in our country, and in countries around the globe, have worked diligently to address the threat posed by the deliberate spread of infectious pathogens and deadly toxins. As potential agents of mass destruction, biological pathogens and toxins are inexpensive, readily accessible in nature, and, if weaponized effectively, particularly dangerous. Meanwhile, the biotechnological revolution has broadened the availability of “dual-use”<sup>2</sup> equipment and expanded exponentially the number of individuals with the knowledge necessary to engage in nefarious biological weapons research.

Although biological weapons are often put in the same category as nuclear and chemical munitions by national security specialists, there is one fundamental and important difference: pathogens are living organisms. The implications of this are clear. While the damage caused by a chemical or nuclear weapon would be a single event causing potentially devastating damage over the immediate

site of its target, the release of a lethal pathogen could efficiently spread from victim to victim over time, creating a cascade of disease that could threaten the entire global population.

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Pathogens are unseen, multiply within the victim and can manifest in lethal, contagious and disfiguring symptoms. Toxin weapons range in effect from disabling to lethal and often require only very small quantities to create great harm. For example, botulinum toxin is the most deadly compound known to man. A botulinum toxin-based product or the raw toxin itself could be obtained and misapplied with the intent of producing a series of botulism cases. While it is not self-replicating,<sup>3</sup> a series of botulinum attacks in five US population centers would cause a major panic and confusion to ensue.<sup>4</sup>

Aside from the widespread loss of human life, a bioterrorist incident could yield deep economic losses. A declassified study by the Government of Canada’s Health Ministry found that, absent an immediate and effective prophylaxis regimen, a deliberate biological attack using aerosolized anthrax could result in direct economic losses of up to

C\$6.5 billion. A similar attack using botulinum toxin would generate economic losses of up to C\$8.6 billion.<sup>5</sup>

Table # 1		
<b>Total Cases, Deaths, Hospitalizations and Cost After Anthrax and Botulinum Toxin Exposure by Day</b>		
	<b>Anthrax</b>	<b>Botulinum Toxin</b>
Total Cases	50,000	50,000
Total Deaths	32,875	30,000
Total Days of Hospitalization	33,2500	4,275,000
<b>Total Cost</b>	<b>C\$6.5 billion</b>	<b>C\$8.6 billion</b>
Source: R. St. John, B. Finlay, C. Blair, "Bioterrorism in Canada: An Economic Assessment of Prevention and Post-attack Response," <i>Canadian Journal of Infectious Diseases</i> , 2001; 12(5): 275-284.		

Terrorist objectives are rarely limited to just physical violence: The goal is almost always to induce intense psychological distress in individuals and to cause political and social disruption on society as a whole. John Negroponte, the former Director of National Intelligence, testified to the US Senate, "We are...concerned about the threat from biological agents...which would have psychological and possibly political effects far greater than their actual magnitude."<sup>6</sup> This was reinforced by his agency's 2007 Annual Threat Assessment in a discussion of intelligence about terrorist groups attempting to acquire biological weapons and materials.<sup>7</sup>

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***A deliberate biological attack using aerosolized anthrax could result in direct economic losses of up to C\$6.5 billion.***

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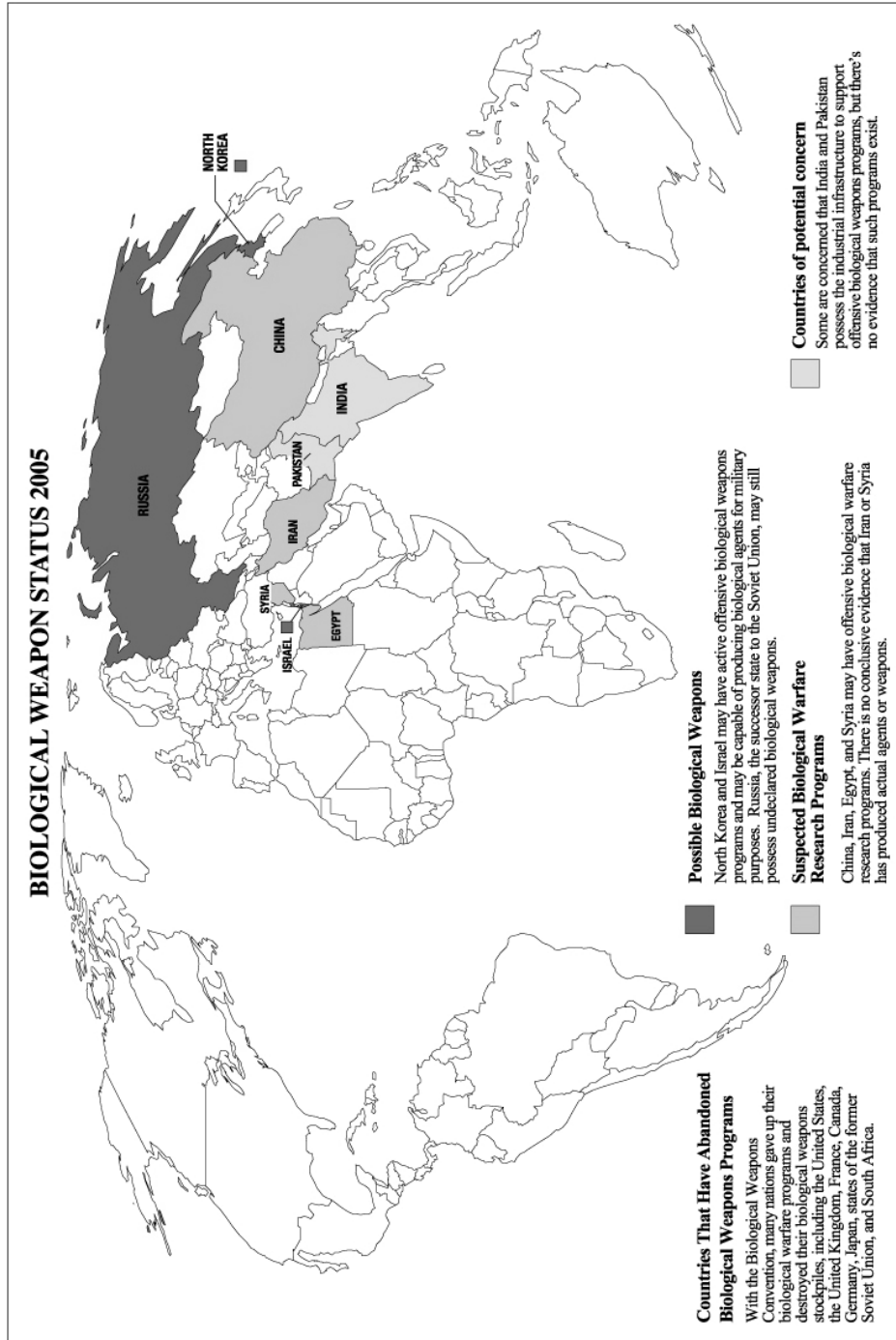
The US also continues to suspect that Iran, North Korea, Syria, China, Egypt, and Algeria have, or seek to have, biological weapons programs, in contravention of their obligations under the Biological and Toxin Weapons Convention (BWC). Several of these countries are also suspected of state-

sponsored terrorism. The 2005 assessment of biological weapon status produced by the Carnegie Endowment for International Peace underscores the global threat (see Figure #1).

There is also precedent for the use of pathogens and toxin as bioweapons by sub-state terrorist groups. On at least three occasions, Aum Shinrikyo, the Japanese cult responsible for the 1995 sarin gas attacks in the Tokyo subway system, dispersed botulinum toxin aerosols at multiple sites in downtown Tokyo and at US military installations in Japan. Fortunately, their dissemination attempts were unsuccessful in causing fatalities, seemingly "due to faulty microbiological technique, deficient aerosol-generating equipment, or internal sabotage."<sup>8</sup> If the operations of this group had not been



**Figure #1**  
**Biological Weapons Status 2005<sup>9</sup>**



disrupted by Japanese authorities, it is presumed that it would have eventually overcome the technical hurdles and successfully weaponized the toxin. Aum Shinrikyo also experimented with both anthrax and Ebola cultures.

The ease of access to biological agents and weapons expertise by state and non-state actors has greatly increased and become widely recognized as a serious domestic and international security threat. This concern has only been heightened with scientific advances, the collapse of the former Soviet Union, the events of September 11, 2001, and the dissemination of the spore-forming bacterium that causes anthrax through the US postal system in October 2001.

## BIODEFENSE AND PREPAREDNESS

These realities, catalyzed by the 2001 anthrax attacks, brought about a fundamental reordering of the US government's budgetary priorities to address the emerging threat. The US policy response in its various manifestations has come under significant criticism

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*Independent analyses almost always concentrate their attention on the national security and law enforcement agencies and their role in proliferation prevention and response; comparatively little thought has been given to the growing role of public health agencies and industry—specifically the biotech and pharmaceutical sectors.*

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by independent experts and the news media—particularly during the past seven years. While independent analyses almost always concentrate their attention on the national security and law enforcement agencies and their role in proliferation prevention and response, comparatively little thought has been given to the growing role of public health agencies and industry—specifically, the biotech and pharmaceutical sectors.

Recognizing industry's growing interest in developing and marketing pharmaceutical products that contain or bear "select agents"<sup>10</sup>—which we refer to as "select products"—the Cooperative Nonproliferation Program at The Henry L. Stimson Center undertook an independent assessment of the potential risks associated with these products.

This study, published in 2007, concluded that while it is unlikely that products on the US market today would be reverse-engineered into biological weapons of mass destruction (WMD), access to the technologies necessary to develop these pharmaceutical products could provide would-be bioterrorists with critical knowledge in the development of a potentially devastating weapon of mass destruction. Moreover, the illicit diversion, tainting and/or misapplication of these products could inspire a mass panic akin to the use of a radiological weapon.<sup>11</sup> Recent intelligence indicates that terrorists and terrorist states are devoting ever-increasing resources to the development of biological agents for the purpose of causing mass casualties. As a result, governments around the world have been

investing heavily in select agent research and development (R&D) for the development of biological countermeasures.<sup>12</sup> This reality further challenges the ability of national governments to exercise effective oversight of potentially hazardous research.

This report updates the findings of our initial assessment, *Regulating Access to and Control of Dangerous Pathogens: Implications for the Pharmaceutical Industry*, published in February 2007, and further highlights the growing discontinuities among the national security agencies, law enforcement agencies, and public health agencies of the US government.

## SUMMARY OF THE STIMSON CENTER'S 2007 STUDY

The findings of the Stimson Center's February 2007 study<sup>13</sup> emerged from discussions with the private sector, industry, and national security experts, as well as intensive research on the security implications of potentially dangerous agents and products. The study examined:

- General bioweapons threats in the wake of recent acts of terrorism carried out worldwide;
- Specific proliferation and bioterrorism threats posed by the accumulation of “bulk” toxins currently used in the manufacture of pharmaceuticals produced either on the “black market” or by legitimate sources with inadequate regulation; and,
- Public health concerns regarding the possible misuse or unlicensed use of biological pathogens and toxins, as exemplified by the 2004 Florida case involving the paralysis of four victims from unapproved use of botulinum toxin type A (BTTA).

From this assessment, we identified three main vulnerabilities in the public health and bioterrorism prevention and response strategies of the United States. We concluded that present oversight mechanisms fall short in the following key areas:

1. **An inability to adequately monitor the custody of bulk biological** material produced domestically or imported from foreign manufacturers;
2. **A lack of common standards governing chain of custody or “pedigree requirements”** for pharmaceutical products, particularly those which bear or contain select biological agents and toxins; and,
3. **A failure to track the dissemination of the product to the end user**, which could be achieved through unique nomenclature identities in the drug coding system for disparate types of products that are manufactured from the same raw material, particularly those that contain biological agents and toxins.

Ultimately, our report warned that the rapidly expanding market for therapeutic biologics generally, and medical biological agents and toxins specifically, may present new avenues for international or domestic bioterrorists to attack the United States. By

identifying multiple vulnerabilities in the command-and-control of raw agents and finished products circulating within US borders, the report established the need for a new “**cradle to grave**” mechanism to ensure the nonproliferation of select agents outside of the controlled channels. The need is particularly acute for those medical products that are, bear or contain select agents. To this end, the report provided a series of pragmatic recommendations to the US government, to private industry, and to the international community on:

- Biological weapons proliferation prevention and biosecurity;
- Counterfeit pharmaceuticals; and,
- Potential misuse of legitimate pharmaceutical or cosmetic products.

The authors of the original report interviewed a broad cross-section of individuals within relevant government agencies and across the private sector. Nonetheless, since the 2007 study was published, there have been significant shifts in the political and scientific environments that warrant re-examination of our findings and recommendations. Among the many evolving events are the forthcoming presidential elections, legislative activity in the 110<sup>th</sup> Congress, greater media and congressional attention to the proliferation of biosafety level 3 and 4 labs, accidents in US and international high-containment labs, and public safety concerns about the importation of pharmaceuticals and other products from China and other developing countries.

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<sup>1</sup> Dana A. Shea, “Terrorism: Background on Chemical, Biological, and Toxin Weapons and Options for Lessening Their Impact,” Congressional Research Service (December, 1 2004): 5, accessed at: <http://www.fas.org/irp/crs/RL31669.pdf>.

<sup>2</sup> The phrase dual-use is defined as goods, technologies or know-how that have the potential for both military and civil uses.

<sup>3</sup> Shea, “Terrorism: Background on Chemical, Biological, and Toxin Weapons...,” 2.

<sup>4</sup> There are seven distinct botulinum toxins (A-G) produced by different strains of the bacterium, each producing a different immunological response.

<sup>5</sup> Ronald St. John, Brian Finlay, and Curtis Blair, “Bioterrorism in Canada: An Economic Assessment of Prevention and Post-attack Response,” *Canadian Journal of Infectious Diseases*, Volume 12, Number 5 (Oakville, ON: Pulsus, 2001): 275-284.

<sup>6</sup> John D. Negroponte, “Annual Threat Assessment of the Director of National Intelligence for the Senate Select Committee on Intelligence” (February 2, 2006), accessed at: [http://www.dni.gov/testimonies/20060202\\_testimony.pdf](http://www.dni.gov/testimonies/20060202_testimony.pdf).

<sup>7</sup> John D. Negroponte, “Annual Threat Assessment of the Director of National Intelligence,” presented to the Senate Select Committee on Intelligence (January, 11 2007), accessed at: [http://www.dni.gov/testimonies/20070111\\_testimony.pdf](http://www.dni.gov/testimonies/20070111_testimony.pdf).

<sup>8</sup> Working Group on Civilian Biodefense (Stephen S. Arnon et al.), “Botulinum Toxin as a Biological Weapon,” *Journal of the American Medical Association*, Volume 285, Number 8, (Chicago, American Medical Association, 2001): 142.

<sup>9</sup> Joseph Cirincione, Jon Wolfsthal and Miriam Rajkumar, *Deadly Arsenals: Nuclear, Biological, and Chemical Threats*, Second Edition (Washington: Carnegie Endowment for International Peace, 2005), accessed at: <http://www.carnegieendowment.org/static/npp/deadlymaps.cfm>.

