REGULATING ACCESS TO AND CONTROL OF DANGEROUS PATHOGENS: IMPLICATIONS FOR THE PHARMACEUTICAL INDUSTRY

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PREFACE

Dear Reader,

I am pleased to present to you an updated Stimson Center publication, Regulating Access to and Control of Dangerous Pathogens: Implications for the Pharmaceutical Industry. It was written by Rita Grossman-Vermaas, Brian Finlay and Elizabeth Turpen, and is based on original, in-depth research into a new security issue that demands attention and policy response.

In the complicated world of terrorism and evolving biotechnology, the US and other governments have worked hard to cut off access to potentially dangerous materials by people who would use those substances to wreak havoc and violence on innocent civilians. One potential threat that has not received enough attention is the prospect of biologic products developed for therapeutic use being misused once in the hands of criminals or terrorists. This emerging issue calls out for a tightening of regulatory practices in the interest of public safety and security.

This project and its report underscore how much the national security field is changing, and now involves diverse actors, including people in industry and private sector research. We are pleased with the constructive collaboration between experts in the private sector, government and think tanks who contributed to this study. The analysis and recommendations are those of the authors alone, but we are grateful for the many important insights provided by those in industry and in government. We hope that this report will be of use to those concerned about evolving biological threats.

Sincerely,

Ellen Laipson

EXECUTIVE SUMMARY

Seven days after the September 11 attacks on the World Trade Center and the Pentagon, anthrax spores were spread through the US Postal Service to a variety of news services and public officials. Within three months, eighteen people were known to have been infected, five of whom ultimately died. The personal tragedy was compounded by widespread economic and social disruption in the United States and around the world. Since then, the US Government has undergone a fundamental reordering of budgetary and institutional alignments to combat global weapons diffusion. Addressing the threat posed by dangerous pathogens has focused almost exclusively on controlling access to the most hazardous pathogens, and monitoring research on a defined list of potentially dangerous agents. To date, little attention has focused on the movement of these dangerous pathogens beyond their collection and R&D stages. We find that the rapidly expanding market for biologics for therapeutic uses generally, and medical bioagents and toxins specifically, may present new avenues for bioterrorists to attack the United States.

The following study represents the culmination of intensive research and discussions with the private sector, industry and security experts on the national security implications of potentially dangerous biological agents and products. It offers a wide spectrum of proposals and recommendations designed to provide a layered defense against the misuse or misapplication of 'select agents' as well as pharmaceuticals derived from that category of biological materials—what we term, 'select products.'

The study examines the emerging challenges surrounding the misuse of 'biologics' in the United States and abroad. It recognizes the attention that prescription drugs, particularly biologics, or biopharmaceuticals, are being given in the 110th Congress. Two key themes are generic biopharmaceuticals, or 'follow-on' biologics, and personal drug importation. As the biopharmaceutical industry expands to include a follow-on market, careful attention should be paid to ensure that new companies that handle select agents and/or produce follow-on biologics that contain select agents are required to undergo rigorous product review, and come under the strictest standards of possession, management and use of both agent and finished product. As noted above, US public health and bioterrorism prevention and response strategies to date have not considered pharmaceutical products derived from select agents as a potential future source of bioterrorist threats. At a macro level, the study argues that present bio-agent and pharmaceutical 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 contain biological agents and toxins; and
3. A **failure to provide unique nomenclature identities** in the current pharmaceutical drug coding system for products that are manufactured from the same raw material, particularly those which contain biological agents and toxins.

In short, we conclude that the proliferation and potential misuse of biological agents are security challenges that must not be overlooked. In an effort to enhance national security as it relates to these challenges, we recommend the following upgrades to existing precautionary practices:

1. Ensure effective domestic and international measures for the oversight of the storage, transfer, and research of select agents;
2. Develop greater awareness among the public, policy community, private industry and the international community about the potential health and security threats posed by the development and distribution of therapeutic products derived from select agents;
3. Ensure rapid implementation of federal standards against counterfeiting, misuse and diversion;
4. Implement a standardized system of advanced pedigree requirements for select agent and product distribution to prevent groups and businesses from 'opportunity shopping' and diversion;
5. Amend the current drug nomenclature and coding system to achieve new levels of public health safety and bioterrorism preparedness.

Given the deficiencies in current oversight and tracking mechanisms, and the potential threat posed by pharmaceuticals derived from select biological agents and toxins, a need for a multi-tiered solution is clear. As a beginning, existing mechanisms should be upgraded. The following report provides a series of recommendations to improve these mechanisms which fall into three interrelated categories of biological weapons prevention/biosecurity; counterfeit pharmaceuticals; and the possible misuse of legitimate pharmaceutical products.

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INTRODUCTION

In February 2006, the Cooperative Nonproliferation Program at the Henry L. Stimson Center undertook an independent assessment of the potential for pharmaceutical products derived from select biological agents and toxins to be used as biological weapons (BW). Recent intelligence indicates that terrorists and terrorist states are devoting ever increasing resources to the development of biological agents for the purposes of causing mass casualties. As a result, governments around the world have been investing heavily in select agent R&D for the development of biological countermeasures.[1] In an unrelated development, select agents are also being viewed by the pharmaceutical industry as potential new sources for miracle drugs. This study represents the culmination of intensive research and discussions with the private sector, industry and security experts on the subject and considers:

- 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 over the possible misuse or unlicensed use of biological pathogens and toxins, as exemplified by a recent Florida case involving the paralysis of four victims from unapproved use of botulinum toxin type A (BTTA).

This study examines the myriad issues surrounding the misuse of biologics in our country and abroad. While much attention since the October 2001 anthrax attacks in the United States has focused on regulating access to dangerous pathogens and ensuring the peaceful uses of biotechnology, **we find that the rapidly expanding market for therapeutic biologics generally, and medical biological agents and toxins specifically, may present new avenues for bioterrorists to attack the United States. This study identifies three such vulnerabilities in United States public health and bioterrorism prevention and response strategies. It argues 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 contain biological agents and toxins; and

[1] NATO Parliamentary Assembly, Resolution 321 on Terrorism with chemical, biological, radiological and nuclear weapons (2002) (www.nato-pa.int); Department of Defense Chemical, Biological, Radiological and Nuclear Defense Program, Annual report to Congress, May 2004 (www.fas.org/irp/threat/cbw/dod-cbnrd-2004.pdf); David Press, 'Experts concerned about biological research at DHS's NBACC', 4 August 2006 Biosecurity Briefing, Center for Biosecurity (www.upmc-biosecurity.org); Project Bioshield Act of 2004, Public Law 108-276; Statement by the Director of National Intelligence, John D Negroponte to the Senate Select Committee on Intelligence, 2 February 2006.

3. A failure to provide unique nomenclature identities in the drug coding system for disparate types of products that are manufactured from the same raw material, particularly those which contain biological agents and toxins.

This study emerges from discussions with the private sector, industry and security experts, as well as intensive research on the national security implications of potentially dangerous agents and products. It is structured as follows:

1. Overview and analysis of related findings in the context of a post-September 11 security environment.
2. Presentation of our findings and recommendations for regulating control of potentially dangerous agents which fall into three interrelated categories of:
    - biological weapons prevention/biosecurity;
    - counterfeit pharmaceuticals; and
    - the misuse of legitimate pharmaceutical or cosmetic products.

Within each category, our team offers pragmatic recommendations to the US government, industry and the international community.

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BACKGROUND

SECURITY REDEFINED: PREVENTING THE PROLIFERATION AND USE OF BIOLOGICAL WEAPONS

The end of the Cold War created profound changes in international politics and priorities. In the past sixteen years, the world's attention has shifted from the great power standoff between the US and the Soviet Union as myriad other challenges have come to dominate the global security agenda. In response, the activities of international organizations such as the United Nations and national governments have vastly increased in scope and complexity to deal with emerging challenges and their attendant social and political consequences. These challenges are a blend of 'hard' and 'soft' security issues—a line of distinction which has become increasingly blurred in current US and international policy arenas. They include, *inter alia*, regional and intra-state conflict, weapons proliferation, outbreaks of infectious diseases, terrorism, drug trafficking, state failure, state building, humanitarian intervention, population growth, and climate change. A new security-oriented terminology has evolved to address these interwoven issues, made evident by the use of phrases such as 'health security', 'human security', and 'environmental security'.

Beyond the obvious security challenge of terrorism itself, perhaps no other threat has approached the level of concern or complexity than has the widespread recognition of emerging infectious diseases as a burgeoning transnational security threat. While concerns about biological weapons 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 'bioterrorist' threat, it became clear that this new challenge lay at the doorstep of agencies and government departments that had never before been part of the national security dialogue.

To combat a disease outbreak, federal and local health departments would need to play a pivotal role. In 1998 the US Centers for Disease Control and Prevention (CDC) laid out its strategy to modernize and rebuild the US public health system for the twenty first century by improving disease surveillance, detection, prevention and response.[2] The Department of Health and Human Services (HHS) saw a strengthened public health system as key to mitigating the effects of both naturally emerging outbreaks as well as bioterrorism. Since the attacks of September 11, 2001 and the subsequent dissemination of anthrax through the US postal system, stemming bioterrorism has become a top national priority, although some analysts feel that the threat has been exaggerated to the detriment of public education about the actual threat bioterrorism poses. Across all sectors a greater

[2] 'Preventing emerging infectious diseases: A strategy for the 21st century', Department of Health and Human Services, Centers for Disease Control and Prevention, Atlanta, Georgia, October 1998.

awareness of the factors that contribute to disease threats, new sources from which bioterrorism could originate, and a realistic assessment of the threat of bioterrorism are necessary to effectively tailor US and international prevention strategies. The existing strategies are a beginning, but now is the time to consider how to integrate, improve and refine them.

PHARMACEUTICALS: A SOURCE FOR BIOWEAPONS DEVELOPMENT?

THE ISSUE:

PHARMACEUTICAL PRODUCTS DERIVED FROM 'SELECT AGENTS' ARE UNLIKELY TO BE USED AS MASS-CASUALTY BIOLOGICAL WEAPONS. HOWEVER, THERE IS A GROWING SUBSET OF PHARMACEUTICALS WHICH ARE DERIVED FROM SELECT AGENTS. THESE AGENTS OR A PRODUCT DERIVED FROM SUCH AGENTS MISUSED TO INCITE PANIC COULD BE CONSIDERED AN EFFECTIVE TERRORIST WEAPON.

'By their nature, terrorist events are unexpected…and…evoke a sense of fear and uncertainty'.[3] Biological and toxin weapons contribute additional factors, which magnify their potential impact, using only very small quantities of material. Pathogens are unseen, they multiply within the victim, and can manifest in lethal, contagious and disfiguring symptoms. Toxin weapons range in effect from disabling to lethal. For example, botulinum toxin, the most deadly compound currently known, is a bacterial toxin, but is not self-replicating.[4] Should a botulinum toxin-based product or the raw toxin itself be obtained and misapplied with the intention of producing a series of botulism cases in, for example, five US population centers, panic and confusion could potentially ensue.[5] Terrorist objectives may not necessarily be limited to physical violence; oftentimes the goal may be to induce intense psychological distress and political and social disturbance. John Negroponte, former Director of National Intelligence (DNI) and now Deputy Secretary of State, 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'.[6] This was underscored in Negroponte's 2007 Annual Threat Assessment in a discussion of intelligence about terrorist groups attempting to acquire biological weapons and materials.[7]

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[3] Dana A Shea, 'Terrorism: Background on chemical, biological and toxin weapons and options for lessening their impact', Congressional Research Service, updated 1 December 2004, 5.

[4] 'Terrorism: Background on chemical, biological and toxin weapons and options for lessening their impact', Congressional Research Service, updated 1 December 2004, 2.

[5] There are seven distinct botulinum toxins (A-G) produced by different strains of the bacterium, each producing a different immunologic response. Currently in the US, botulinum toxin types A and B are used in two brand-name pharmaceutical products distributed both here and worldwide for therapeutic and/or cosmetic application. A third product is already in wide distribution outside the US and is expected to be approved by the FDA in 2008.

[6] Statement by the Director of National Intelligence, John D Negroponte to the Senate Select Committee on Intelligence, 2 February 2006.

[7] John D. Negroponte, Annual Threat Assessment of the Director of National Intelligence, presented to the Senate Select Committee on Intelligence, 11 January 2007.

There is precedent for the use of the toxin as a bioweapon. On at least three occasions Aum Shinrikyo, the Japanese cult responsible for the 1995 sarin attacks in the Tokyo subway system, dispersed botulinum toxin aerosols at multiple sites in downtown Tokyo and at US military installations in Japan. The natural habitat of *Clostridium botulinum* is soil, 'from which it can be isolated without undue difficulty',[8] and was the source from which the perpetrators collected their samples. Fortunately, their dissemination attempts were unsuccessful in causing fatalities, seemingly 'due to faulty microbiological technique, deficient aerosol-generating equipment, or internal sabotage'.[9] Had Aum's operations not ultimately been disrupted by the Japanese authorities, it is presumed that the group would have eventually overcome the technical hurdles and successfully weaponized the toxin to devastating effect.

With the past decade's scientific advances and the break-up of the former Soviet Union, the ease of access to biological agents and weapons expertise by state and non-state actors alike has greatly increased and become widely recognized as a serious domestic and international security threat. This concern has only heightened since the events of September 11, 2001 and the dissemination of *Bacillus anthracis*—the spore-forming bacterium which causes anthrax—through the US postal system one month later. In combination with the realities of a growing biologics industry, consideration should be given to the 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, to be used for nefarious purposes. This is particularly true of those defined as 'select agents' by the US Centers for Disease Control and Prevention (CDC).[10] The high technical and financial barriers to extracting an agent from a pharmaceutical product in order to develop and disseminate a mass casualty biological weapon are sufficient to deter a person or group from doing so. There are far simpler and cheaper means to commit a terrorist act if casualties are the objective. However, **the diversion, tainting or misuse of products derived from select agents—herein referred to as '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 very 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.

[8] Stephen S Arnon, Robert Schechter, Thomas V Inglesby, et al, 'Botulinum toxin as a biological weapon', in *Bioterrorism: Guidelines for medical and public health management*, eds Donald A Henderson, Thomas V Inglesby, and Tara O'Toole, *JAMA & Archives Journals* (2002), 144.

[9] Arnon et al, 'Botulinum toxin as a biological weapon', *JAMA & Archives Journals*, 142.

[10] Centers for Disease Control and Prevention Select Agent Program (www.cdc.gov/sap).

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INTERNATIONAL AND DOMESTIC APPROACHES TO MONITORING BIOLOGICAL AGENTS AND TOXINS

THE ISSUE:

WHILE THERE ARE REGULATIONS AND MECHANISMS TO PREVENT BW POSSESSION AND USE, THEY ARE INSUFFICIENT TO MEET EMERGING SECURITY CHALLENGES.