<sup>10</sup> Biological pathogens and toxins that might be used for terrorism have been listed by the US Centers for Disease Control and Prevention as “select agents”—potential weapons whose transfer in the scientific and medical communities is regulated to keep them out of unfriendly hands. These “select agents” are varied and include viruses, bacteria, rickettsiae, fungi and biological toxins.

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<sup>11</sup> There are interesting parallels between needed select agent/product tracking systems and existing control systems for radiopharmaceuticals. Nuclear materials and sources are abundant and are used in a wide range of applications beyond weapons, from smoke detectors to medical diagnostics. Radiopharmaceuticals, which use medical isotopes from uranium and other radioactive materials, are an example of the use of nuclear materials in medicine—they are used in the diagnosis and treatment of many diseases involving the brain, thyroid, lungs, liver, kidneys, and for research and development. With much debate, particularly in the nonproliferation community, *The Energy Policy Act of 2005* made it possible to export highly-enriched uranium (uranium that can be used in nuclear weapons), for medical isotope production to Canada, Belgium, France, Germany, and the Netherlands. But, presumably with concern for the potential of theft, diversion, and proliferation, it also mandated that a tracking system be developed for high-consequence radiation sources in the United States. Specifically, it mandated that the system should enable the identification of each radiation source by serial number or other unique identifier; reporting within 7 days of any change of possession of a qualifying radiation source; and reporting within 24 hours of any loss of control of, or accountability for a radiation source (Section 630, *Energy Policy Act of 2005*, Public Law 109-058, July, 29 2005). There are similarities between this radiological source tracking system and the pharmaceutical tracking/select agent program, including the potential danger of the materials. But the system for select agents has yet to be effectively integrated into a seamless mechanism that crosses industrial sectors and government stovepipes. Perhaps when it is developed, strategists should borrow lessons from the decades of concern over radiological materials and source protection.

<sup>12</sup> NATO Parliamentary Assembly, “Resolution 321 on Terrorism with Chemical, Biological, Radiological and Nuclear Weapons”(2002), accessed at: <http://www.nato-pa.int/default.Asp?SHORTCUT=284>; Department of Defense Chemical, Biological, Radiological and Nuclear Defense Program, *Annual Report to Congress* (Washington: Department of Defense, 2004), accessed at: <http://www.fas.org/irp/threat/cbw/dod-cbnrd-2004.pdf>; David Press, “Experts Concerned about Biological Research at DHS’s NBACC,” Biosecurity Briefing, UPMC Center for Biosecurity (August 4, 2006), accessed at: <http://www.upmc-biosecurity.org>; US Congress, *Project Bioshield Act of 2004*, Public Law 108-276 (July 21, 2004), accessed at: <http://thomas.loc.gov/cgi-bin/bdquery/z?d108:s.00015;>; Negroponte, “Annual Threat Assessment of the Director of National Intelligence...” (February 2, 2006).

<sup>13</sup> “Regulating Access to and Control of Dangerous Pathogens” is available on the Stimson Center’s website at: [http://www.stimson.org/cnp/pdf/Regulating\\_Access\\_03.07.pdf](http://www.stimson.org/cnp/pdf/Regulating_Access_03.07.pdf).



**CRADLE TO GRAVE:  
ELEMENTS OF A  
COMPREHENSIVE SAFEGUARDS SYSTEM FOR  
SELECT AGENTS AND PHARMACEUTICAL PRODUCTS**

At present, the system used by the United States government to track select agents—and subset of pharmaceutical products that are, bear or contain select agents—is inadequate, beset by bureaucratic inefficiencies and challenged by stovepipes in the policymaking and policy execution phases. Governments' ability to effectively regulate this growing industry is complicated by the growth of the market and the proliferation of private companies involved in research, development and sale of products that capitalize on both legitimate market forces and illicit opportunities. Thus, we reiterate the need to develop an integrated "cradle to grave" system that tracks bulk biological agents and toxins from their raw form, all the way through to their point of use as finished pharmaceutical products.

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We define five distinct "links" to an inviolable chain of custody. A weakness or failure in any one link could result in a catastrophic failure to prevent proliferation:

1. Acquisition and transportation of the raw toxin
2. Research and development
3. Production
4. Distribution
5. Injection/Use by the end user

Currently, US and international regulation of these links consists of a patchwork of regulations by government security and public health agencies. These federal agencies have failed to work together effectively to establish a seamless safeguards system that would prevent the illegal diversion of raw materials and products, leaving open the possibility for a potentially catastrophic national security and public health emergency.

We therefore conclude that a cradle-to-grave system of oversight and regulation should include:

- New efforts to **control bulk biological materials** of proliferation concern;
- A systematic approach to **oversight and regulation during the research and production phases of drug development**;
- Innovative new efforts to ensure the **security of finished products** that contain select agents; and,
- New **awareness-raising measures** across private industry and the US government designed to break down the stovepipes between public health and national security.

This “Chain of Custody” approach that tracks so-called “select products” from start to end is best illustrated in [Figure #2](#) (see fold-out).

The following sections discuss the challenges to achieving coherent and cohesive regulation within each of the five “links” of our proposed chain of custody. The goal of this system is to prevent the illicit diversion of potentially dangerous select agents anywhere along the acquisition, transportation, research, development, production, and distribution chain. Critical elements include:

**LINK ONE: Securing bulk biological material**

- Amending the Select Agent Program
- Controlling the proliferation of Biosafety Lab Level 3 (BSL-3) and Biosafety Lab Level 4 (BSL-4) research facilities

**LINK TWO: Preventing diversion of select agents in research and development**

- Policing the growing number of innovator companies that experiment with and use select agents to develop pharmaceutical products
- Regulating new “follow-on” companies (generics) entering the marketplace that experiment with or use select agents to develop pharmaceutical products

**LINK THREE: Regulating production involving select agents**

- Policing innovator companies in the manufacture of “select products”
- Regulating new “follow-on” companies (generics) in the manufacture of “select products”

**LINK FOUR: Protecting products that contain or bear select agents as they move through distribution channels**

- Disrupting and eliminating the foreign and domestic counterfeit drug market, as well as sources of diversion
- Managing the challenges of drug importation and re-importation
- Tracking drug pedigrees through the distribution chain

**LINK FIVE: Ensuring safe delivery to the patient**

- Drug tracking and drug coding



# OLD PLAGUES, NEW THREATS

## Chain of Custody for Regulating Access to and Control of Dangerous Pathogens and Toxins



### Securing Select Agents



### Research and Development



### Production



### Distribution



### Injection Into Customer

Develop and implement a system to track the distribution of bulk biological material produced domestically or imported from foreign manufacturers

Ensure all R&D facilities that possess select agents meet strict biosafety and biosecurity standards

Ensure all manufacturing facilities that possess select agents meet strict biosafety and biosecurity standards

Ensure the rapid implementation of a federal standard for chain-of-custody requirements, or 'pedigree requirements' for pharmaceutical products, particularly those most susceptible to counterfeiting and diversion including 'select products'

Revise the current medicare drug coding system, and the reimbursement structure that flows from this system, in order to maintain unique nomenclature identities

Prevent unlicensed individuals or companies from obtaining select agents

Designate single agency responsible for accurate accounting of all BL-3 and BL-4 facilities and standards

Expand upon a national program for counterfeit 'susceptible products' by establishing a sub-category of pharmaceuticals and other products derived from select agents

Ensure all distribution facilities that possess select agents meet strict biosafety and biosecurity standards

Institute routine reviews of efficacy of the Select Agent Program

Establish common biosafety and biosecurity training

Strengthen FDA's ability to conduct foreign inspections

Pursue advanced anti-counterfeiting and pedigree tracking measures that will mitigate public health threats from counterfeit products

*Note: Point of Diversion*

Ensure innovator and follow-on companies exercise strict controls over select agents and select products

Create stricter uniform standards for state requirements governing the licensure and oversight of wholesale distributors

Develop incentives for private companies to encourage investment in and use of anti-counterfeit technologies, such as RFID technology

Collaborate with foreign stakeholders to develop strategies to deter and detect counterfeit drugs globally

Establish a multi-disciplinary task force comprised of representatives from national security, law enforcement, the life sciences, and private industry to develop a sustained communication network to develop a strategy to mitigate the risks of counterfeit products, misuse of legitimate products, and linkages to bioterrorism

Participate in and assist the further development of the 'Counterfeit Alert Network'

*Note: Point of Diversion*



## LINK ONE: SECURING BULK MATERIAL

In 2004, a physician suspended from his medical practice ordered a vial of botulinum toxin type A from a northern California manufacturer and supplier of bacterial toxins.<sup>1</sup> The company, List Biological Laboratories in Campbell, California, did not give due diligence to vetting the customer. It requested only a name, address, and billing information to process his order.<sup>2</sup> The vial, intended for research purposes only, contained as much as ten million units of the toxin—10,000 times that of a normal dose of a standard Food and Drug Administration-approved BTTA pharmaceutical product. The physician attempted to reconstitute the raw toxin into a “home-made” version of a popular brand-name drug, “BOTOX®”, and injected himself and three others. All four persons were hospitalized with critical symptoms of botulism poisoning.

In the course of the investigation of these cases, it was also discovered that the physician was involved in a scheme to market and distribute an unapproved and unlicensed botulinum toxin product to other physicians and consumers through a company called Toxin Research International. Medical practitioners in the US were targeted and offered a reduced price on an alleged brand-name product. Ultimately, three doctors and four corporations were charged in this scheme for distributing the counterfeit product for unlicensed use on humans. They had obtained over 3,081 vials, each containing five nanograms of BTTA and other ingredients, in a formulation intended to replicate a licensed product.

### US CONTROL MEASURES

A major component of America’s biodefense strategy is prevention and counterproliferation, largely by controlling access to dual-use agents and the technology and know-how that can be used for both legitimate research and for bioweapons development. While the national security community has been preoccupied with the threat of bioterrorism, particularly since the 2001 anthrax attacks, the mandate is rarely extended to US public health agencies that possess critical competencies and are important potential partners in prevention. An integrated strategy requires coordination among all federal public health and security agencies responsible for “select agent” control, as well as with the biotech/pharmaceutical industry and stakeholders across the US drug supply chain. This section addresses elements of the US biosecurity and countermeasure development strategies, along with vulnerabilities identified through research and interviews with Congressional and agency staff. Of course, to be effective, domestic interventions must extend beyond the borders of the United States to other would-be providers around the globe. While a detailed assessment of preventative international measures is beyond the scope of this report, Appendix II contains an overview of the international controls, treaties, resolutions, and arrangements that help to prevent the unlawful development and use of biological materials, technology and weapons.<sup>3</sup>

## THE SELECT AGENT PROGRAM

The 1996 *Antiterrorism and Effective Death Penalty Act*<sup>4</sup> provided the first list of biological agents and toxins—or select agents—whose transfer between laboratories was to be regulated. The *Public Health Security and Bioterrorism Preparedness and Response Act of 2002* revised and expanded the Select Agent Program.<sup>5</sup> The list includes

*An integrated strategy requires coordination among all federal public health and security agencies responsible for select agent control.*

human, plant and animal pathogens. Controls over human pathogens are administered by the US Centers for Disease Control and Prevention (CDC). Controls over animal and plant pathogens are overseen by the US Department of Agriculture (USDA). This list is also consistent with the Australia Group control lists (See Appendix II), as well as the BWC Draft Protocol—with the exception of Severe Acute Respiratory Syndrome (SARS).

The list includes many of the most dangerous pathogens and toxins known, including the Ebola virus, *Bacillus anthracis* (anthrax), conotoxins, botulinum neurotoxins, and *Yersinia pestis* (the plague). The US Select Agent Regulations created a method by which all legal entities in possession of the above-listed agents must register with the CDC:

1. Possession of any of the listed agents (the comprehensive Select Agent List can be found in Appendix III of this study),
2. Activities related to the use of the agents (i.e., research use, receipt, transfer),
3. Quantity of the agent and the biosafety precautions used in storage and research activities.<sup>6</sup>

Table #2  
**Sample List of Select Agents as Regulated by the Department of Health and Human Services**

Botulinum neurotoxins  
 Conotoxins  
 Ebola  
 Marburg Virus  
 Monkeypox Virus  
 Ricin  
 Tetrodotoxin  
 Shigatoxin  
 Smallpox Virus  
*Yersinia pestis* (plague)

Source: DHHS and USDA Select Agents and Toxins, 7 CFR Part 331, 9 CFR Part 121, and 42 CFR Part 73; accessed at: <http://www.cdc.gov/od/sap/docs/salist.pdf>

The purpose of the Select Agent program is to protect these materials from theft and diversion. The USA PATRIOT Act also contained additional restrictions regarding access to these agents.

Despite the legislative actions to ensure security of these agents, the patchwork of agencies having different missions leads to a particularly incoherent approach to this safety and security challenge. For example, once a select agent becomes part of product development, it leaves the purview of CDC. The Food and Drug Administration (FDA) is then responsible for overseeing clinical trials for pharmaceuticals and for product safety. Perhaps in the higher levels of policymaking, FDA officials are broadly aware of the Select Agent Program. But, in its day-to-day operations, anecdotal evidence suggests that FDA does not distinguish products that bear or contain select agents from its oversight of any other pharmaceutical product under its regulatory control. Similarly, FDA reviews the safety of imported drugs in addition to Customs and Border Protection (CBP), which regulates the importation of pharmaceutical products, including those derived from select agents, but does so to identify counterfeit and adulterated products with no apparent distinction of the potential risks stemming from importation of select agents. Since 2007, Congress has relaxed the laws on the personal importation of pharmaceuticals entering the US, further increasing the potential public safety threat from counterfeit, as well as licit products derived from select agents.

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*Anecdotal evidence suggests that FDA does not distinguish products that bear or contain select agents from its oversight of any other pharmaceutical product.*

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In separate jurisdictional domains, the Bureau of Industry and Security at the Department of Commerce oversees a separate select agent export program for transfers abroad in accordance with US obligations to the Australia Group. The Departments of Defense and State also have responsibility for select agents, insofar as the listed pathogens intersect with export control guidelines. It is clear that these intersecting federal agencies routinely fail to coordinate across the select agent mandate. After being transferred to the finished pharmaceutical product stage, there exists a virtual vacuum of security authority, leaving select agents vulnerable to diversion for illegitimate and untraceable uses. **In the interest of public health and national security, the disconnect and absence of communication among these agencies must be rectified.**

With respect to coordination, CDC partners with USDA to ensure standardized regulations and works with the Department of Justice (DoJ) in conducting security risk assessments of individuals and entities seeking to register with the program. But, neither select agent research nor oversight is systematically coordinated among the numerous other agencies that research or ensure the security of these pathogens.