This section addresses the international and domestic controls, treaties, resolutions and arrangements which seek to prevent the unlawful development and use of biological materials, technology and weapons. It will begin with a brief summary of key international control measures and how they are verified, monitored and enforced, followed by a discussion of US domestic measures in the same manner. Recommendations for each level of regulation are provided. However, in line with the scope of this study, those related to domestic efforts receive more attention.

THE GENEVA PROTOCOL AND THE BWC

The 1925 Geneva Protocol[11] established an international norm against the use of chemical and biological weapons as a means of warfare. 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 (BWC)[12], entered into force. This was a defining moment in the field of disarmament, as the BWC was the first treaty to ban the development, production, stockpiling and transfer of an entire category of weapons of mass destruction (WMD)—nuclear, chemical and biological weapons inclusive. At present, 155 countries have ratified the treaty, and there are sixteen signatories. However, the BWC faces some major shortcomings, namely the absence of a verification system and 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, 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 a voluntary undertaking. At the Sixth Review Conference in 2006, states parties agreed to establish a small Implementation Support Unit. States parties could not agree on establishing a full, independent

[11] Protocol for the Prohibition of the Use in War of Asphyxiating, Poisonous or Other Gases, and of Bacteriological Methods of Warfare (Geneva Protocol), 17 June 1925 (cns.miis.edu/pubs/inven/pdfs/genev.pdf).

[12] Convention on the prohibition of the development, production and stockpiling of bacteriological (biological) and toxin weapons and on their destruction, 10 April 1972 (www.opbw.org/convention/documents/btwctext.pdf).

body similar to that which exists for implementing the Chemical Weapons Convention. As such, the ISU will be located in the UN Department for Disarmament Affairs and promote the universalization of the Convention and support the exchange of confidence-building measures. Most other issues remain unresolved among parties. A second intersessional program will be 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 chemical and biological weapons (CBW) verification gaps, in 1982 the United Nations General Assembly (UNGA) endorsed the authority of the UN Secretary-General to investigate any situation which 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 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.[13]

THE AUSTRALIA GROUP

During UN investigations in Iran and Iraq in 1984 it was discovered that Iraq had used chemical weapons in violation of the 1925 Geneva Protocol, and that 'at least some of the precursor chemicals and materials for its [chemical weapons] CW program had been sourced through legitimate trade channels'.[14] 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.'[15] It should be noted that their controls target only the activities of state actors. In addition, while the Australia Group asserts its belief that the 1993 Chemical Weapons Convention (CWC)[16], 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 which believe that it only adds constraints on their economic development. 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

[13] 'WMD verification and compliance: The state of play', prepared by the Verification Research, Training, and Information Centre (VERTIC), London for the Weapons of Mass Destruction Commission (Report 19). (www.wmdcommission.org).

[14] Website of the Australia Group (http://www.australiagroup.net).

[15] Australia Group website (www.australiagroup.net) Accessed 17 March 2006.

[16] Convention on the prohibition of the development, production, stockpiling and use of chemical weapons and on their destruction, 13 January 1993 (www.opcw.org/docs/cwc_eng.pdf).

bioterrorism concerns, we therefore urge all participating states to redouble their efforts to ensure compliance with Australia Group guidelines.

THE CHEMICAL WEAPONS CONVENTION: A COMPARISON

The 1993 CWC replaced the Geneva Protocol as the primary disarmament agreement in the chemical weapons (CW) 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.[17] Nevertheless, the CWC and the organization that oversees its implementation, the Organisation for the Prohibition of Chemical Weapons (OPCW), 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.[18]

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).[19] 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.[20] 133 UN member states have submitted national reports detailing their implementation status, and the term of the UN committee established to assess compliance has been extended.[21] As the sole piece of international regulation that specifies all states 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 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 which should be comprehensively supported. Further improvements are being made as well; the widespread implementation of

[17] 'WMD verification and compliance: The state of play', VERTIC, 25.

[18] Ibid., 26.

[19] S/RES/1540 (28 April 2004) (disarmament2.un.org/Committee1540/Res1540(E).pdf).

[20] Scott Jones, 'Resolution 1540: Universalizing export control standards'?, *Arms Control Today*, May 2006.

[21] Figures are from December 2006. George Bunn, 'Enforcing International Standards: Protecting Nuclear Materials From Terrorists Post-9/11', Arms Control Today, January/February 2007.

Resolution 1540 is one such example. While an in-depth analysis of how to strengthen the above agreements and arrangements is out of 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. The remainder of this section proceeds with a discussion of US domestic measures to control biological agents and toxins, and provides recommendations for their improvement.

US CONTROL MEASURES

America's bioterrorism prevention strategy is focused on controlling access to dual-use agents, technology and know-how that can be used for both legitimate research and for bioweapons development. Through the Select Agent Program, the CDC seeks to monitor and regulate researchers and facilities that possess, use and transfer nearly forty (40) dual-use pathogens and toxins identified as having the potential to pose a severe threat to human health and safety and to be used as weapons by criminals or terrorists.[22] This includes the protection of these materials from theft and diversion, i.e. biosecurity measures. The USA PATRIOT Act contains further restrictions regarding access to these agents. In addition, Customs and Border Protection (CBP), with assistance from CDC and the Food and Drug Administration (FDA), regulates the importation of pharmaceutical products, including those derived from select agents, largely for the purpose of identifying counterfeits. The Bureau of Industry and Security, Department of Commerce, oversees a separate select agent export program for transfers abroad in accordance with US obligations to the Australia Group. See Annex 1 for a chart on each agency's function. For instance, *Clostridium botulinum,* botulinum neurotoxins and products derived from botulinum neurotoxins are controlled under the direction of these agencies in compliance with federal and international law.

THE SELECT AGENT PROGRAM

The Select Agent Program has generated new intelligence on the uses, whereabouts and origins of the most high-consequence pathogens and toxins. Many in the security policy community believe the regulatory scheme that governs these agents is a valid approach to preventing a biological weapons incident; however one need not look far among scientists and researchers to find disagreement.[23] A

[22] See the Public Health Security and Bioterrorism Preparedness and Response Act of 2002 (Public Law 107-188). There are also select agents and toxins which are overseen by the US Department of Agriculture for their potential to harm animals and agriculture, as well as a category of 'overlap' agents and toxins which have the potential to affect both humans and animals. 350 entities are registered with the CDC as possessing select agents with the capability to affect human health. They break down into the following categories: 105 academic/university; 104 state/local government; 61 federal government; 39 commercial; 35 private/non-profit/research institutions; 6 other. Federal Register, Vol. 70, no. 52, Friday March 18, 2005, Rules and Regulations, 13315.

[23] There has yet to be a cost-benefit assessment of the Program's goals and implementation. The authorization to appropriate funds for the program will expire in 2007, offering an opportunity to review the program's effectiveness and its impact on life sciences research. 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

shortcoming not necessarily considered by scientists, but one that is particularly relevant to this study is that the program does not track the chain of custody of biological agents from their raw, research stage through their development into pharmaceutical products. More importantly, there are no standardized government or industry regulations that sufficiently prevent unlicensed persons or companies from obtaining access to raw biological agents. A related issue is the emergence of a generic biopharmaceutical, or 'follow-on' biologics, industry. As this industry expands, the FDA, CDC and Department of Homeland Security should work assiduously with Congress to ensure that, oversight over both raw agents and finished product is maintained from "cradle-to-grave" for both existing and new companies that handle these agents. As the industry and market develop, 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. **As this 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.**

If these gaps are not addressed, events such as those which led to the 2004 botulism poisoning cases in Florida will occur more frequently. In this instance, a physician suspended from practice ordered a vial of botulinum toxin type A (BTTA) from a northern California manufacturer and supplier of bacterial toxins.[24] 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.[25] The vial, intended for research purposes, contained as much as ten million units of the toxin—10,000 times that of a normal dose of a standard FDA-approved BTTA pharmaceutical product. The physician attempted to reconstitute the raw toxin and injected himself and three others as though it were a medical product. All four persons were hospitalized with symptoms of botulism. **Regulations over the illegitimate production and use of pathogens and toxins must be strengthened.**

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 (TRI). Medical practitioners in the US were targeted and offered a reduced price brand-name product. Three

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 health and the benefits of scientific openness' (Henry L Stimson Center, 2006).

[24] United States District Court, Southern District of Florida, 'Affadavit of FDA Special Agent Susan J. Leeds in support of United States' motion for temporary restraining order, preliminary injunction and permanent injuction', Case no. 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 (ATCC). To obtain the vials, he presented certification from the American Society for Microbiology and falsified documents. See American Society for Microbiology, 'April 10, 2000 – Promoting Research Integrity at the American Society for Microbiology', (www.asm.org); Dempsey, Eileen, 'Lab Blamed in Bubonic Plague Case', *Columbus Dispatch*, 20 May 1995.

[25] 'Reports blame Florida botulism cases on misused toxin', Center for Infectious Disease Research & Policy, University of Minnesota, 15 December 2004.

doctors and four corporations—all established by the same people—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.

The Florida events illustrate the ease by which bulk toxin can be obtained and misused, and the public health impact that could follow. While in this scenario the perpetrators were motivated by money, one cannot discount the potential for the nefarious use of botulinum toxin or other select agents as weapons of mass panic.

In the absence of comprehensive international BW regulatory framework and the inability of existing domestic oversight mechanisms to regulate access to bulk agents and toxins and their development into final products, **we suggest the following measures be considered by the US government, private industry, and the international community**.

RECOMMENDATIONS

FOR THE UNITED STATES GOVERNMENT

RECOMMENDATION	RATIONALE
DEVELOP AND IMPLEMENT A SYSTEM TO TRACK THE DISTRIBUTION OF BULK BIOLOGICAL MATERIAL PRODUCED DOMESTICALLY OR IMPORTED FROM FOREIGN MANUFACTURERS.	Tracing the chain of custody of biological agents is particularly important given their bioterrorist potential as weapons of mass panic.
INCREASE AWARENESS IN THE POLICY COMMUNITY ABOUT THE POTENTIAL BIOWEAPONS THREAT FROM DUAL-USE BIOTECHNOLOGY, AND THE NEED FOR STRICT BIOSECURITY MEASURES IN LABORATORIES AND RESEARCH CENTERS ACROSS THE COUNTRY THAT POSSESS, USE AND TRANSFER PATHOGENIC MICROORGANISMS AND TOXINS.	The sources and relative likelihood of potential threats are not widely understood. Such awareness building must include industry to ensure buy-in and respect intellectual property. For the purposes of this report, 'biosecurity' refers to the protection of pathogenic microorganisms and toxins from theft and diversion.

FOR INDUSTRY

RECOMMENDATION	RATIONALE
ENSURE 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 OR MALICIOUS DIVERSION.	Such measures support the objectives of the Select Agent Program and UN Security Council resolution 1540.

FOR THE INTERNATIONAL COMMUNITY

RECOMMENDATION	RATIONALE
SUPPORT ONGOING EFFORTS TO DEVELOP INTERNATIONAL NORMS/CODES OF CONDUCT FOR BIOTECHNOLOGY RESEARCH.	While this study focuses on the physical products yielded by such research, a layered protection strategy necessarily includes regulation of research, raw materials, and finished product.
ENCOURAGE ALL PARTIES TO THE BWC TO ENSURE COMPLIANCE WITH THEIR OBLIGATIONS TO PROHIBIT THE DEVELOPMENT, PRODUCTION, AND STOCKPILING OF BIOLOGICAL AGENTS AND TOXINS USED FOR NON-PEACEFUL PURPOSES.	To date, the BWC has been ratified by 155 states and has an additional 16 signatory states. Its absence of a verification system and only rudimentary compliance mechanisms has been a subject of intense international debate.
URGE PARTICIPATING STATES TO ENSURE COMPLIANCE WITH AUSTRALIA GROUP GUIDELINES.	Concern has been expressed about 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 the light of proliferation and bioterrorism concerns, full compliance with Group guidelines is essential.
INCREASE AWARENESS AMONG THE SCIENTIFIC, RESEARCH AND PRIVATE SECTOR COMMUNITIES ABOUT DUAL-USE BIOTECHNOLOGY.	In 2004, the National Academies of Science commissioned a study on ways to minimize threats from biological warfare and bioterrorism without hindering the progress of biotechnology. The "Fink Report", so named after the committee chairman,

	recommended, "that national and international professional societies and related organizations and institutions [should] create programs to educate scientists about the nature of the dual use dilemma in biotechnology and their responsibilities to mitigate its risks." This recommendation should extend to raising awareness among manufacturing and distributing firms, in addition to those in the life sciences community.

— 4 —
CONTROLLING COUNTERFEIT PHARMACEUTICALS

THE ISSUE:

THE GROWING US PRESCRIPTION DRUG MARKET, INCREASED DEMAND FOR HIGH-END PHARMACEUTICAL PRODUCTS AND THE INCREASING COSTS ASSOCIATED WITH THOSE PRODUCTS HAVE RESULTED IN EXTRAORDINARY NEW PRESSURES TO FIND LOWER-COST MEDICINES. THIS REALITY HAS DRIVEN A BURGEONING MARKET IN COUNTERFEIT DRUGS WHICH POSES NOT ONLY A REAL PUBLIC HEALTH THREAT, BUT A NEW AND POTENTIALLY DIRECT CHALLENGE TO US AND INTERNATIONAL SECURITY.

THE COUNTERFEIT DRUG INDUSTRY

A recent World Health Organization (WHO) study stated that various estimates on the percent of the total pharmaceutical market that counterfeit drugs represent range from 'as high as 50% to as low as 1%'.[26] **This includes both brand-name and generic, or comparable, products.** The rate of counterfeiting tends to range 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, EU, Japan, New Zealand, and the US. But, recent trends indicate an increase in counterfeits in such countries. Furthermore, according to recent analysis, medicines purchased over the internet from sites that conceal their physical address are counterfeit over 50% of the time.[27]

As counterfeit drugs are produced without any active ingredient, or in insufficient quantities, or contain a toxic substance, they have little or no therapeutic, diagnostic or prophylactic value. Without a sufficient amount of the active ingredient, a person 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 and, by one estimate, counterfeits cost the pharmaceutical industry $46 billion per year in lost profits.[28] In the case of infectious diseases, where the largest burden of disease falls in the 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'.[29]

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[26] 'Combating counterfeit drugs: A concept paper for effective international cooperation', World Health Organization, 27 January 2006, 3.

[27] International Medical Products Anti-Counterfeiting Taskforce, 'Counterfeit Medicines: an update on estimates', 15 November 2006.

[28] Susannah Patton, 'Cracks in the pharmaceutical supply chain', *CIO Magazine*, 15 January 2006.