Within the narrower bounds of counteragent research, the Select Agent Program has generated new intelligence on the uses, whereabouts and origins of the most high-consequence pathogens and toxins. Since its implementation in 2005, CDC, along with USDA and DoJ, has conducted 607 inspections to ensure that proper biosafety and biosecurity measures are in place; authorized 2,199 requests to transfer select agents; and granted access approvals to 14,868 individuals to work with select agents. As of September 25, 2007, there have been 37 violations referred to the Department of Health and Human Services (DHHS) for investigation, of which DHHS has levied civil penalties against ten.<sup>7</sup> There have been no confirmed losses or thefts of a select agent. However, there have been three confirmed accidental releases of a select agent, which were identified by illnesses in five lab workers who were exposed to the agents.<sup>8</sup>

Many in the national security policy community believe that the program is a valid, effective approach for preventing a biological weapons incident. But one does not have to dig too deeply among the opinions of various scientists and researchers to find disagreement.<sup>9</sup> As one scholar suggested, some complaints about the rules may be regarded as typical growing pains associated with a new system being imposed in a sector that has not been heavily regulated. Other objections are more serious, reflecting fundamental philosophical differences regarding whether the current system overemphasizes the “guards, gates, and guns” approach to physical security, and diverts resources that might be more fruitfully applied to research or more effective means of security.<sup>10</sup>

In 2000, The Henry L. Stimson Center conducted a study to enhance understanding about the impact of these regulations on a typical select agent researcher. That study found:

1. *Logistical issues and immediate impact:* Early implementation of the select agent rules was both chaotic and inconsistent. Many institutions and professional societies found that the rules were not clear and were inconsistent.
2. *Paperwork burden:* Many researchers found that the new regulations placed an undue burden on their time, diverting resources from research and supervision to paperwork.
3. *Physical security:* Many researchers complained that the physical security upgrades imposed upon institutions and academic research facilities were better suited to nuclear or chemical facilities, rather than biological stockpiles. They also complained that the standards would fail to detect the surreptitious removal of a small amount of pathogen that would be sufficient to start a new culture.
4. *Personnel security:* Researchers have long complained that security screening, like other clearance reviews, is slow and overly cumbersome.
5. *Destroying pathogen stocks:* The requirements for the physical security and inspection process apply an all-or-nothing standard, demanding the same degree of protection without concern for situation-specific security planning.
6. *Impact on international collaborations:* Restrictions placed on collaborations with foreign colleagues—a major conduit for the exchange of both samples and

scientific information—have significantly hampered the ability of US researchers to engage in foreign research partnerships.<sup>11</sup>

Many argue that not only does the program itself have loopholes that are easily circumvented, but also that the current list of agents is misguided. Some also argue that US biosecurity standards and requirements are insufficiently sensitive to foreign contexts. For instance, what would be considered an exotic disease in the US might be common in another part of the world, thereby making it impossible to systematically prevent its acquisition, such as naturally occurring Ebola in Africa. Similarly, as the US encourages other countries to adopt the Select Agent Program and other aspects of US biosecurity and biosafety standards in order to harmonize laboratory practices, it fails to take into account different levels of capacity in other public health systems. The lack of flexibility creates a barrier to international scientific collaboration and training, which is ultimately detrimental to US public health and security. Balance between security concerns and the needs of the US and global scientific community must be found. **At a minimum, particularly with advances in technology, CDC and its federal partners should routinely review the select agent program and its implementation to ensure effective response against new threats and vulnerabilities.**

An additional shortcoming is that the program does not track the chain of custody of biological agents from their raw material stage, through the research phase, and then through their development into pharmaceutical products. More importantly, there are no standardized government or industry regulations that adequately prevent unlicensed persons or companies from obtaining access to raw biological agents. **Regulations covering the legal and illegal production and use of pathogens and toxins must be strengthened.**

## **PROLIFERATION OF BIOSAFETY LEVEL 3 AND 4 LABORATORIES**

In August 2007, contamination of foot-and-mouth disease was discovered at several farms near Pirbright in the United Kingdom. Pirbright is the site of several high containment labs that work with the virus. An ensuing investigation found that poor maintenance practices were the culprit of the outbreak. Long-term damage and leakage of the drainage system that serviced the Pirbright site had resulted from cracked and leaky pipes, displaced joints, debris buildup, and tree root ingress. Furthermore, it was found that preventative maintenance was not a regular practice. While the findings were not conclusive, it is believed contaminated waste leaked from deteriorated drainage pipes at Pirbright into the surrounding soil. The live virus was then carried offsite by vehicles splashed with contaminated mud. The incident highlights that ongoing maintenance plays a critical role in ensuring safe and secure laboratory operation. It also raises concerns about compromised standards at other labs around the world.<sup>12</sup>

A significant new development in the biosecurity and bioterrorism arena is the proliferation of high-containment biosafety laboratories in the United States and abroad. “High containment” generally refers to research being conducted at the two highest











biosafety levels, BSL-3 and BSL-4. According to the Center for Biosecurity at the University of Pittsburgh Medical Center, “BSL-3 laboratories are used to study biological agents that are potentially lethal and transmissible by the aerosol route and require special safety design features, such as sealed windows and specialized ventilation systems. BSL-4 laboratories are typically used to study lethal agents for which no vaccine or therapy is available. They incorporate the BSL-3 laboratory safety features, plus additional safety features such as full body suits ventilated by life support systems.”<sup>13</sup>






Biodefense research, which impacts bioterrorism prevention and infectious disease surveillance and response capacities, including development of countermeasures, is a critical component of the broader US strategy to protect populations against a biological weapons attack. Much of this research, particularly on some of the most harmful pathogens, is conducted at the growing number of high-containment facilities, in many cases, by researchers with little or no laboratory experience with dangerous agents. This not only increases the risk of an accidental release of biological weapons agents, but also gives larger numbers of people access to the materials, technologies and knowledge that could be used to undertake a bioweapons attack. The rapid increase in the numbers of these facilities has also raised policy questions from the public and scientific community, including personnel training in biosafety standards, the adequacy of existing biosafety and biosecurity measures, and transparency of policies and research directions. Even the rationale justifying expansion has been called into question.<sup>14</sup> Because of the inherent dual-use nature of biodefense research, US activities have not only created skepticism within the US about the intentions, but perhaps of more grave consequence, in the international community. Suspicions have spurred other countries to pursue their own biodefense research programs, an unintended consequence of US policy.

Since September 11, 2001, annual funding for research and development on medical and other countermeasures to biological weapons has increased from \$580 million to more than \$3 billion in fiscal year (FY) 2007.<sup>15</sup> Part of the funding has supported two initiatives designed to spur countermeasure research: Project BioShield, which has yet to realize its full potential, and the Biological Advanced Research and Development Agency, which was created to correct the perceived shortcomings of BioShield. Another large part of the funding has been used to construct additional high-containment laboratories.<sup>16</sup> Currently, there are five operational BSL-4 labs in the US and four more are under construction. The total number of federal and non-federal BSL-3 labs is unknown, but in addition to those in existence, thirteen additional BSL-3 laboratories are being built specifically for biodefense research. These are principally funded by the National Institute of Allergy and Infectious Diseases (NIAID).<sup>17</sup>

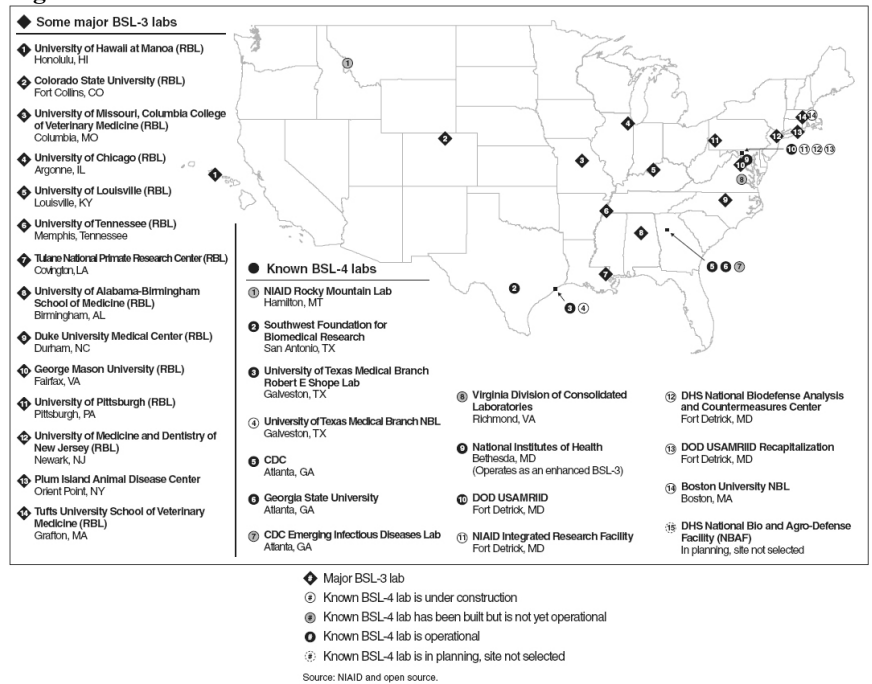
There are at least fifteen federal agencies that have some connection with BSL-3 and BSL-4 labs in the US, whether they own labs, provide funding, or are responsible for regulation. Table #3 depicts the various agencies involved.



Table #3 US Government Agencies with BSL-3 and 4 Laboratory Connections	
	<b>Centers for Disease Control and Prevention</b>
	The CDC has its own high-containment labs and regulates that portion of labs working with select agents and toxins that represent a risk to human health and safety
	<b>U.S. Department of Agriculture</b>
	The USDA has its own labs and regulates labs working with select agents and toxins posing a risk to animal and plant health
	<b>National Institute of Allergy and Infectious Diseases</b>
	The NIAID has its own labs and is a major funding source for construction and research involving high-containment labs
	<b>National Institutes of Health (NIH)</b>
	The NIH both funds research requiring high containment and provides guidance that is widely used to govern many of the activities in high-containment labs
	<b>Food and Drug Administration</b>
	The FDA has its own labs and regulates manufacturing of biological products, some of which require high-containment labs
	<b>Department of Commerce</b>
	The Commerce Department regulates the export of agents and equipment that have both military and civilian uses, which are often found in high-containment labs
	<b>Department of Defense</b>
	The Defense Department has its own labs and funds research requiring high-containment labs
	<b>Department of Labor's Occupational Safety and Health Administration (OSHA)</b>
	OSHA regulates some activities within high-containment labs, as well as general safety in most high-containment labs
	<b>Department of State</b>
	The State Department regulates the export of agents and equipment that are specifically designed for military use from defense-related high-containment labs and maintains a listing of some high-containment labs as part of the US commitments under the Biological and Toxin Weapons Convention
	<b>Department of Justice's Federal Bureau of Investigation (FBI)</b>
	The FBI uses high-containment labs when their forensic work involves dangerous biological agents

	<b>Department of Homeland Security</b> DHS has its own labs and funds a variety of research requiring high-containment labs
	<b>Department of Energy</b> The Department of Energy has several BSL-3 labs doing research to develop detection and response systems to improve preparedness for biological attack
	<b>Department of the Interior</b> The Department of the Interior has its own BSL-3 labs for work with infectious animal diseases
	<b>Department of Veterans Affairs (VA)</b> The VA has research and clinical BSL-3 labs for its work with veterans
	<b>Environmental Protection Agency (EPA)</b> The EPA has its own labs and also coordinates use of various academic, state, and commercial high-containment labs nationwide, as part of its emergency response mission

**Figure #3 - Selected BSL-3 and BSL-4 Laboratories in the United States<sup>18</sup>**

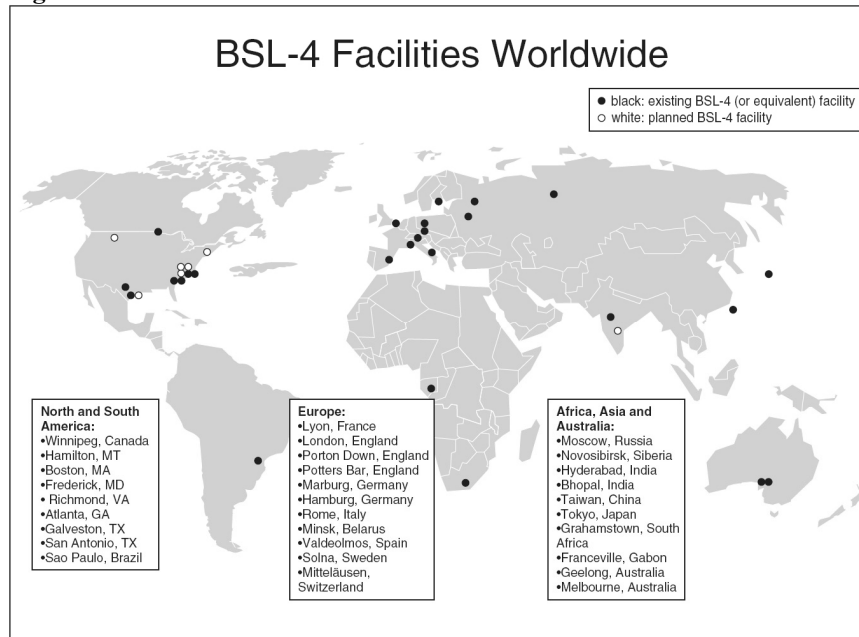


Information is available about laboratories that are registered with the CDC and USDA Select Agent Program and that receive federal funding. But comparatively little is known about the location, activities, and ownership of private laboratories outside the program.

The fact that the US government does not know the total number of such labs is a serious security concern.<sup>19</sup> We know that the number of active or planned BSL-4 labs in the US has increased from five, before September 2001, to fifteen at present.<sup>20</sup> With respect to BSL-3 labs, the Department of Homeland Security (DHS) and DHHS report that 633 high-containment laboratories are registered with the Select Agent Program.<sup>21</sup> A National Institutes of Health survey reported 277 BSL-3 facilities, both federal and non-federal, in the US with about 600 individual laboratories.<sup>22</sup> According to the Government Accountability Office (GAO), there are a total of at least 1,356 such labs. In addition to the worrying uncertainty about actual numbers is the fact that no one agency has the mandate to track the overall number of labs.

Table #4				
Summary of Known BSL-4 Labs Built in the United States, by Sector				
Sector	Before 1990	1990-2000	2001-Present	Total
Federal Government	2	1	6	9
Academic	0	1	3	4
State	0	0	1	1
Private	0	1	0	1
<b>Total</b>	<b>2</b>	<b>3</b>	<b>10</b>	<b>15</b>
BSL-3 Labs Registered with the CDC and USDA Select Agent Program, by Sector				
Sector	CDC-registered labs	USDA- registered labs	Total	
Federal Government	291	167	458	
Academic	429	58	487	
State	248	20	268	
Private	74	69	143	
<b>Total</b>	<b>1042</b>	<b>314</b>	<b>1356</b>	
Source: Rhodes, "High Containment Biosafety Laboratories."				

There are also an increasing number of high-level containment labs being constructed globally. South and Southeast Asia appear to be particular growth areas. In India, sixteen new laboratories were slated to become operational in 2006; five in Thailand; two in Indonesia; one in Bangladesh; and one in Myanmar.<sup>23</sup> Undoubtedly, the standards and processes that make US laboratories safer could help inform safety standards developed elsewhere in the world. In doing so, the US should not lose sight of managing its own capacity challenges as well.