[29] Patton, 'Cracks in the pharmaceutical supply chain', *CIO Magazine*. 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 the

Developed countries are not immune to the dangers of counterfeit drugs. In 2004 alone, the FDA initiated fifty-eight counterfeit drug cases, increased from the thirty cases initiated in 2003. The number of newly initiated cases dropped to 32 in 2005, but preliminary FDA assessments from July 2006 suggest that this year's cases will rise to 2004 levels again.[30] (See Figure 1). However, agency officials caution against relying on the number of new cases to determine the actual volume of counterfeit drugs or the prevalence of counterfeiting. They merely reflect newly opened cases.

> A single case may involve several types of counterfeit drugs being offered for sale, and multiple doses of each drug. Nearly 4 billion prescriptions were filled last year. That means a very large volume of drugs is moving through the supply chain. The sophistication and precision of some counterfeit copies of legitimate drugs make a reliable estimate of the number of counterfeits impossible.[31]

Moreover, when considering the state of the drug supply chain, one cannot discount the number of large and small wholesalers which take advantage of multi-tiered pricing in the industry, sometimes smuggling lower priced drugs into the US to be sold to large wholesalers for a profit.[32] 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.[33] As mentioned above, 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 introduce them into the legitimate supply chain.

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genuine ingredients. 'Nine killed by fake Chinese drug', *BBC News*, 22 May 2006 (www.bbc.co.uk).

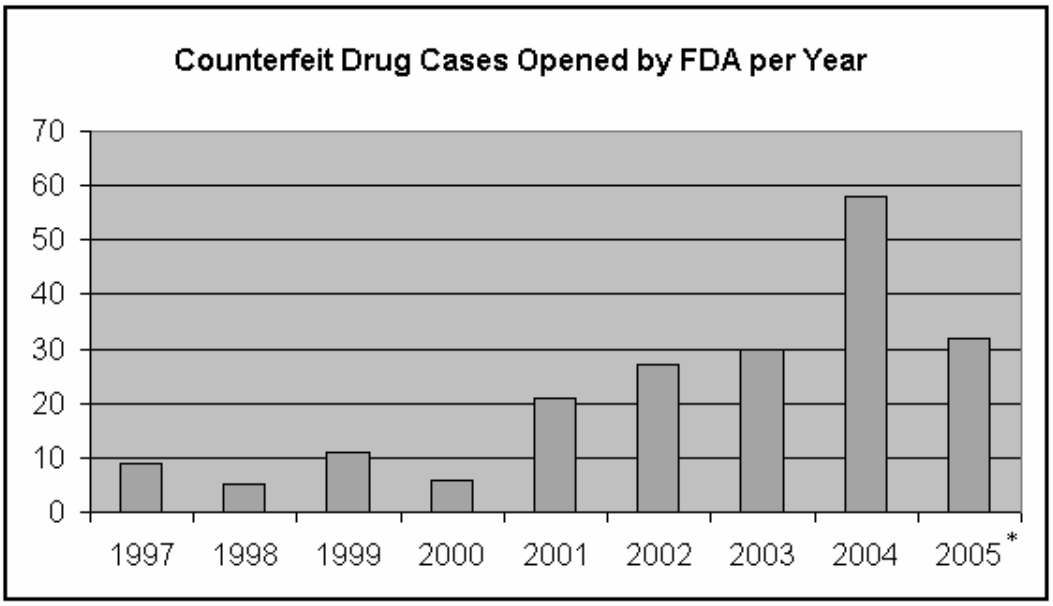
[30] Statement by Randall W Lutter, PhD, Associate Commissioner for Policy and Planning, Food and Drug Administration on Pharmaceutical Supply Chain Security before the House Subcommittee on Criminal Justice, Drug Policy and Human Resources, Committee on Government Reform, 11 July 2006.

[31] Statement by Randall W Lutter before the House Subcommittee on Criminal Justice, Drug Policy and Human Resources, Committee on Government Reform, 11 July 2006.

[32] The discovery of such operations was made during a two-year FDA sting operation called 'operation gray pill'. Patton, 'Cracks in the pharmaceutical supply chain', *CIO Magazine*.

[33] Ibid.

Figure 1[34]



*Preliminary assessments suggest that cases in 2006 will return to 2004 levels.

REIMPORTATION

In addition to opportunists and criminal activity, given the extraordinary cost of prescription drugs in the US relative to other countries, the number of ordinary citizens seeking lower-cost medicines in Canada and elsewhere has skyrocketed. Until last fall, 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 FY 2007 Homeland Security Appropriations Bill, which includes a provision to lift the personal importation ban on small quantities of prescription drugs from Canada, became public law in October 2006. Another bill re-introduced in the current Congress, which would ease restrictions on drug importation from Australia, Canada, the European Union, Japan, New Zealand, Switzerland, and other countries with standards similar to the US, is currently pending. However, in this bill, biologics and injectable drugs are exempt.

Nearly 12 million prescription drug products—tablets, capsules, inhalants, injectables, biologics, generics, brand name drugs and controlled substances—with a value of approximately $700 million entered the US from Canada in 2003 alone. They enter via internet purchases or travel to Canada by US consumers. Sales from licensed Canadian pharmacies were valued at $43.5 million per month in

[34] *Combating Counterfeit Drugs: A Report of the Food and Drug Administration Annual Update*, 18 May 2005 (www.fda.gov). Accessed 31 March 2006.

early 2004.[35] While studies have shown that Canadian drugs have been safe, most that are imported are unapproved for the US market.[36] Moreover, the FDA has argued that it cannot guarantee the chain of custody or integrity of a product 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 United States. While a federal standard is welcomed, not only does the requirement fail to address imported drug products, but will be in conflict with the patchwork of state requirements already in existence for the foreseeable future.

Concerns about safety are on both sides of the border. A 2004 report by the Health and Human Services (HHS) 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.*[37] *(emphasis added).*

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

> *We are concerned that the legitimising 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, believing them to be safe and genuine.*[38]

The new US law creates a regulatory and national security loophole that could imperil the health and safety of Americans. It throws wide open an unregulated avenue of cross-border trade through which counterfeit and tampered products could easily flow, 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.

In light of a rapidly advancing life sciences industry and an evolving security environment, the

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[35] Clifford Krauss, 'Kinks in Canada drug pipeline', *The New York Times,* 6 April 2006.

[36] US Government Accountability Office (GAO), 'Prescription drugs: strategic framework would promote accountability and enhance efforts to enforce the prohibitions on personal importation', December 2005, GAO-05-372.

[37] HHS Task Force on Drug Importation, 'Report on prescription drug importation', December 2004, accessed at: www.hhs.gov/importtaskforce/Report1220.pdf.

[38] Barbara Kermode-Scott, 'US eases its restrictions on prescription drugs from Canada', *British Medical Journal* 2006; 333:824 (21 October).

unlicensed acquisition, proliferation and misuse of select products which are stored and distributed globally may present new avenues through which bioterrorists could attack the United States. With a sanctioned entry-point through which unlicensed products can now travel, select products demand particular attention and oversight at the national level.

To ensure the integrity of products of health and safety concern and the security of consumers and the American public, a special exception to imports should be made for products that contain or are derived from select agents. Moreover, the FDA and manufacturers should continue to work toward a common solution to prevent the importation of counterfeits, particularly those of select agent derived products, while limiting the cost burden on consumers for lower-cost medicines. Although importation from Canada is now legal, counterfeit products from foreign or unidentifiable sources could still enter the system.

STRATEGIES FOR SELECT PRODUCTS AND THE SUPPLY CHAIN

The growth of medical products and therapeutic countermeasures that contain or are derived from select agents is expanding, and a booming counterfeit drug trade already exists. As already seen, this class of select products poses unique new challenges to US and global security.

In response to the rising tide of counterfeit products flooding the US and international markets, trade associations, private industry, and federal and state governments have proposed ways and taken initiatives to combat the threats counterfeits pose. Many of these strategies are useful starting points for dealing with select products.

TARGETING UNLICENSED WHOLESALERS

In the light of increasing concerns related to counterfeits, retailers such as CVS and distributors such as FFF Enterprises have pledged to cut off trade with suppliers that deal in the secondary market. Capitalizing on market concerns, FFF Enterprises has also agreed only to purchase directly from the manufacturer, and has significantly expanded its market share by doing so. **We recommend all companies purchase their 'select products' *only* from the manufacturer, which would reduce the demand for and threat of unlicensed wholesalers and distributors. We further recommend that manufacturers convene a coalition of concerned wholesalers with the federal government to collaborate on a nationwide public/medical community education campaign on counterfeits and gaps in the pharmaceutical supply chain.**

Stricter regulation of wholesalers is another critical strategy. In 2006 the National Association of Boards of Pharmacy (NABP) released an updated *Model Rules of the National Association of Boards of Pharmacy*.[39] They were developed in conjunction with the FDA, the Drug Enforcement Agency (DEA), state regulatory authorities and the wholesale distributor industry and mandate the following:

- stricter state licensing requirements for wholesale distributors and due diligence procedures prior to wholesale transactions;

[39] National Association of the Boards of Pharmacy, 'Model Rules for the Licensure of Wholesale Distributors', 19 June 2006.

- specific pedigree requirements for products that are particularly susceptible to adulteration, counterfeiting or diversion. These products are designated on the 'National Specified List of Susceptible Products'. The pedigree requirements follow and go beyond the effective date of the wholesale distributor guidelines mandated in the federal Prescription Drug Marketing Act (described below); and
- an attempt to reduce redundancy and confusion as states update and adopt regulations.

As such, **we recommend that each state should adopt, implement and enforce the updated Model Rules**. If implemented, the revised rules would help ensure the legitimacy and integrity of wholesalers, align federal and state regulations, reduce incentives for counterfeiting, and ensure the integrity of drug products. **In addition, we recommend that the 'National Specified List of Susceptible Products' be expanded, with industry involvement, to include a subset of pharmaceuticals that pose a public health and security threat given their use of controlled biological agents**. The subcategory would include products not currently on the List and which contain select agents and toxins, as well as those developed as vaccines and toxin antidotes. This list should be dynamic in order to contend with scientific advancements and provided to the CBP and FDA to aid in their anti-counterfeit efforts.

FEDERAL ANTI-COUNTERFEITING STRATEGIES

While private industry has undertaken ad hoc efforts to expose domestic and international counterfeit chains, anecdotal evidence suggests that federal investigation agencies are overburdened with competing demands and low resources, and have assigned a relatively low priority to the threat of counterfeit drugs.[40] **To help ease the burden on federal agencies, we recommend that industry should regularly inform the FDA and FBI about what it has uncovered in terms of risks, threats, etc. and expect that federal investigators will pursue all serious leads.** In addition, the US government should cooperate closely with foreign agencies, such as Health Canada, the UK Ministry of Health, WHO, Interpol and other international public health and law enforcement agencies to expand a global anti-counterfeiting network.

There are areas where 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'.[41] It is updated annually with details on progress and to publicize ongoing debates. The report recommended, *inter alia*, the timely adoption and common use of track and trace technology which 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

[40] Statement of Carl Levin, Senate Committee on Governmental Affairs, 'Buyer beware: The danger of purchasing pharmaceuticals over the internet', 17 June 2004; US Government Accountability Office, 'Prescription drugs: Strategic framework would promote accountability and enhance efforts to enforce the prohibitions on personal importation', 8 September 2005; Statement of Richard M Stana, 'Prescription Drugs: Enhanced efforts and better agency coordination needed to address illegal importation', US Government Accountability Office, 13 December 2005.

[41] 'Combating counterfeit drugs: A report of the Food and Drug Administration', US Food and Drug Administration, February 2004.

drugs. Both standardized track and trace technology and the adoption of laws have had modest success, and will be discussed in further detail below. With respect to a reporting system, the FDA has established a Counterfeit Alert Network (CAN) that links together and enhances existing counterfeit notification systems to provide timely and effective notification to health professionals and consumers. FDA is partnering with national healthcare organizations, consumer groups and industry representatives to deliver time-sensitive messages about counterfeits and about how to report suspect counterfeit products. Sixteen organizations are part of the CAN co-sponsorship agreement.[42]

Another federal initiative is to amend the Federal Food, Drug and Cosmetic Act, which authorizes the FDA to oversee product safety standards[43], with the Counterfeit Drug Prevention Act of 2007.[44] The 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 last Congress.[45] 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 (HHS) to educate public and health care professionals about counterfeit drugs, including techniques to identify drugs as counterfeit.

We recommend that the Counterfeit Drug Prevention Act of 2007 is amended to include the funding and education requirements of the bill mentioned above, as well as amended with particular attention given 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, wide industry cooperation is crucial to this endeavor, without which the effectiveness of the existing 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.

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

[42] 'Combating counterfeit drugs: A report of the Food and Drug Administration Annual Update', 2006.

[43] This includes standards for imported products that are 'adulterated' or 'misbranded'. Federal Food, Drug and Cosmetic Act, 21 U.S.C., Section 801, (www.fda.gov/opacom/laws/fdcact/fdctoc.htm).

[44] 'Counterfeit Drug Prevention Act of 2007', H.R. 780, introduced in the 110th Congress, 1st Session, 31 January 2007.

[45] 'Counterfeit Drug Enforcement Act of 2005', S. 1978, 109th Congress, 1st Session.

state.[46] In December 2006, the Prescription Drug Marketing Act (PDMA)[47], 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.[48] 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.[49] 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.

However, 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 in general allows for multiple opportunities in the distribution process for counterfeits, contamination and diversion. 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 such as are considering similar legislation. But progress is slow.

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. 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 which could impose severe consequences for the company and its consumers.[50] While the FDA has encouraged the rapid implementation of RFID to secure the supply

[46] Patton, 'Cracks in the pharmaceutical supply chain', 15 January 2006.

[47] 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.

[48] Compliance Policy Guide 160.900, Prescription Drug Marketing Act—Pedigree Requirements under 21 CFR Part 203, December 2006.

[49] FDA Counterfeit Drug Task Force Report: 2006 Update, p 6. (www.fda.gov/counterfeit); Department of Health and Human Services Food and Drug Administration, Final Rule (21 CFR Part 203), Federal Register, 18 March 2004, Vol 69, no 53.

[50] Paul Thomas, 'Inside GSK's new RFID pilot', *PharmaManufacturing.com*, 18 May 2006. (www.pharmamanufacturing.com). In addition, FDA has initiated a study to evaluate the impact of radio frequency (RF) on

chain, it has not mandated its use. Piloting and implementing RFID are merely encouraged. An added complication is that RFID, which has its own variations, is not the only track and trace technology in the market. There is continued industry debate about which technologies, or combination of technologies, are best for tracking and protecting patient safety. Nevertheless, outside of paper pedigree tracking standards, it has been the private sector, rather than federal regulators, that have set industry standards for implementing more advanced drug tracking methods.[51] It should be noted, however, that all of these measures target domestic manufacturing and distribution and do not include drugs imported from foreign sources.

Uneven regulation, the involvement of numerous actors in the distribution process, and inadequate resources to address the abovementioned problems allow for multiple entry points for counterfeit drugs, and opportunities for contamination or diversion by persons or groups for nefarious 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 utilize more advanced technologies such as RFID are being implemented independently by industry on a product-by-product basis and may, 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, due to their unique characteristics, particular attention should be given to those products which contain or are derived from select biological agents and toxins. 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 in the interest of national security and public health.