**Figure #4 – BSL-4 Facilities<sup>24</sup>**

Given the increase in the number of BSL-3 and 4 laboratories in the US and abroad and other considerations, **the fifteen federal agencies that have control over such labs should establish a channel of communication that improves awareness regarding others' roles and ongoing research. With respect to non-federal labs, mechanisms should be established that ensure all such labs meet national standards of biosafety and biosecurity and are contained in official inventories.**

<sup>1</sup> United States District Court, Southern District of Florida, “Affidavit of FDA Special Agent Susan J. Leeds in Support of United States’ Motion for Temporary Restraining Order, Preliminary Injunction and Permanent Injunction,” Case Number 06-61717-CIV-COHN. Another example of unlicensed acquisition of deadly agents occurred in 1995. Larry Wayne Harris, a certified microbiologist and member of several extremist organizations, obtained three vials of the plague-causing bacterium *Yersinia pestis* from the American Type Culture Collection. To obtain the vials, he presented certification from the American Society for Microbiology and falsified documents. See Julius Younger, “April 10, 2000—Promoting Research Integrity at the American Society for Microbiology,” available at: <http://www.asm.org/policy/index.asp?bid=3437>; Eileen Dempsey, “Lab Blamed for Bubonic Plague Case,” *Columbus Dispatch* (May 20, 1995), accessed through Nexis.

<sup>2</sup> Center for Infectious Disease Research and Policy, “Reports Blame Florida Botulism Cases on Misused Toxin,” University of Minnesota (December 15, 2004), accessed at: <http://www.cidrap.umn.edu/cidrap/content/bt/botulism/news/dec1504botulism.html>.

<sup>3</sup> For additional recommendations related to international control of “select products,” see: Rita Grossman-Vermaas et al., “Regulating Access to and Control of Dangerous Pathogens: Implications for the Pharmaceutical Industry” (Washington: The Henry L. Stimson Center, 2007), accessed at: <http://stimson.org/pub.cfm?ID=333>.

<sup>4</sup> US Congress, *Antiterrorism and Effective Death Penalty Act of 1996*, Public Law 104-132 (April 24, 1996), accessed at: <http://thomas.loc.gov/cgi-in/bdquery/z?d104:s.00735:>.

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<sup>5</sup> US Congress, *Public Health Security and Bioterrorism Preparedness and Response Act of 2002*, Public Law 107-188 (June 12, 2002), accessed at: <http://thomas.loc.gov/cgi-bin/bdquery/z?d107:h.r.03448>.

<sup>6</sup> As noted in the text, there are also select agents and toxins which are overseen by the US Department of Agriculture for their potential to harm animals and plants, as well as a category of “overlap” agents and toxins which have the potential to affect humans, animals and plants.

<sup>7</sup> Richard E. Besser, “Oversight of Select Agents by the Centers for Disease Control and Prevention,” Statement before the Subcommittee on Oversight and Investigations of the House Committee on Energy and Commerce (October 4, 2007), accessed at: <http://www.hhs.gov/asl/testify/2007/10/t20071004b.html>.

<sup>8</sup> Ibid.

<sup>9</sup> There has yet to be a cost-benefit assessment of the Program’s goals and implementation. Many scientists feel constrained by a top-down regulatory system imposed on a traditionally lightly-regulated community. They believe it incorrectly focuses on “locking up” pathogens (an unrealistic endeavor in itself), establishes undue regulatory costs to institutions, deters future valuable research on select agents, and impractically imposes US regulatory standards and concerns on other nations which may not have similar priorities. These factors serve to hinder international collaboration and scientific openness which create the backbone of scientific advancement and the best chance the world has at protecting itself against both intentional and natural outbreaks of disease. This school of thought believes that the US should redirect its efforts to promote awareness among scientific communities in the US and other nations about improving and adhering to biosafety standards. The potential for a bioterrorism event to arise from suspicious activity within the scientific community could be a part of the awareness strategy, but not its main focus. For an in-depth assessment of the US regulatory framework in the biosciences, see Julie E. Fischer, *Stewardship or Censorship? Balancing Biosecurity, The Public’s Health, and The Benefits of Scientific Openness* (Washington: The Henry L. Stimson Center, 2006).

<sup>10</sup> Fischer, *Stewardship or Censorship?*, 23.

<sup>11</sup> Ibid., 22-39.

<sup>12</sup> The British are not the only developed country to experience biosafety challenges. The recent failure of Texas A&M University to report multiple incidents of exposure to CDC exemplifies the enduring challenges within the United States. One exposure to *Brucella* at the University resulted in illness by a worker not trained or authorized to work with the agent, and several incidents of potential exposure to *Coxiella burnetii*, which causes Q Fever. The University also failed to report specific types of experiments being conducted by researchers, and missing vials and animals. This incident highlights the need to overcome barriers to reporting, and the need for general, as well as agent-specific biosafety training. In June 2007, an hour-long power outage due to a lightning storm at the CDC’s new BSL-4 facility presented serious potential biosafety concern. Both primary and backup power sources to the facility were unavailable, shutting down the negative air pressure system, which keeps dangerous agents from escaping the containment areas. After investigating, CDC determined that a critical grounding cable buried outside the building had been cut by construction workers at an adjacent site. This had gone unnoticed by CDC’s facility managers and compromised the electrical system of the lab. No live agents were in the facility at the time of the outage, but the case resulted in CDC requiring an annual testing of the electrical grounding system. See: Keith Rhodes, “High Containment Biosafety Laboratories: Preliminary Observations on the Oversight of the Proliferation of BSL-3 and BSL-4 Laboratories in the United States,” Testimony before the Subcommittee on Oversight and Investigations of the House Committee on Energy and Commerce (October 4, 2007), accessed at: <http://www.gao.gov/new.items/d08108t.pdf>.

<sup>13</sup> Gigi Kwik Gronvall, Joe Fitzgerald, Allison Chamberlain, Thomas V. Inglesby, and Tara O’Toole, “High-Containment Biodefense Research Laboratories: Meeting Report and Center Recommendations,” *Biosecurity and Bioterrorism: Biodefense Strategy, Practice, and Science*, Volume 5, Number 1 (New Rochelle, NY: Mary Ann Liebert Publisher, Inc., 2007): 75, accessed at: <http://www.liebertonline.com/doi/pdfplus/10.1089/bsp.2007.0902>.

<sup>14</sup> Ibid.

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<sup>15</sup> Center for Arms Control and Non-Proliferation, “Biological and Chemical Weapons” (2007), accessed at: <http://www.armscontrolcenter.org/policy/biochem/>.

<sup>16</sup> Rhodes, “High Containment Biosafety Laboratories.”

<sup>17</sup> Gigi Kwik Gronvall, Testimony before the Subcommittee on Oversight and Investigations of the House Energy and Commerce Committee (October 4, 2007), accessed at: [http://energycommerce.house.gov/cmte\\_mtgs/110-oi-hrg.100407.Gronvall-Testimony.pdf](http://energycommerce.house.gov/cmte_mtgs/110-oi-hrg.100407.Gronvall-Testimony.pdf).

<sup>18</sup> Rhodes, “High Containment Biosafety Laboratories.”

<sup>19</sup> Kwik Gronvall, Testimony before the Subcommittee on Oversight and Investigations....

<sup>20</sup> Rhodes, “High Containment Biosafety Laboratories.”

<sup>21</sup> Department of Homeland Security and Department of Health and Human Services, “Report for Congress: Report Regarding Biocontainment Facilities,” Interim Report (April 18, 2005).

<sup>22</sup> Edward E. Gaunt, mgr., “Survey for Determining the Location, Capacity, and Status of Existing and Operating BSL-3 Laboratory Facilities within the United States,” Constella Health Sciences (June 2, 2005), accessed at: [http://www3.niaid.nih.gov/topics/BiodefenseRelated/Biodefense/PDF/BSL3\\_survey.pdf](http://www3.niaid.nih.gov/topics/BiodefenseRelated/Biodefense/PDF/BSL3_survey.pdf).

<sup>23</sup> Kwik Gronvall et al., “High-Containment Biodefense Research Laboratories...,” 76.

<sup>24</sup> *Ibid.*, 75-85.

## **LINKS TWO AND THREE ENSURING SECURITY: RESEARCH THROUGH PRODUCTION**

In 2000, a group of Australian researchers worked to genetically engineer the mousepox virus to produce a contraceptive vaccine to control mouse populations. Instead, their research yielded a virus so virulent that it killed all of the mice in the experiment within nine days of them being injected. The case has raised fears that the scientific techniques used—and readily available to others—might be co-opted to create biological weapons. Today, many hundreds of laboratories around the globe routinely perform thousands of different types of genetic manipulation experiments on a multitude of different organisms.

### **PHARMACEUTICALS: A SOURCE FOR BIOWEAPONS DEVELOPMENT?**

**A**necdotal evidence suggests that there is a growing interest among biotech companies and pharmaceutical manufacturers in products that bear or contain select agents. These products—herein referred to as select products—are unlikely to be used as mass-casualty biological weapons. However, the select agents within these products continue to be a grave concern for their potential for physical harm as well as a means to incite panic.

State and terrorist interest in biological weapons, alongside a growing biologics industry, necessitates consideration of the harmful potential for the unlicensed acquisition and misuse of raw, or “bulk,” biological agents and toxins that are stored and distributed globally and used to manufacture pharmaceutical products. This is particularly true of those defined as select agents by the CDC (See Appendix III).<sup>1</sup> Of even greater concern is the technical data shared by ostensibly legitimate companies in order to obtain market access to countries of proliferation concern.

In the US, there are currently two FDA-approved pharmaceutical products that use botulinum toxin, a select agent, as a main ingredient. BOTOX® uses botulinum toxin type A and Myobloc® uses botulinum toxin type B. A BOTOX® competitor, Reloxin®, is scheduled to come on the US market in 2009, but is already in wide circulation as Dysport in Europe, Latin America and Asia. At least four other select agents—conotoxins, Tetrodotoxin, ricin and abrin—are in the research and development phases for pharmaceutical products to treat pain and forms of cancer.

Box # 1

### The Growing “Select Product” Market

#### **METABOLIC PHARMACEUTICALS**

Metabolic Pharmaceuticals Limited (Metabolic) is a Melbourne-based biotechnology company in advanced human clinical development of a new drug for neuropathic pain. The drug in question, ACV1, is a synthetic 16-amino acid peptide drug designed from a component of the venom of the Australian marine cone snail, *Conus victoriae*. Cone snails contain conotoxins—a DHHS identified Select Agent.

#### **WEX PHARMACEUTICALS, INC.**

WEX Pharmaceuticals, Inc. is a Canada-based publicly listed company focused on the development and commercialization of innovative drug products, primarily for pain management. The company is developing a new pain reliever using Tetrodotoxin (TTX), a natural substance found primarily in the puffer fish. Currently, the Company is focusing its resources on the global development and commercialization of Tectin™ using TTX for analgesia.

#### **TWINSTRAND THERAPEUTICS**

Twinstrand Therapeutics is a privately-owned biopharmaceutical company focused on discovering and developing targeted prodrugs. The company is experimenting with ricin and abrin and has commenced a Phase I trial for the treatment of solid tumor forms of cancer. Phase II trials will target small cell lung cancer and ovarian cancer.

See:

Metabolic Pharmaceuticals: [http://www.metabolic.com.au/html/s02\\_article/default.asp?nav\\_top\\_id=50&nav\\_cat\\_id=127](http://www.metabolic.com.au/html/s02_article/default.asp?nav_top_id=50&nav_cat_id=127); Wex Pharmaceuticals: <http://www.wexpharma.com/>; Twinstrand Therapeutics: <http://www.twinstrand.com/index.php>; also authors’ interviews with Dr. Jennifer Hanneschlager, Senior Advisor, McKenna, Long and Aldridge.

There are high technical and financial barriers to extracting a select agent from a finished pharmaceutical product in order to develop and disseminate a mass casualty biological weapon. These appear to be sufficient to deter a person, group or state from doing so. If casualties are the objective, there are simpler and cheaper means to commit a terrorist act using biological agents.



Table #5 <b>Financial Challenges to Reverse Engineering BOTOX® into a Biological Weapon</b>		
<b>Amount of Toxin</b>	<b>Number of Vials</b>	<b>Total Cost*</b>
1 kilogram	200 billion	\$105 trillion USD
200 grams	40 billion	\$21 trillion USD
30 grams	6 billion	\$3.15 trillion USD
1 gram	200 million	\$105 billion USD
0.0001 grams	20,000	\$10.5 million USD
0.0000003 grams	60**	\$31,500 USD
* USD\$525/100 unit vial ** Estimated LD50 dose of botulinum toxin if inhaled is 3 micrograms (0.0000003g). Assuming direct inhalation of the toxin, an estimated 60 vials would be required to produce an LD50 dose in a single individual.		

However, the diversion, tainting, or misuse of products derived from select agents—select products—could pose a credible threat to US public health and security if used as weapons of mass panic. While government and industry attention has been focused on regulating the transport, import and export of high-consequence pathogens and toxins and monitoring the manipulation of biotechnology, the use of bulk biological agents or select agent-derived products as a weapon of mass panic remains a real possibility. All levels of government should join private industry and global partners to prepare for and respond to such threats in the future. Today’s security environment warrants a broader look at potential sources for bioterrorism and a reexamination of existing prevention strategies. This must include pharmaceutical products that are, bear, or contain select agents, as well as the technical data necessary to stabilize and produce these products.

## **FOLLOW-ON BIOLOGICS**

Biologics are the fastest growing and highest priced set of drugs in the US healthcare system. Sales for such drugs exceed \$30 billion annually.<sup>2</sup> As national governments seek innovative methods to reduce health care costs, a generic biopharmaceutical, or “follow-on” biologics, industry is likely to emerge to offer lower cost alternatives to higher priced, “name-brand” medical products. Macro-industry trends and public policy discussions suggest a growing interest in the establishment of a legal and regulatory framework for expedited approval or licensure of generic biopharmaceuticals. These “follow-on biologics” are second and subsequent versions of biologics that are independently developed and approved after an innovator company has developed the original version. In February 2007, the *Access to Life-Saving Medicine Act* was introduced to establish an abbreviated process for the FDA to approve lower-cost, follow-on biologics.<sup>3</sup> In January 2007, another bill was introduced that amends the Medicare program to exclude all brand-name drugs from coverage, unless a generic is not available.<sup>4</sup>

Generics are common in many other types of drug products, but there is no similar market at present for biologics. As the biopharmaceutical industry expands to include a follow-on market (and as additional innovator companies enter the market), potentially serious impacts on national security must be considered. New companies that handle select agents and/or produce follow-on biologics that contain select agents should be required to:

1. Meet strict requirements for the management and handling of raw agents;
2. Ensure stringent controls over the possession, management, and shipment of the finished product; and,
3. Undergo additional and rigorous reviews by FDA, CDC, and the Department of Homeland Security to ensure that oversight over both the raw agents and finished product are maintained from cradle to grave and that the companies handling these agents and products are both legitimate and competent.

With the certain emergence of a generic biopharmaceutical, or “follow-on” biologics industry, the FDA and Congress should work assiduously to require strict oversight of these new products—particularly those derived from select agents. As more raw agents are cultivated for research and development purposes by a wider set of companies and new products begin to move from R&D to full scale production, the number and quantity of select agents in circulation domestically will increase. Thus, the risk of misuse, diversion or theft of select agents will also increase.

As Congress promotes the development of a follow-on industry, special consideration should be given to that subset of products that contain CDC defined select agents, in the interest of national security. Any relaxation of standards governing the acquisition, handling and use of select agents should be discouraged. **As this industry grows, any company that handles select agents must be required to undergo a rigorous product and safety competence review and abide by a standardized and stringent set of controls over the possession, management and use of select agents to ensure public health and security.**

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<sup>1</sup> Defined as a category of nearly forty dual-use pathogens and toxins with the potential to pose a severe threat to human health and safety and to be used as weapons by criminals or terrorists. See the CDC’s Select Agent Program website (<http://www.cdc.gov/od/sap/>) and Appendix III of this publication.

<sup>2</sup> IMS Health, *IMS National Sales Perspectives* (February 2006).

<sup>3</sup> US Congress, *Access to Life-Saving Medicine Act*, H.R. 1038 (introduced on February 14, 2007), accessed at: <http://thomas.loc.gov/cgi-bin/bdquery/z?d110:h.r.01038:>.

<sup>4</sup> US Congress, *Generics First Act of 2007*, S. 28 (introduced on January 4, 2007), accessed at: <http://thomas.loc.gov/cgi-bin/bdquery/z?d110:s.00028:>.

## LINK FOUR

### ENSURING SECURITY: DISTRIBUTION THROUGH SUPPLY CHAIN

Supply chain security presents a daunting threat to the health of Americans. Counterfeit drugs, foreign-sourced and re-imported drugs, and unlicensed wholesalers present a range of challenges across the pharmaceutical industry. When involving products that are, bear, or contain select agents—so-called select products—the national security implications are clear.

In September 2007, federal authorities uncovered an underground network operating in the US distributing steroids, human growth hormone, and illegal body building drugs supplied by 37 Chinese companies. Most of those arrested allegedly bought bulk chemicals—some over the Internet from ads posted by the companies—from China, and processed them in home labs for illicit use. Such products are illegal to buy without a prescription and illegal to sell without a Drug Enforcement Agency (DEA) license. Authorities seized \$6.5 million in cash, 25 vehicles, 3 boats, 27 pill presses and 71 weapons while executing 143 search warrants at 56 makeshift labs. Thousands of buyers have been identified through Internet transactions and private chat rooms. The DEA believes that the chemicals used in 99% of such illicit drugs come from China.<sup>1</sup>

Ensuring supply chain security is a growing challenge across the pharmaceutical industry. Counterfeit drugs represent “as high as 50% to as low as 1%” of the total pharmaceutical market.<sup>2</sup> This includes both brand-name and generic, or comparable, products. The rate of counterfeiting ranges from 10-30% in countries or regions where there is less regulatory oversight, including parts of Asia, Africa, Latin America and states of the former Soviet Union. The 1% figure is generally applied to the counterfeit rate in developed countries such as Australia, Canada, the European Union, Japan, New Zealand, and the US.

According to recent analysis, medicines purchased through the Internet from sites that conceal their physical addresses are counterfeit more than 50% of the time.<sup>3</sup> Moreover, trends suggest a massive increase in counterfeit drug sales, to US\$75 billion globally in 2010—an increase of more than 90% from 2005.<sup>4</sup> Because counterfeit drugs are produced without any active ingredient(s), in insufficient quantities or contain a toxic substance, they have little or no therapeutic, diagnostic, or prophylactic value and may be fatal. Without a sufficient amount of the active ingredient, a person

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*Counterfeit drugs represent “as high as 50% to as low as 1%” of the total pharmaceutical market.*

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may not recover from his/her condition or will have a delayed recovery. Thousands of people die each year around the world from ingesting counterfeit drugs. Furthermore, by one estimate, counterfeits cost the pharmaceutical industry \$46 billion per year in lost profits.<sup>5</sup> In the case of infectious diseases, where the largest burden of disease falls on developing countries, “counterfeit drugs lead to the selection of drug-resistant pathogens, increased morbidity, mortality and a significant economic burden on developing regions of the world.”<sup>6</sup>

But developed countries are not immune to the dangers of counterfeit or contaminated drugs. The FDA regularly issues counterfeit drug alerts on some of the most popular prescription drugs. Reports about contamination of a range of products, including toothpaste, pet food, and cancer treatments fill the headlines.<sup>7</sup> As nearly four billion prescriptions are filled every year worldwide, a very large volume of drugs is moving through the supply chain. But, the sophistication and precision of some counterfeit copies of legitimate drugs make a reliable estimate of the number of counterfeits impossible.<sup>8</sup>

Moreover, when considering the state of the drug supply chain, one cannot discount the number of large and small wholesalers who take advantage of multi-tiered pricing in the industry (i.e., the practice of adjusting pricing to local economies and standards of living), sometimes smuggling lower priced drugs into the US to be sold to large wholesalers for a profit.<sup>9</sup> Nor can one discount the growing number of Internet pharmacies, businesses (including manufacturers, labelers and distributors) and criminal groups seeking higher profits and lesser penalties from counterfeit pharmaceuticals than they would receive if caught trafficking narcotics.<sup>10</sup> Many counterfeiters exploit the lax regulations in free trade zones as a way to hide a drug’s origins or to make or adulterate products.<sup>11</sup> These groups are also becoming more technologically savvy, seeking new technologies to produce high-quality replicas of finished products and sell them on the black market, through the Internet, or to introduce them into the legitimate supply chain.

A case from September 2007 exemplifies numerous global supply chain security challenges. A complex supply chain of a huge cache of counterfeit pharmaceuticals began in Hong Kong, went through a free-trade zone in the United Arab Emirates—where product origins were obscured—and then proceeded on to London and the Bahamas. The counterfeit drugs ended up at a Canadian Internet pharmacy whose American customers believed they were purchasing Canadian medicine.<sup>12</sup>

When considered alongside the growth of pharmaceutical products that are, bear, or contain select agents, the dangers presented by counterfeits are magnified and present legitimate national security threats.

While private industry has undertaken ad hoc efforts to try and expose domestic and international counterfeit chains, mounting evidence suggests that federal investigation agencies are overburdened with competing demands and insufficient resources and have assigned a relatively low priority to the threat of counterfeit drugs.<sup>13</sup> **To ease the burden**

**on federal agencies, we recommend that industry strengthen its communication links with the FDA and FBI to regularly inform them about what it has uncovered in terms of risks and threats. We also recommend that federal investigators have the resources they need to pursue all serious leads.** In addition, the US government should cooperate closely with foreign agencies, such as Health Canada, the United Kingdom Ministry of Health, the World Health Organization, Interpol, and other international public health and law enforcement agencies, to create a cohesive global anti-counterfeiting network.

There are areas in which progress is being made to address counterfeit drugs. In 2004, the FDA’s Counterfeit Drug Task Force published its recommendations for creating a “comprehensive framework for a pharmaceutical supply chain that will be secure against modern counterfeit threats.”<sup>14</sup> It has been updated annually, until 2006, with details on progress and ongoing public debates. The Task Force recommended, *inter alia*, the timely adoption and common use of track-and-trace technology that would provide an accurate drug pedigree, the adoption and enforcement of anti-counterfeiting laws and regulations by the states, and the development of an effective reporting system for counterfeit drugs. Both standardized track-and-trace technology and the adoption of laws have had modest success and are addressed below. With respect to a reporting system, the FDA established a Counterfeit Alert Network (CAN) that links together and enhances existing counterfeit notification systems to provide timely and effective notification to health care professionals and consumers. FDA is partnering with national health care organizations, consumer groups and industry representatives to deliver time-sensitive messages about counterfeits and to explain how to report suspected counterfeit products. Sixteen organizations are part of the CAN co-sponsorship agreement.<sup>15</sup> However, there is concern is that no new organizations have joined since 2006.

Another national initiative is to amend the *Federal Food, Drug and Cosmetic Act* through the *Counterfeit Drug Prevention Act of 2007*.<sup>16</sup> The proposed Act would establish criminal penalties for handling, selling or distributing a counterfeit drug. Similar, and more comprehensive, legislation was introduced in 2005 as the *Counterfeit Drug Enforcement Act of 2005*, but died with the 109<sup>th</sup> Congress.<sup>17</sup> That bill would have not only established criminal penalties for “adulterating, misbranding or misrepresenting a prescription drug as an approved drug,” but also:

- Increased funding for FDA inspections and examinations; and,
- Required the Department of Health and Human Services to educate public and health care professionals about counterfeit drugs, including techniques to identify drugs as counterfeit.

**In the interest of national security, we recommend that the provisions embedded within the Counterfeit Drug Prevention Act be expanded to include the funding and education requirements of the bill mentioned above. In doing so, we recommend**

**that Congress give particular attention to the subset of products derived from controlled agents and toxins.**

The enactment of such legislation would solve many issues related to insufficient law enforcement methods of identifying counterfeit/misbranded products. However, industry-wide cooperation is crucial to the success of this endeavor; without it, the effectiveness of the proposed provisions will ultimately be vitiated. Therefore, Congress should lead a consultation with industry to solicit feedback and industry buy-in designed to appropriately amend the bill and balance public health challenges with industry concerns.

## **TARGETING A SPECIFIC THREAT: CHINA TOXINS**

Chinese chemical companies have left a path of destruction worldwide as a loophole in their State Food and Drug Administration allows them to produce low-quality, dangerous, and illegal drug ingredients and even finished drug products. In the mid-1990s, a Chinese chemical company sold a tainted ingredient that killed 88 Haitian children. Again in 2006, a Chinese firm was responsible for the deaths of 138 Panamanians because of a mislabeled poison used in cold medicine. Most recently, in 2007, the product called diethylene glycol, surfaced again in Panama in toothpaste, killing at least 51 people. In the summer of 2007, US officials busted an extensive underground steroid network supplied mainly by Chinese chemicals. Many such companies have become the source of active pharmaceutical ingredients for counterfeit medicines, even advertising them on their own websites. As one salesman said, they only export their ingredients to even poorer regulated countries or when, “we can earn really good profits.” Greed, shoddy manufacturing processes, and both poor national and international inspection have unleashed drugs of dubious quality upon the world and even, potentially, the United States.<sup>18</sup>

Because many chemical companies cross over into the production of pharmaceutical ingredients, they fall into a regulatory loophole in China where their exports may neither be certified nor inspected by Chinese federal health regulators. Health officials regulate pharmaceutical companies, but they have no jurisdiction over chemical companies. As a result, there have been several public health disasters about which Chinese health officials have known since at least the mid-1990s, but have yet to rectify.

The problems with the Chinese manufacturing standards and export regulations are numerous and well documented. Statistics such as, “China is the world’s biggest supplier of counterfeit drugs” and “China has an estimated 80,000 chemical companies, and the FDA does not know how many sell ingredients used in drugs consumed by Americans” represent the extent and gravity of the challenges outlined in this report. The potential for select agents and products to be diverted and misused is magnified in a world of counterfeit drugs, importation, border controls, Internet pharmacies, free-trade zones, and limited inspection capacities.<sup>19</sup> Below, the remainder of these issues is systematically addressed.

With FDA’s limited capacity to oversee the safety and effectiveness of imported drugs manufactured abroad, and multiple recent cases of tainted products from China, the issue of pharmaceutical product safety will be a major one for Congress in the coming year. With respect to foreign inspection capacity, “FDA does not know how many foreign establishments are subject to inspection.”<sup>20</sup> This is due to having multiple databases that cannot be electronically integrated or interact with one another, as well as inaccuracies in the existing systems due to errors in manual data entry. According to a GAO analysis of FDA data, there were an estimated 3,249 foreign establishments subject to inspection in FY2007. The table below<sup>21</sup> shows the number of FDA inspections per year for the ten most frequently inspected countries.

**Table # 6**

Number of FDA Inspections of Foreign Establishments Involved in the Manufacture of Drugs for the US Market, by Country for the 10 Most Frequently Inspected Countries, FY2002 through FY2007									
Country	FY2002	FY2003	FY2004	FY2005	FY2006	FY2007	Total	Number of Establishments	
India	11	19	38	33	34	65	200	410	
Germany	24	15	35	25	19	22	140	199	
Italy	17	30	26	21	18	19	131	150	
Canada	29	12	17	23	23	19	123	288	
United Kingdom	19	22	15	18	15	13	102	169	
France	14	15	19	12	16	24	94	162	
China	11	9	17	21	17	13	88	714	
Japan	11	13	14	21	13	15	87	196	
Switzerland	12	12	11	17	9	14	75	83	
Ireland	11	5	11	14	3	11	55	61	
All Other Countries	63	38	63	61	45	80	350	817	
Total	222	190	260	266	212	295	1,445	3,249	

Source: United States Government Accountability Office, GAO Testimony Before the Subcommittee on Oversight and Investigations, Committee on Energy and Commerce, House of Representatives, *Medical Devices: Challenges for FDA in Conducting Manufacturer Inspections*, Statement of Marcia Crosse, accessed at: <http://www.gao.gov/new.items/d08428t.pdf>

Somewhat like weapons inspections in the national security realm, foreign drug inspections are complex and differ from domestic inspection processes. Such complexities include: the specific protocols that must be respected; inspectors cannot arrive at foreign facilities unannounced; it is difficult to extend an inspection if problems arise; and language barriers are exacerbated by the fact that FDA does not provide translators for inspections. In some countries, FDA inspectors need authorization from the relevant government to enter and inspect facilities. Moreover, while registered domestic facilities that are approved to market their drugs in the US are required to be inspected by the FDA every two years, there is no comparable requirement for foreign establishments—nor does the FDA have the authority to require these measures. However, it does have the authority to physically inspect imported products or deny entry at the border.<sup>22</sup> Therefore, at the very least, **FDA should be given the means, or be provided with assurances, that foreign facilities involved in manufacturing drugs for the US market meet US and global standards. In addition, particularly where select products are concerned, it is imperative that border inspection capacities are well resourced and meet, if not exceed, common standards of effectiveness.**

## IMPORTATION AND REIMPORTATION

In February of 2003, a shipment of unlicensed botulinum toxin was imported into the US via an international express mail service.<sup>23</sup> It did not have a proper declaration of contents, and was being sent directly to physicians from foreign pharmacies. Botulinum toxin may only be imported if it is manufactured under US license and bears the US license number on its label. The case points to a number of issues related to importation and the counterfeit drug trade. In recent years, there has been an explosion of websites, many purportedly based in Canada, offering low-cost prescription drugs and services. However, more often than not, the origin of the drugs or the location of the service is unknown, exposing people to potentially harmful ingredients and highlighting the ease with which products move across borders. As the trade grows, it puts more pressure on already over-burdened and under-resourced inspection capacities. Since the personal importation ban on foreign pharmaceuticals has been lifted, so have the burdens on customs inspectors. At the same time, it has left a gaping hole in trans-border safety.