AWARENESS AND COMMUNICATION

In the event of an intentional dissemination of a biological agent, or the nefarious misuse of an agent-derived product, access to information by response agencies and the public can serve to mitigate a potential panic and public safety threat. An infrastructure to collect and share information exists, but it is not sufficient. **Innovative new measures should be considered to foster pre-attack awareness as well as post-attack responses.** Creating federal regulatory standards, developing standardized track and trace technologies, and raising awareness about dual-use agents and products are some preliminary steps that could help meet this objective.

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biological products, the effects of which are currently undetermined. The results are expected to be publicly distributed by the end of 2006. Department of Health and Human Services, 'FDA Counterfeit drug task force report: 2006 Update', 8 June 2006. (www.fda.gov).

[51] 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 (NDC) has been suggested, raising concerns over patient privacy. The technology is not only used in prescription-medicine packing, but also credit cards, computer equipment, TV's, clothes and cell phones, unbeknownst to most consumers. 'Consumer Reports finds personal privacy concerns in planned uses of Radio Frequency Identification Tags (RFIDs)', US Newswire, 4 May 2006. (releases.usnewswire.com).

LESSONS LEARNED FROM REAL-WORLD EVENTS

The response to the 2001 anthrax attacks revealed many inter-agency coordination issues, many of which remain unresolved.[52] Agencies such as the CDC and FBI viewed the challenges before them differently and took opposing approaches to their responses—the CDC took an epidemiological approach, whereas the FBI sought to pursue a criminal investigation. One result of these clashing perspectives was poor communication among response agencies, as well as with the public. Similarly, during the investigation of the 2004 Florida botulism cases, federal and state investigation agencies lost valuable response time due to disputes over authority and what information should or should not be released. Rapid reaction and fluid communications were necessary to reassure the public of the absence of a threat. From the lessons of these real-world events, the US must increase its efforts to ensure that all stakeholders, especially those that would be involved in crisis response, understand the value of information in mitigating fear in a crisis and preventing further harm. In addition, all relevant communities must work to increase awareness about the risks of counterfeit products, misuse of legitimate products, and linkages to bioterrorism. We recommend that the US establish a task force comprised of representatives from national security, law enforcement, the life sciences and private industry to develop a sustained communication network and to develop a strategy that addresses the above-mentioned risks. The task force should also be responsible for establishing a crisis management communication/authority structure. Lessons learned from the November 2004 incident involving raw toxins in Florida should be taken into account and a regularized cross-sectoral response plan should be established.

A detailed list of the recommendations discussed in this section is outlined below:

RECOMMENDATIONS

FOR THE US GOVERNMENT

RECOMMENDATION	RATIONALE
EXPAND UPON A NEW NATIONAL PROGRAM FOR COUNTERFEIT 'SUSCEPTIBLE PRODUCTS' BY ESTABLISHING A SUB-CATEGORY OF PHARMACEUTICALS AND OTHER PRODUCTS DERIVED FROM SELECT AGENTS.	'Susceptible products' would be defined by the National Association of the Boards of Pharmacy (NABP) with industry involvement. The plan would build upon the existing list and include a subset of pharmaceuticals that pose a public health and security threat given their use of controlled biological agents and substances.

[52] US Government Accounting Office, Report to the Honorable Bill Frist, Majority Leader, US Senate, 'Bioterrorism: Public health response to anthrax incidents of 2001', GAO-04-152, October 2003.

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'.	Current pedigree standards are being developed on a state-by-state basis. Such a patchwork system not only affords opportunities for terrorists and counterfeiters to choose a locale offering the path of least resistance, it also places an undue burden upon industry. Even with the implementation of the PDMA, the rate of pedigree adoption will be staggered and not necessarily standardized across the industry rapidly. In developing standards, particular attention should be given to those products which contain biological agents and toxins due to their unique characteristics. Relevant industry representatives should be included in this process.
INCLUDE AN EXCEPTION IN THE PERSONAL IMPORTATION LAW FOR IMPORTS OF PRODUCTS DERIVED FROM SELECT AGENTS AND TOXINS. IN ADDITION, WORK WITH MANUFACTURERS TOWARD A COMMON SOLUTION TO PREVENT THE IMPORTATION OF COUNTERFEITS, PARTICULARLY THOSE OF SELECT AGENT DERIVED PRODUCTS, WHILE LIMITING THE COST BURDEN ON CONSUMERS FOR PRESCRIPTION DRUGS.	The removal of restrictions on personal importation creates specific vulnerabilities and opportunities through which counterfeit products could enter the system from foreign sources. This is particularly worrisome when considering the potential for select products to be misused or misapplied.
DEVELOP INCENTIVES FOR PRIVATE COMPANIES TO ENCOURAGE INVESTMENT IN AND USE OF ANTI-COUNTERFEIT TECHNOLOGIES, SUCH AS RFID TECHNOLOGY.	Cutting edge technologies provide an opportunity to interrupt the production and movement of counterfeit products. Recognizing the public health threats associated with counterfeit products, the federal government should consult with industry to offer incentives for the development and use of appropriate technologies for susceptible products.
CREATE STRICTER UNIFORM STANDARDS FOR STATE REQUIREMENTS GOVERNING THE LICENSURE AND OVERSIGHT OF WHOLESALE DISTRIBUTORS.	The NABP has suggested measures to update and strengthen the Model Rules for Wholesale Distributor Licensing. Each state should adopt, implement and enforce the updated Model Rules. If implemented, the revised rules would help ensure the legitimacy and integrity of wholesalers, reduce incentives for counterfeiting, and ensure the integrity of drug products.

COLLABORATE WITH FOREIGN STAKEHOLDERS TO DEVELOP STRATEGIES TO DETER AND DETECT COUNTERFEIT DRUGS GLOBALLY.	While private industry has undertaken ad hoc efforts to expose international counterfeit chains, federal enforcement agencies are overburdened and have assigned a reduced priority to the threat of counterfeit drugs. But, the worldwide counterfeit industry has a negative impact on US markets and public health. To assist federal efforts, industry should regularly inform the FDA and FBI about what it has uncovered in terms of risks, threats, etc. The US government should cooperate closely with foreign health and law enforcement agencies.
ESTABLISH A MULTIDISCIPLINARY 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.	The task force should also be responsible for establishing a crisis management communication/authority structure. Lessons learned from the 2001 anthrax dissemination and the 2004 incident involving bulk toxins in Florida should be taken into account and a regularized cross-sectoral response plan should be established.
INCREASE AWARENESS IN THE PUBLIC AND POLICY COMMUNITY ABOUT THE PUBLIC HEALTH AND SECURITY IMPLICATIONS OF COUNTERFEIT DRUGS.	The Counterfeit Drug Prevention Act of 2007 should be strengthened to include the funding and education requirements of the Counterfeit Drug Enforcement Act of 2005, which died in the last Congress. Particular attention should be given to the subset of products which uses agents and toxins regulated by CDC, FDA, and the Department of Commerce. This type of public information campaign should work hand-in-glove with industry without unduly concerning patients prior to public incidents. The plan should also set in place a coordinated strategy to help stem the threat of panic derived from misinformation during and after crises.