A component of the counterfeit drug trade is the skyrocketing number of ordinary citizens seeking lower-cost medicines in Canada and elsewhere. Until October 2006, personal reimportation of even US-made drugs was illegal, except under particular circumstances, although this did little to discourage the acquisition of affordable drugs. The only legal way to import drugs from any foreign source was for a manufacturer to do so. After years of bills being introduced in Congress to ease restrictions on importation of pharmaceuticals from foreign countries, the House *FY2007 Homeland Security Appropriations Bill* included a provision to lift the personal importation ban on small quantities of prescription drugs from Canada, i.e., drugs that are not controlled or a biological product, and in quantities not to exceed a 90-day supply.<sup>24</sup> On May 8, 2007, the Senate passed a different bill (S. 1082) on a 49-40 vote which, among other things, also allowed the personal importation of prescription drugs from Canada, also in a quantity not to exceed a 90-day supply, and it waived the limitation on importing



prescription drugs that have been exported from the US—or, as the term is used, “reimported.”<sup>25</sup> The bill would have created a requirement for the FDA to certify the safety and effectiveness of imported drugs before they enter the US. But, as they have responded to other initiatives over the past few years, agency officials have stated that they cannot verify the origin and safety of drugs from outside the United States.

Tens of millions of prescription drug products—tablets, capsules, inhalants, injectables, biologics, generics, brand-name drugs and controlled substances—enter the US from Canada annually. Largely, they enter via mail from Internet purchases or by travel to Canada by US consumers. Sales from licensed Canadian pharmacies were valued at \$43.5 million per month in early 2004.<sup>26</sup> While studies have shown that Canadian drugs have been safe, most that are imported are unapproved for the US market.<sup>27</sup> Moreover, the FDA has argued that it cannot guarantee the chain of custody or integrity of a product

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*The FDA has argued that it cannot guarantee the chain of custody or integrity of a product of foreign origin.*

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of foreign origin. In other words, it cannot guarantee that a drug from Canada is actually from Canada. The FDA has recently implemented a requirement that is meant to ensure the chain of custody of products manufactured and distributed in the US. While a federal standard is welcomed, not only does the requirement fail to address imported drug products, it is also in conflict with the patchwork of state requirements already in existence.

Concerns about safety exist on both sides of the border. A 2004 report by the Health and Human Services Task Force on Drug Importation stated,

Some sellers of imported drugs are “rogue” Internet pharmacies that pretend to be legitimate and operate behind facades. Many of the drugs sold over the Internet claim to be interchangeable with the approved US drug, but are not....American consumers currently purchasing drugs from overseas are generally doing so at significant risk.... [Creating] an opening in the “closed” [distribution] system would increase the opportunity for counterfeit and other substandard drugs to enter and be dispersed into the US drug distribution system.<sup>28</sup> (emphasis added).

In a *British Medical Journal* article in October 2006, the CEO of the Ontario Pharmacists’ Association stated,

We are concerned that the legitimizing of Internet drug purchases by Americans encourages fraud by offshore criminals posing as Canadian pharmacists and selling counterfeit drugs. This is a health and safety threat to both American and Canadian patients who buy drugs from what they believe are Canadian Internet pharmacies and which they believe to be safe and genuine.<sup>29</sup>

As noted, the market for medical products and therapeutic countermeasures that bear or contain select agents is expanding. At the same time, the ease of access to biological

agents and weapons expertise by state and non-state actors alike has greatly increased. In light of a rapidly advancing life sciences industry and an evolving security environment, the unlicensed acquisition, global proliferation and misuse of select products may present new avenues through which bioterrorists could attack the United States. With sanctioned entry-points through which unlicensed products can travel, select products demand particular attention and oversight at the national level.

Now that importation from Canada is permitted—albeit in small quantities—it adds to the existing regulatory and national security loopholes that could imperil the health and safety of the US and global public. It opens an additional avenue of cross-border trade through which counterfeit and tampered products could more easily flow across an already porous border, and through which bioterrorists could access or proliferate the materials needed for a small-scale biological weapon. While the barriers to employ such a scheme are significant, they are not impossible. A recent assessment of US-Canada border security states, “The possibility that terrorists and criminals might exploit border vulnerabilities and enter the United States poses a serious security risk, especially if they were to bring radioactive material or other contraband...such as explosives, drugs, counterfeit money and bogus credit cards...with them.”<sup>30</sup>

To ensure the integrity of products of proliferation concern, the security of consumers and the American public, The Henry L. Stimson Center finds that **in the interest of national security, a special exception or additional safeguards to imports should be made for products that bear or contain select agents.**

## PEDIGREE TRACKING AND LEGISLATION

In the United States, the FDA regulates the safety and efficacy of a product and the conditions in which it is manufactured. But at present, regulating the product distribution process, without clear knowledge of the number of illegitimate distributors involved, remains the responsibility of each state.<sup>31</sup> In December 2006, the *Prescription Drug Marketing Act* (PDMA),<sup>32</sup> which mandates full pedigree information for drugs manufactured and distributed in the US, was fully implemented after years of delays. The delays were due, in part, to industry and Congressional objections to ill-defined and incomplete requirements for who is required to pass on a pedigree, as well as the implementation of track-and trace technology. As a more immediate measure to deal with counterfeits and other supply chain insecurities, the FDA released a compliance policy guide that outlines a risk-based enforcement effort to target prescription drugs that have:

- a) a high value in the US market;
- b) prior indicators of having been counterfeited or diverted in the US; or,
- c) a reasonable probability to be counterfeited or diverted.<sup>33</sup>

With respect to track-and-trace technology, the FDA believed that stakeholders would be able to voluntarily implement such technologies by 2007, which would have generated a “de facto e-pedigree,” obviate stakeholder concerns about who passes on a pedigree, and

fulfill the pedigree requirements established in existing legislation.<sup>34</sup> Industry-wide adoption of electronic track-and-trace technology has not happened, but the FDA believes that full implementation of PDMA will accelerate this process and thus provide more clarity and security throughout the entire US drug supply chain.

Meanwhile, the standardization of even paper pedigree tracking has not been implemented by governments or the pharmaceutical industry in any systematic way. The absence of universal tracking standards allows for multiple counterfeiting, contamination and diversion opportunities in the distribution process. Before the full implementation of PDMA, some states and industry members took it upon themselves to adopt pedigree requirements and mechanisms to plug these holes in the pharmaceutical supply chain. Arizona, California, Florida, Indiana, Iowa, Nevada, New Jersey, New Mexico, Oklahoma, Texas and Virginia have taken the lead in this area. Other states are considering similar legislation, but progress is slow and regulations remain varied among states.

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*The absence of universal tracking standards allows for multiple counterfeiting, contamination, and diversion opportunities in the distribution process.*

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Outside of paper pedigree tracking, it has been the private sector, rather than federal regulators, that have set industry standards for implementing more advanced drug tracking methods.<sup>35</sup> At the industry level, some large pharmaceutical companies have invested in new electronic pedigree tracking mechanisms, such as radio-frequency identification (RFID), which can track products from site of manufacture through to the end user—distributor, pharmacy, physician, or licensed practitioner inclusive. Many large companies, such as GlaxoSmithKline, have initiated pilot projects to test RFID, recognizing not only the opportunity for cost savings, but also for increased product security against counterfeits and diversion that could impose severe consequences for the company and its consumers.<sup>36</sup>

While the FDA has encouraged the rapid implementation of RFID to secure the supply chain, it has not mandated its use. The implementation of track-and-trace technology generally is mandated; piloting and implementing RFID specifically are only strongly encouraged because it is “the most promising technology for implementing electronic track and trace.”<sup>37</sup> The authors have not evaluated the various forms of tracking technology and do not advocate one technology over another. However, RFID is gaining traction in the pharmaceutical industry and is already popular in other industry sectors, such as the retail sector and airline industry. But, like all technologies, RFID has its own variations and corporate and public concerns about privacy, accuracy, and definitive data on how it affects sensitive products such as biologics. There is continued industry debate about which technologies, or combination of technologies, best address these issues. Whatever technology is ultimately used, it is critical that profit-seeking is not made a top

priority at the expense of the supply chain being exposed to counterfeits and an unsafe medicine supply. Government and industry need to agree on uniform, consistent standards that enable pedigree tracking throughout the entire life cycle of a product.<sup>38</sup>

Uneven regulation, the involvement of numerous actors in the distribution process, and inadequate resources to address the above-mentioned problems allow for multiple entry points for counterfeit drugs, and opportunities for contamination or diversion by persons or groups for illegal and illicit purposes. It also makes it nearly impossible to determine the origin or integrity of a drug before it reaches the end user. This issue becomes particularly worrisome when one considers the potential for pharmaceutical products derived from biological agents and toxins to be inadvertently misapplied or intentionally misused to instill public panic. Because current paper pedigree standards are being developed on a state-by-state basis, and efforts to use more advanced technologies such as RFID are being implemented independently by industry on a product-by-product basis, such a patchwork system affords opportunities for terrorists and counterfeiters to choose a locale or product offering the path of least resistance. Therefore, **not only should pedigree requirements be standardized across the country and ultimately across the globe, particular attention should be given to those products that bear or contain select biological agents and toxins and pose the greatest potential harm to public health and national security. Relevant industry representatives should be involved in the development of these standards. Moreover, we believe that government incentives should be offered to spur the pharmaceutical industry to introduce such tracking capabilities—particularly with products that are, bear or contain select agents—in the interest of national security and public health.**

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<sup>1</sup> Duff Wilson and Michael S. Schmidt, “DEA Exposes a Steroid Web with China Tie,” *The New York Times* (September 25, 2007), accessed at: <http://www.nytimes.com/2007/09/25/sports/25steroids.html>.

<sup>2</sup> Michele Forzley, “Combating Counterfeit Drugs: A Concept Paper for Effective International Cooperation,” revised by the World Health Organization (January 27, 2006): 3, accessed at: <http://www.who.int/medicines/events/FINALBACKPAPER.pdf>.

<sup>3</sup> World Health Organization, “Counterfeit medicines,” Fact Sheet Number 275 (November 14, 2006), accessed at: <http://www.who.int/mediacentre/factsheets/fs275/en/>.

<sup>4</sup> Ibid.

<sup>5</sup> Susannah Patton, “Cracks in the Pharmaceutical Supply Chain,” *CIO Magazine* (January 15, 2006), accessed at: [http://www.cio.com/article/16565/Cracks\\_in\\_the\\_Pharmaceutical\\_Supply\\_Chain](http://www.cio.com/article/16565/Cracks_in_the_Pharmaceutical_Supply_Chain).

<sup>6</sup> Ibid. A recent example of the potentially fatal impact of counterfeits is the death of nine people in China after being injected with a drug containing a toxic chemical instead of genuine ingredients. “Nine Killed by Fake Chinese Drug,” *BBC News* (May 22, 2006), accessed at: <http://news.bbc.co.uk/2/hi/asia-pacific/5003548.stm>.

<sup>7</sup> Jane Hooker and Walt Bogdanich, “Tainted Drugs Linked to Maker of Abortion Pill,” *The New York Times*, (January 31, 2008).

<sup>8</sup> Ibid.

<sup>9</sup> The discovery of such operations was made during a two-year FDA sting operation called “Operation Gray Pill.” See: Patton, “Cracks in the Pharmaceutical Supply Chain.”

<sup>10</sup> Ibid.

<sup>11</sup> Walt Bogdanich, “Counterfeit Drugs’ Path Eased by Free Trade Zones,” *The New York Times* (December 17, 2007).

<sup>12</sup> Ibid.

<sup>13</sup> Carl Levin, “Buyer Beware: The Danger of Purchasing Pharmaceuticals over the Internet - Day 2: Federal and Private Sector Responses,” Statement to Senate Committee on Governmental Affairs (June 17, 2004), accessed at: <http://hsgac.senate.gov/index.cfm?Fuseaction=Hearings&TestimonyID=661&HearingID=183>; US Government

Accountability Office, “Prescription Drugs: Strategic Framework Would Promote Accountability and Enhance Efforts to Enforce the Prohibitions on Personal Importation” (September 8, 2005), accessed at: <http://www.gao.gov/new.items/d05372.pdf>; Richard M. Stana, “Prescription Drugs: Enhanced Efforts and Better Agency Coordination Needed to Address Illegal Importation,” Testimony Before the Subcommittee on Oversight and Investigations of the House Committee on Energy and Commerce (December 13, 2005), accessed at: <http://www.gao.gov/new.items/d06175t.pdf>.

<sup>14</sup> US Food and Drug Administration, “Combating Counterfeit Drugs: A Report of the Food and Drug Administration,” US Department of Health and Human Services (February 2004), accessed at: [http://www.fda.gov/oc/initiatives/counterfeit/report02\\_04.html](http://www.fda.gov/oc/initiatives/counterfeit/report02_04.html).

<sup>15</sup> Ibid.

<sup>16</sup> US Congress, *Counterfeit Drug Prevention Act of 2007*, H.R. 780 (introduced January 31, 2007), accessed at: <http://thomas.loc.gov/cgi-bin/bdquery/z?d110:h.r.00780>.

<sup>17</sup> US Congress, *Counterfeit Drug Enforcement Act of 2005*, S. 1978 (introduced November 9, 2005), accessed at: <http://thomas.loc.gov/cgi-bin/bdquery/z?d110:s.01978>.

<sup>18</sup> Walt Bogdanich, “Chinese Chemicals Flow Unchecked Onto World Drug Market,” *The New York Times* (December 31, 2007); Manuel Jimenez, “Dominican Republic Bans Tainted Chinese Toothpaste,” *Reuters* (May 22, 2007), accessed at: <http://www.alertnet.org/thenews/newsdesk/N22441956.htm>.

<sup>19</sup> Bogdanich, “Chinese Chemicals Flow Unchecked Onto World Drug Market.”

<sup>20</sup> Marcia Crosse, “Drug Safety: Preliminary Findings Suggest Weaknesses in FDA’s Program for Inspecting Foreign Drug Manufacturers,” Testimony before the Subcommittee on Oversight and Investigations of the House Committee on Energy and Commerce (November 1, 2007): 10, accessed at: <http://www.gao.gov/new.items/d08224t.pdf>.

<sup>21</sup> Ibid., 15.

<sup>22</sup> Ibid., 15, 28.

<sup>23</sup> Wilson and Schmidt, “DEA Exposes a Steroid Web with China Tie.”

<sup>24</sup> US Congress, *Department of Homeland Security Appropriations Act, 2007*, Public Law 109-295 (October 4, 2006), accessed at: <http://thomas.loc.gov/cgi-bin/bdquery/z?d110:h.r.05441>.

<sup>25</sup> US Congress, *Food and Drug Administration Revitalization Act*, S. 1082 (passed in the Senate on May 9, 2007), accessed at: <http://thomas.loc.gov/cgi-bin/bdquery/z?d110:s.01082>.

<sup>26</sup> Clifford Krauss, “Kinks in Canada Drug Pipeline,” *The New York Times* (April 6, 2006), accessed at: <http://www.nytimes.com/2006/04/06/business/worldbusiness/06canada.html>.

<sup>27</sup> GAO, “Prescription Drugs: Strategic Framework....”

<sup>28</sup> Richard H. Carmona, Chair, *Report on Prescription Drug Importation*, HHS Task Force on Drug Importation (Washington: Department of Health and Human Services, 2004), accessed at: <http://www.hhs.gov/importtaskforce/Report1220.pdf>.

<sup>29</sup> Barbara Kermode-Scott, “US Eases Its Restrictions on Prescription Drugs from Canada,” *British Medical Journal*, Volume 333, Number 7573 (London: BMJ Publishing Group Ltd, 2006): 824, accessed at: <http://www.bmj.com/cgi/content/full/333/7573/824-c?rss>.

<sup>30</sup> Gregory D. Kutz and John W. Cooney, “Border Security: Security Vulnerabilities at Unmanned and Unmonitored U.S. Border Locations,” Statement before the Senate Committee on Finance (September 27, 2007), accessed at: <http://www.gao.gov/new.items/d07884t.pdf>.

<sup>31</sup> Patton, “Cracks in the Pharmaceutical Supply Chain.”

<sup>32</sup> The *Prescription Drug Marketing Act of 1987* (Public Law 100-293), as modified by the *Prescription Drug Amendments of 1992* (PDA) (Public Law 102-353, 106 Stat. 941), amended sections 301.303, 503, and 801 of the *Food, Drug and Cosmetic Act*.

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<sup>33</sup> “Compliance Policy Guide 160.900: Prescription Drug Marketing Act—Pedigree Requirements under 21 CFR Part 203” (December 2006), accessed at:

[http://www.fda.gov/ora/compliance\\_ref/cpg/cpggenl/CPG160.900.pdf](http://www.fda.gov/ora/compliance_ref/cpg/cpggenl/CPG160.900.pdf).

<sup>34</sup> FDA Counterfeit Drug Task Force, “FDA Counterfeit Drug Task Force Report: 2006 Update” (February 2005): 6, accessed at: [http://www.fda.gov/oc/initiatives/counterfeit/report6\\_06.html](http://www.fda.gov/oc/initiatives/counterfeit/report6_06.html); “Prescription Drug Marketing Act of 1987; Prescription Drug Amendments of 1992; Policies, Requirements, and Administrative Procedures; Delay of Effective Date; Correction (21 CFR Part 203),” *Federal Register* Volume 69, Number 53 (March 18, 2004): 12792, accessed at: <http://a257.g.akamaitech.net/7/257/2422/14mar20010800/edocket.access.gpo.gov/2004/pdf/04-6094.pdf>.

<sup>35</sup> Some groups have raised concerns about the potential use of RFID for “snooping.” For pharmaceutical products, linking an RFID tag with a drug’s National Drug Code has been suggested, raising concerns over patient privacy. The technology is not only used in prescription medicine packing, but also credit cards, computer equipment, TVs, clothes, and cell phones, unbeknownst to most consumers. See: “Consumer Reports Finds personal privacy concerns in planned uses of Radio Frequency Identification Tags (RFIDs),” *US Newswire* (May 4, 2006), accessed through Nexis.

<sup>36</sup> Paul Thomas, “Inside GSK’s New RFID Pilot,” *PharmaManufacturing.com* (May 18, 2006), accessed at: <http://www.pharmamanufacturing.com/articles/2006/098.html>; FDA Counterfeit Drug Task Force, “FDA Counterfeit Drug Task Force Report: 2006 Update.”

<sup>37</sup> FDA Counterfeit Drug Task Force, “FDA Counterfeit Drug Task Force Report: 2006 Update.”

<sup>38</sup> John M. Gray, “John M. Gray, President and CEO, HDMA, Testifies in FDA Hearing on February 9, 2006” (February 9, 2006), accessed at: [http://www.healthcaredistribution.org/gov\\_affairs/testimony/j\\_grey\\_fda\\_02092006.asp](http://www.healthcaredistribution.org/gov_affairs/testimony/j_grey_fda_02092006.asp). It should be noted, however, that all of the measures discussed only target domestic pharmaceutical manufacturing and distribution and do not address drugs imported from foreign sources.

## LINK FIVE

### ENSURING SECURITY: ADMINISTRATION TO PATIENT

In the fall of 1982, seven Chicago area residents fatally ingested Extra-Strength Tylenol capsules laced with cyanide. Each capsule contained ten thousand times more poison than was necessary for a fatal dose. The bottles were taken from different stores over a period of weeks or months, and returned contaminated to the shelves of five stores in the Chicago area. Once the contamination was publicized, a nationwide panic ensued. How Johnson & Johnson (the corporate parent of Tylenol's manufacturer McNeil Consumer Products) reacted and dealt with the public has become a model for crisis communication.<sup>1</sup> The model is reflected in the recent worldwide recall of Bausch & Lomb's ReNu with MoistureLoc lens-care solution after discovering it was causing a rare fungal infection that damages the cornea. Over 100 cases were reported in the US and are under investigation. Bausch & Lomb executives initially reported its product was not related to the outbreak of infections, but were quick to correct initial errors in their press statements and suggested discontinued use of the product. Moreover, as of May 11, 2006, company and FDA investigators were able to confirm that the actual product, not the generic brands, were the source of contamination.<sup>2</sup>

Similarly, in the case of the Tylenol poisonings, because authorities were able to trace the laced Tylenol to shipments from different plants to the Chicago area, they concluded that any tampering must have occurred once the Tylenol reached Illinois—not at the manufacturing facilities. Officials at McNeil Consumer Products immediately made this clear and publicized the company's strict quality control procedures. Johnson & Johnson then alerted consumers across the nation not to consume any type of Tylenol product until the extent of the tampering could be determined. It then stopped production and advertising of Tylenol, and recalled approximately thirty-one million bottles of the product, with a retail value of more than one hundred million dollars. What made the Tylenol scare controllable, and likely prevented a panic from the infection caused by ReNu, was that investigators were able to trace the contamination through the product's chain of custody. In addition, the manufacturers took immediate action to communicate with the public. In the case of the Tylenol poisonings, authorities and consumers alike could thus direct their response toward a specific product distinguishable by labels that read "Extra Strength Tylenol."

In contrast, the current US process for tracking for Medicare reimbursement, commonly known as the "J-code system," does not make distinctions among similar products. This lack of distinct codes for similar products means that in the event of a bioterrorism incident, there would be insufficient information regarding the origins and chain of custody for the product—it is cloaked precisely at the point of end-use and detection of a problem. Had a J-code system been applied to over-the-counter drugs, the panic and risk to public health from the abovementioned Tylenol incident would have been immeasurably worse. The J-code version of the Tylenol incident renders all similar products in the drug store as "pain relievers." Because of the lack of information at the

point of use, one would not be able to determine where the contamination occurred or how to control it. If the coding system were enhanced to provide distinct codes for similar select agent derived products, such a scenario could be averted.

## THE DRUG CODING AND TRACKING SYSTEM

Tracking finished select products through their point of use is the last link of the “cradle-to-grave” chain. Fortunately, unlike other links in the process, the US government has systems in place that can be easily adapted to track product to the end user without the need for onerous new guidelines and regulations.

Within the *Health Insurance Portability and Accountability Act of 1996*, Congress mandated a single national system of codes required for all taxpayers to get reimbursement for medical services. The Healthcare Common Procedure Coding System (HCPCS) is divided into two principal subsystems. Level I is a numeric system comprising Current Procedural Terminology (CPT) codes that is overseen by the American Medical Association. Level II of the HCPCS, which applies alpha-numeric coding to products, is a standardized system used to identify products, supplies and services not included in the CPT codes. Drugs in this category are classified by a “J-code,” which the Centers for Medicare and Medicaid Services have the authority to oversee and grant. The J-code system is used to process claims for high-cost, injectable pharmaceuticals, the category under which existing select products fall. As noted, rather than basing that code on the unique properties of individual products, it is assigned based upon broad similarities. In addition, different brands of drugs manufactured from the same raw material are not differentiated—with either a unique nomenclature or unique J-codes. They are identified based upon a common ingredient without regard for different dosages, applications or manufacturing processes. There are three issues that further complicate this challenge: 1) the growing counterfeit drug industry worldwide, 2) the recent allowance of personal importation of prescription drugs from Canada and elsewhere, and 3) the likelihood of a new generic biopharmaceutical, or follow-on biologics, industry to emerge. As this industry develops, and more select agent derived products move from R&D to full scale production, the number and quantity of select agents moving throughout the country will increase. Therefore, the risk of misuse, diversion or theft of select agents will also increase.

The failure to provide unique non-proprietary nomenclature and the unique J-codes that would flow from that decision create the potential for product confusion that could lead to medical errors. More importantly, by the point at which a specific product is applied, its chain of custody through the already vulnerable drug delivery system is masked by an opaque coding system. This information could be critical for the investigation of an intentional tainting of, for example, a botulinum toxin, ricin, or similar select agent-derived pharmaceutical product. Without unique nomenclature and product identities, this current coding scheme unnecessarily veils information about products that might have been easily collected and shared with law enforcement, first responders, national security officials, and ultimately, the public, during a bioterrorism incident.



There is a second type of coding system called the National Drug Code (NDC). The FDA assigns an NDC to all prescription drugs or insulin products covered under a pharmacy benefit—or which can be dispensed by a retail pharmacy. Each drug has a distinct NDC and identifies each product down to the package size. It would be ideal to use this system, one which has a unique identifier for each product, to identify potential misuse or diversion of select products. But, there are two flaws to this approach: One is that NDCs do not provide information at the point of use. The second is that they do not apply to the category of high-cost, injectable medications into which all current select products fall.

These two systems were set up for Medicare reimbursement purposes—not for national security investigations. Nonetheless, with minor adjustments, they would be ideal to enhance national security objectives. There are at least two steps. The first is to use the NDC system for data and trend analysis on where products are flowing. NDCs do not provide information at their point of use, but because of their application to a wide range of products, they could be useful. The second is to modify the J-code system to allow for unique codes to be applied to unique products. Because the type of specialty pharmaceuticals that require J-codes is exploding and because J-codes can provide information at the point of use, they would thus fill the gap left by the NDC system. Ideally, both of these existing systems should be leveraged in support of each other for the dual benefits of national security and public health.

Given the deficiencies in current tracking systems in the US and the emerging threat posed by products derived from biological agents, the need for a solution is clear. **The potential use of biological agents and toxins to incite mass panic in the United States should motivate government officials to use all means available to track, trace and secure the movement of both raw toxin and prescription products.**

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<sup>1</sup> The poisonings posed a considerable public health and public relations challenge for Johnson & Johnson. Once broad details were confirmed, all three national television networks reported the deaths on their evening news broadcasts, police drove around Chicago announcing a warning over loudspeakers, and the FDA advised consumers to avoid Tylenol capsules until more information could be determined. Robert D. McFadden, “Poison Deaths Bring US Warning on Tylenol Use,” *The New York Times* (October 2, 1982), accessed through Times Select.

<sup>2</sup> US Food and Drug Administration, “Bausch & Lomb Global Recall of ReNu with MoistureLoc Contact Lens Cleaning Solution,” FDA Statement (May 15, 2006), accessed at: <http://www.fda.gov/bbs/topics/NEWS/2006/NEW01371.html>; “Maker Says Not to Use Contact Lens Solution,” *CNN.com* (April 14, 2006), accessed at: <http://www.cnn.com/2006/HEALTH/conditions/04/14/bausch.eye.fungus/index.html>; “CDC: Most Infected Lens Wearers Used Same Cleaner,” *CNN.com* (May 10, 2006).

# — APPENDIX I —

## RECOMMENDATIONS:

PROTECTING THE HOMELAND: A COMPREHENSIVE PLAN FOR CRADLE-TO-GRAVE TRACKING OF DANGEROUS PATHOGENS AND TOXINS	
<p style="text-align: center;"><b>Securing Bulk Material</b></p>	<p>Develop and implement a system to track the distribution of bulk biological materials produced domestically or imported from foreign manufacturers.</p> <p>Ensure that manufacturing and distribution facilities/institutions that possess, use and transfer pathogenic micro-organisms and toxins have adequate biosecurity measures in place to safeguard against theft and diversion.</p> <ol style="list-style-type: none"> <li>1. At a minimum, CDC, USDA, FDA and CBP should open channels of communication and coordinate their responsibilities as they pertain to monitoring and using select agents to ensure a seamless transition as bulk materials are moved into product development. With respect to non-federal labs, mechanisms should be established that ensure all such labs meet national standards of biosafety and biosecurity.</li> <li>2. At a minimum, particularly with advances in technology, CDC and its federal partners must routinely review the select agent program and its implementation to ensure effective response against new threats and vulnerabilities.</li> <li>3. One of the 15 federal agencies that own or regulate high-containment laboratories should be responsible for maintaining an accurate accounting of all of the BSL-3 and BSL-4 facilities in the United States. Similarly, all relevant directors, investigators and researchers should undergo common, and agent-specific, biosecurity and biosafety training.</li> <li>4. The US Government should establish a task force composed of representatives from national security, law enforcement, the</li> </ol>

		<p>life sciences, and private industry to develop: a sustained communication network and a strategy to mitigate the risks from release of an agent, misuse of legitimate products, and linkages to bioterrorism.</p>
<p style="text-align: center;"><b>Ensuring Security During Research, Development, and Production</b></p>	<p>Public health and biosecurity strategies must account for new trends in the pharmaceutical industry, particularly with respect to the use of select agents. Anti-counterfeiting strategies need to be tightened and better coordinated. Pedigree requirements for pharmaceutical products should be standardized across the country and ultimately across the globe, and due to their unique characteristics, particular attention should be given to those products which bear or contain select biological agents and toxins. Relevant industry representatives should be involved in the development of these standards.</p>	<ol style="list-style-type: none"> <li>1. As the follow-on biologics industry grows, any company that handles select agents must be required to undergo a rigorous product and competence review and abide by a standardized and stringent set of controls over the possession, management and use of select agents to ensure public health and security.</li> <li>2. FDA should be given the means, or be provided with assurances, that foreign facilities involved in manufacturing drugs for the US market meet US and global standards. In addition, particularly where select products are concerned, it is imperative that border inspection capacities are adequately resourced and meet, if not exceed, standards of effectiveness.</li> <li>3. With respect to the new laws on importation, a special exception to imports should be made for products that bear or contain select agents.</li> <li>4. States should work with FDA, Congress and industry to pass uniform anti-counterfeiting laws and stricter uniform standards governing the licensure and oversight of wholesale distributors that will minimize “opportunity shopping” by criminals seeking to exploit loopholes in the drug supply chain.</li> <li>5. All companies should purchase their select products <i>only</i> from the manufacturer, which would reduce the demand for and threat of unlicensed wholesalers and distributors.</li> </ol>

6. Manufacturers should convene a coalition of concerned wholesalers with the federal government to collaborate on a nationwide public/medical community education campaign on counterfeiters and gaps in the pharmaceutical supply chain.
7. Industry should regularly inform the FDA and FBI about any potential risks and threats it has uncovered.
8. The US government should collaborate with foreign stakeholders to develop strategies to deter and detect counterfeit drugs globally.
9. The National Association of the Boards of Pharmacy, with industry involvement, should include a sub-category of "select products" on its susceptible products list.
10. Industry partners should work together to develop and implement electronic pedigree tracking mechanisms.
11. The government should offer incentives to spur the pharmaceutical industry to introduce tracking capabilities in the interest of national security and public health.
12. Congress should amend the *Counterfeit Drug Prevention Act of 2007* to include better funding and anti-counterfeiting education, with particular attention given to the subset of products derived from select agents.

<b>Tracking Finished Product</b>	<p>Given the deficiencies in current tracking systems in the US and the emerging threat posed by products that are, bear or contain select agents, a need for a solution is clear. The potential use of biological agents and toxins to incite mass panic in the United States should motivate government officials to use all means available to track, trace and secure the movement of both raw toxin and prescription products.</p>	<p>The National Drug Code and the HCPCS J-Code systems should be carefully examined to assess how they could be modified and leveraged to complete pedigree data for select products at their point of use.</p>
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— APPENDIX II —  
**INTERNATIONAL APPROACHES  
TO MONITORING  
BIOLOGICAL AGENTS AND TOXINS**

This section addresses the international controls, treaties, resolutions and arrangements that seek to prevent the unlawful development and use of biological materials, technology and weapons. It provides a brief summary of key international control measures and how they are verified, monitored and enforced

**THE GENEVA PROTOCOL AND THE BWC**

The 1925 Geneva Protocol established an international norm against the use of chemical and biological weapons (CBW) as a means of warfare.<sup>1</sup> It remains in force today, but does not have provisions for monitoring or verifying compliance. It was not until fifty years later that the primary agreement on biological weapons, the Biological and Toxin Weapons Convention,<sup>2</sup> entered into force. This was a defining moment in the field of disarmament because the BWC was the first treaty to ban the development, production, stockpiling and transfer of an entire category of weapons of mass destruction—including nuclear, chemical, and biological weapons. At present, 156 countries have ratified the treaty and there are sixteen additional signatories. However, the BWC faces major shortcomings, namely, the absence of a verification system and the use of only rudimentary mechanisms to enforce compliance. In 2001, by rejecting a BWC protocol that would have addressed many outstanding verification issues, the US brought six years of negotiations to a halt. Since then, BWC states parties have participated in formal discussions to strengthen the treaty, including topics such as national implementing legislation; capabilities to investigate and respond to BW use and infectious disease outbreaks; and professional codes of conduct for scientists, which at present remain voluntary. At the Sixth Review Conference in 2006, states parties agreed to establish a small Implementation Support Unit (ISU). States parties could not agree on establishing a full, independent body similar to the one that exists for implementing the Chemical Weapons Convention (CWC). As such, the ISU is located in the UN Department for Disarmament Affairs and promotes the universalization of the Convention and supports the exchange of confidence-building measures. Most other issues remain unresolved among parties. A second inter-sessional program is in place from 2007-2010 until the Seventh Review Conference in 2011. Although a modest step toward strengthening the Convention has been made, there remains a clear need for strong domestic and international support and action to strengthen the treaty and ensure its success.

## **THE UN SECRETARY-GENERAL'S MECHANISM**

Intended as a temporary mechanism to fill CBW verification gaps, the United Nations General Assembly endorsed the authority of the UN Secretary-General in 1982 to investigate any situation that threatens international peace and security, with specific regard to the alleged use of chemical, biological and toxin weapons. The mechanism has been used on several occasions in the past to investigate allegations of CBW use by state and non-state actors in Afghanistan and Indochina in 1981 and 1982; in Iran and Iraq during their eight-year war between 1980 and 1988; and in Mozambique and Azerbaijan in 1992. In the absence of other verification mechanisms, it remains available today, albeit in a deteriorated state.<sup>3</sup> Optimistically, not only has the UN Secretariat taken the initiative to reinvigorate parts of the mechanism by beginning to update its roster of experts, but in September 2006, the General Assembly encouraged the Security Council to pursue its own efforts to update it as well. It appears that this was due, in large part, to the adoption of the UN Global Counter-Terrorism Strategy in 2006.

## **THE AUSTRALIA GROUP**

During UN investigations in Iran and Iraq in 1984 it was discovered that Iraq had used chemical weapons (CW) in violation of the 1925 Geneva Protocol and that “at least some of the precursor chemicals and materials for its CW program had been sourced through legitimate trade channels.”<sup>4</sup> As a result, an informal consortium of fifteen like-minded states introduced export controls on certain chemicals that could be used to develop CW. Today, the Australia Group, as it is known, has expanded in membership and scope. It is composed of forty participants that aim to harmonize their export licensing measures to ensure that “exports of certain chemicals, biological agents and dual-use chemical and biological manufacturing facilities and equipment do not contribute to the spread of CBW.”<sup>5</sup> It should be noted that their controls target only the activities of state actors. In addition, while the Australia Group asserts that the 1993 Chemical Weapons Convention,<sup>6</sup> which will be discussed in further detail below, is the primary instrument to deal with chemical weapons, the Group's existence is nevertheless contentious among many developing country CWC states parties that believe it only adds constraints on their economic development by prohibiting access to technology. Moreover, industry representatives in the US have expressed concern about some states breaching their commitments with respect to the transfer of certain critical technologies related to the production of select agents and the end products in which they are used. In light of proliferation and bioterrorism concerns, we therefore urge all participating states to redouble their efforts to ensure compliance with the guidelines of The Australia Group.

## **THE CHEMICAL WEAPONS CONVENTION: A COMPARISON**

The 1993 CWC replaced the Geneva Protocol as the primary disarmament agreement in the chemical weapons area. Like the BWC, it targets an entire category of WMD, banning the use, development, production, acquisition, stockpiling, retention or transfer of CW. In contrast to the BWC, however, it established a comprehensive multilateral

verification system, including provisions for challenge inspections and investigations of alleged CW use.<sup>7</sup> Nevertheless, the CWC and the organization that oversees its implementation, the Organization for the Prohibition of Chemical Weapons, are not without challenges to overcome, including where verification activities and resources are focused, the ability or willingness of parties to carry out their treaty obligations in full, and adjusting to the changed nature in the way the global chemical industry is organized since the treaty was negotiated.<sup>8</sup>

## SECURITY COUNCIL RESOLUTION 1540

The most recent measure to address WMD proliferation threats was the unanimous adoption of UN Security Council Resolution 1540 (April 2004).<sup>9</sup> The resolution was passed after revelations about the extensive nuclear black market network run by Abdul Qadeer Khan, former director of Pakistan's uranium enrichment project. It is unprecedented in mandating that all UN member states enact measures to criminalize non-state actor development, acquisition, manufacture, transport or transfer of all WMD and their means of delivery, and "to maintain appropriate physical protection measures" for these items. Furthermore, it seeks to develop universal standards for export controls well beyond the limited controls of existing multilateral regimes.<sup>10</sup> Of the 192 UN member states, only 137 (as well as the European Union) have submitted national reports detailing their implementation status. The term of the UN committee established to assess compliance has been extended until April 2008.<sup>11</sup> As the sole piece of international regulation that specifies all states to prevent WMD proliferation to or by non-state actors, we strongly urge all UN members to ensure full and effective implementation of Resolution 1540.

The primary purpose of the above descriptions is to provide background on the relevant international mechanisms for monitoring and controlling biological materials, technology and weapons. There are gaps in the international regulatory framework, but the agreements have established universal norms against the misuse of biological materials and technology that should be comprehensively supported. Further improvements are being made as well, for example, the widespread efforts to implement Resolution 1540. While a detailed analysis of how to strengthen the above agreements and arrangements is beyond this study's scope, it is important to describe their value, shortcomings and relationships to provide a sense of existing international initiatives and where support can be directed.

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<sup>1</sup> *Protocol for the Prohibition of the Use in War of Asphyxiating, Poisonous or Other Gases, and of Bacteriological Methods of Warfare* (signed June 17, 1925), accessed at: <http://cns.miis.edu/pubs/inven/pdfs/genev.pdf>.

<sup>2</sup> *Convention on the Prohibition of the Development, Production and Stockpiling of Bacteriological (Biological) and Toxin Weapons and on Their Destruction* (signed April 10, 1972), accessed at: <http://www.opbw.org/convention/documents/btwcetxt.pdf>.



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<sup>3</sup> Trevor Findlay, Erik Asplund, Andreas Persbo, and Angela Woodward, “WMD Verification and Compliance: The State of Play,” Submitted by Foreign Affairs Canada and Prepared by VERTIC, Report 19 (October 23, 2004), accessed at: <http://www.wmdcommission.org/files/No19.pdf>.

<sup>4</sup> The Australia Group, “The Origins of the Australia Group” (2007), accessed at: <http://www.australiagroup.net/en/origins.html>.

<sup>5</sup> The Australia Group, “Objectives of the Group” (2007), accessed at: <http://www.australiagroup.net/en/objectives.html>.

<sup>6</sup> Convention on the Prohibition of the Development, Production, Stockpiling and Use of Chemical Weapons and on Their Destruction (signed on January 13, 1993), accessed at: [http://www.opcw.org/docs/cwc\\_eng.pdf](http://www.opcw.org/docs/cwc_eng.pdf).

<sup>7</sup> Findlay et al., “WMD Verification and Compliance...,” 25.

<sup>8</sup> *Ibid.*, 26.

<sup>9</sup> United Nations Security Council, “Resolution 1540 (2004),” S/RES/1540 (April 28, 2004), accessed at: <http://www.un.org/sc/1540/resolutionstatements.shtml>.

<sup>10</sup> Scott Jones, “Resolution 1540: Universalizing Export Control Standards?” *Arms Control Today* Volume 36, Number 4 (Washington: Arms Control Association, 2006), accessed at: [http://www.armscontrol.org/act/2006\\_05/1540.asp](http://www.armscontrol.org/act/2006_05/1540.asp).

<sup>11</sup> United Nations Security Council, “Resolution 1673 (2006),” S/RES/1673 (April 27, 2006), accessed at: <http://www.un.org/sc/1540/resolutionstatements.shtml>.

— APPENDIX III —  
**THE SELECT AGENT LIST**

**DHHS SELECT AGENTS AND TOXINS**

Abrin

Cercopithecine herpesvirus 1 (Herpes B virus)

*Coccidioides posadasii*

Conotoxins

Crimean-Congo hemorrhagic fever virus

Diacetoxyscirpenol

Ebola virus

Lassa fever virus

Marburg virus

Monkeypox virus

Reconstructed replication competent forms of the 1918 pandemic influenza virus containing any portion of the coding regions of all eight gene segments

Ricin

*Rickettsia prowazekii*

*Rickettsia rickettsii*

Saxitoxin

Shiga-like ribosome inactivating proteins

South American Hemorrhagic Fever viruses

Flexal

Guanarito

Junin

Machupo

Sabia

Tetrodotoxin

Tick-borne encephalitis complex (flavi) viruses

Central European Tick-borne encephalitis

Far Eastern Tick-borne encephalitis

Kyasanur Forest disease

Omsk Hemorrhagic Fever

Russian Spring and Summer encephalitis

Variola major virus (Smallpox virus) and Variola minor virus (Alastrim)

*Yersinia pestis*

## USDA SELECT AGENTS AND TOXINS

African horse sickness virus  
 African swine fever virus  
 Akabane virus  
 Avian influenza virus (highly pathogenic)  
 Bluetongue virus (Exotic)  
 Bovine spongiform encephalopathy agent  
 Camel pox virus  
 Classical swine fever virus  
*Cowdria ruminantium* (Heartwater)  
 Foot-and-mouth disease virus  
 Goat pox virus  
 Japanese encephalitis virus  
 Lumpy skin disease virus  
 Malignant catarrhal fever virus (Alcelaphine herpesvirus type 1)  
 Menangle virus  
*Mycoplasma capricolum*/ M.F38/*M. mycoides Capri* (contagious caprine pleuropneumonia)  
*Mycoplasma mycoides mycoides* (contagious bovine pleuropneumonia)  
 Newcastle disease virus (velogenic)  
 Peste des petits ruminants virus  
 Rinderpest virus  
 Sheep pox virus  
 Swine vesicular disease virus  
 Vesicular stomatitis virus (Exotic)

## USDA PLANT PROTECTION AND QUARANTINE SELECT AGENTS AND TOXINS

*Candidatus Liberobacter africanus*  
*Candidatus Liberobacter asiaticus*  
*Peronosclerospora philippinensis*  
*Ralstonia solanacearum* race 3, biovar 2  
*Schlerophthora rayssiae* var *zeae*  
*Synchytrium endobioticum*  
*Xanthomonas oryzae* pv. *oryzicola*  
*Xylella fastidiosa* (citrus variegated chlorosis strain)

## **OVERLAP SELECT AGENTS AND TOXINS**

*Bacillus anthracis*

Botulinum neurotoxins

Botulinum neurotoxin producing species of *Clostridium*

*Brucella abortus*

*Brucella melitensis*

*Brucella suis*

*Burkholderia mallei* (formerly *Pseudomonas mallei*)

*Burkholderia pseudomallei* (formerly *Pseudomonas pseudomallei*)

*Clostridium perfringens* epsilon toxin

*Coccidioides immitis*

*Coxiella burnetii*

Eastern Equine Encephalitis virus

*Francisella tularensis*

Hendra virus

Nipah virus

Rift Valley fever virus

Shigatoxin

Staphylococcal enterotoxins

T-2 toxin

Venezuelan Equine Encephalitis virus

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## ABOUT THE AUTHORS

The authors draw upon a substantial and unique history of involvement in this area. The Cooperative Nonproliferation Program has fostered long and established relationships with the relevant US executive agencies, Congress, key non-governmental organizations, and with private industry. This study was led by two Stimson Center Senior Associates, Dr. Elizabeth Turpen and Brian Finlay, and was supported full-time by Research Associate Rita Grossman-Vermaas. The team offers a considerable breadth of knowledge regarding issues pertinent to this study, including: the proliferation threat of dangerous biological agents, issues related to domestic preparedness, terrorism, the trans-shipment of illicit and dangerous substances, as well as a deep understanding of Congress, the executive agencies, and US domestic licensing and law enforcement. They also hold a keen interest in the intersection of national security and the biotechnology sector. Biographies of the authors are provided below.

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## **ABOUT THE HENRY L. STIMSON CENTER**

Founded in 1989, The Henry L. Stimson Center is a nonprofit, nonpartisan institution devoted to enhancing international peace and security through a combination of rigorous analysis and results-oriented outreach on many of the most urgent national and international security challenges. The Center focuses on three major priorities and areas of work:

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- Building regional security; and,
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The Cooperative Nonproliferation Program at the Stimson Center offers innovative, functional approaches to address the most significant threat to international security today: the spread of weapons of mass destruction. It seeks to bridge the gap between traditional “hard” security (proliferation) and “soft” security objectives (capacity-building, global development and public health). We partner with the public and private sector—an under-exploited resource—to achieve mutual security and development objectives. Only by exploring and leveraging all available means to address the growing threat of proliferation can we begin to treat its causes rather than its symptoms. For detailed information about our projects, please visit: <http://www.stimson.org/cnp>.