FOR INDUSTRY

RECOMMENDATION	RATIONALE
PURSUE ADVANCED ANTI-COUNTERFEITING AND PEDIGREE TRACKING MEASURES THAT WILL MITIGATE PUBLIC HEALTH THREATS FROM COUNTERFEIT PRODUCTS.	Many private firms already use authentication technologies such as holograms or color-shifting ink. They should also consider adopting Radiofrequency Identification (RFID) tagging of products to track select products from production through to end-user. These and other proven validation technologies should also be encouraged through a system of incentives offered by federal and state authorities (see above).
PARTICIPATE IN AND ASSIST THE FURTHER DEVELOPMENT OF THE 'COUNTERFEIT ALERT NETWORK' (CAN).	
RETAILERS SHOULD ADOPT THE 'CVS MODEL' OF CUTTING OFF TRADE WITH SUPPLIERS THAT DEAL IN THE SECONDARY MARKET.	This would help stem the threat of unlicensed wholesalers and distributors.
MANUFACTURERS MUST TAKE MEASURES TO ENSURE THE SECURITY OF THEIR DRUG SUPPLY AND DISTRIBUTION CHAIN.	For example, manufacturers could: demand wholesalers and pharmacies purchase their products ONLY from the manufacturer or from their authorized distributors; make clear that any distributor caught buying product from an unauthorized wholesaler will be terminated; use different color coded products for different national markets; ship product directly to the end user and pharmacies in order to shrink the distribution chain; limit to one month's supply the amount that wholesalers and end users can buy in advance, making diversion and speculative buying more difficult.
INDUSTRY SHOULD CONTINUE TO MONITOR FOR TRAFFICKING IN COUNTERFEITS AND THE IDENTIFICATION OF ILLEGAL MANUFACTURERS AND IMPORTERS.	This would help prevent public health consequences of counterfeit products as well as unlawful diversion from the supply chain.

MANUFACTURERS SHOULD CONVENE A COALITION OF CONCERNED WHOLESALERS WITH THE FEDERAL GOVERNMENT TO COLLABORATE ON A NATIONWIDE PUBLIC/MEDICAL COMMUNITY EDUCATION CAMPAIGN.	This would promote the community of wholesalers who agree only to purchase directly from the manufacturer, such as FFF Enterprises which has capitalized upon market concerns and significantly expanded its market share by pledging not to purchase from secondary wholesalers.
INCREASE AWARENESS AMONG PRODUCT CONSUMERS WHILE NOT ELICITING UNDUE CONCERNS ABOUT PRODUCT SAFETY.	Industry should collaborate closely with Congress to strengthen and support the implementation of legislation that criminalizes counterfeiting and mandates a public education campaign by the Department of Health and Human Services. [NB: SEE above]
DEVELOP AWARENESS AMONG END-USERS ABOUT THE RISKS ASSOCIATED WITH THE MISAPPLICATION OF PRODUCTS WHICH CONTAIN HIGH-CONSEQUENCE BIOLOGICAL AGENTS AND TOXINS.	Additional contingency plans for a public information campaign should be implemented should a crisis occur. [NB: SEE Florida case]

FOR THE INTERNATIONAL COMMUNITY

RECOMMENDATION	RATIONALE
SUPPORT THE DEVELOPMENT OF AN INTERNATIONAL FRAMEWORK CONVENTION TO COMBAT COUNTERFEIT DRUGS.	As above, and in support of both domestic and international security, particular attention should be devoted to counterfeits of products which contain potentially dangerous agents and toxins. An international convention would help establish international guidelines for protecting against counterfeit drugs, as well as develop harmonized standards. Industry should be widely consulted and intimately involved in implementation.
CREATE AN INTERNATIONAL TASK FORCE TO MONITOR THE MAJOR PRODUCERS OF COUNTERFEIT DRUGS AND STEM THE IMPORT OF SUCH DRUGS INTO DOMESTIC SUPPLY CHAINS.	

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ADDITIONAL TRACKING FOR POTENTIALLY DANGEROUS PRODUCTS: UPGRADING THE DRUG CODING SYSTEM

THE ISSUE:

IN ADDITION TO THE INEFFECTIVE OVERSIGHT OF BULK BIOLOGICAL AGENTS AND INADEQUATE DRUG TRACKING IN THE US, THE CURRENT DRUG CODING SYSTEM USED FOR CERTAIN PHARMACEUTICALS CREATES OPACITY AT THE POINT OF USE THAT COULD BE DETRIMENTAL TO NATIONAL SECURITY INTERESTS IN TRACKING THE ORIGINS AND CHAIN OF CUSTODY FOR SPECIFIC PRODUCTS.

WE FIND THAT MODEST ADJUSTMENTS TO THE EXISTING SYSTEM COULD PROVIDE IMMEDIATE, INEXPENSIVE AND IMPORTANT INTELLIGENCE TO PUBLIC HEALTH OFFICIALS AND TO LAW ENFORCEMENT IN THE EVENT OF DIVERSION OR MISUSE OF POTENTIALLY DANGEROUS PHARMACEUTICAL PRODUCTS.

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 Codes (HCPCS) are divided into two principal subsystems. Level I is a numeric system comprised of Current Procedural Terminology (CPT) codes, and is overseen by the American Medical Association (AMA). 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'. In October 2003, the Secretary of Health and Human Services (HHS) delegated authority to the Centers for Medicare and Medicaid Service (CMS) to oversee and grant Level II codes.53 The J-code system is generally used process claims for higher-cost, injectable pharmaceuticals, the category under which existing select products fall.

While this system provides a straightforward mechanism for common coding and reimbursements, it fails to leverage existing capabilities in support of national security and public safety goals. Four examples are presented below to illustrate why an improved coding system is necessary for strengthening public health and security.

SELECT PRODUCTS

While financial and technical hurdles make pharmaceutical products derived from select agents unattractive to terrorists intent on causing mass destruction, the potential use of a select product to

[53] See the Centers for Medicare and Medicaid Services (www.cms.hhs.gov).

incite panic within the United States and the potential harm that could come from counterfeit drugs should motivate government regulators to utilize all means available to track and trace the movement of both bulk agent and finished product. Under the existing HCPCS system, pharmaceuticals are given a J-code. Regrettably, rather than basing that code on the unique properties of individual products, CMS currently assigns those codes based upon broad similarities. In addition CMS does not distinguish between different brands of drugs that are manufactured from the same raw material—with either a unique nomenclature or unique J-codes. Rather it identifies them based upon a common ingredient without regard for different dosages, applications or manufacturing processes. The possibility of a new generic biologics market creates an added layer of risk and confusion to this issue and will be discussed below in further detail. The failure to provide unique non-proprietary nomenclature, and the unique J-codes that flow from that decision, creates the potential for product confusion leading to medical errors. More importantly, by the point at which a specific product is applied, its chain of custody through the drug delivery system is lost. This information could prove critical for an investigation of an intentional tainting of a select pharmaceutical product. Without unique nomenclature and product identities, the current coding scheme unnecessarily veils information about products that might have easily been collected and shared with law enforcement, first responders and national security officials during a bioterrorism incident.

FOLLOW-ON BIOLOGICS

When considering supply chain safety, relevant authorities must also consider comparable products—particularly follow-on biologics, or generic biopharmaceuaticals. Biologics are the fastest growing and highest priced set of drugs in the US healthcare system. Sales for such drugs jumped 17.2% in 2005 to $32.8 billion.[54] 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.[55] 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.[56] These measures are clearly intended to create incentives for generic drug use and to reduce cost burdens on US consumers. While generics are common in many other types of drug products, at present, there is no similar market for biologics. As the biopharmaceutical industry expands to include a follow-on market, in the interest of national security, new companies that handle select agents and/or produce follow-on biologics that contain select agents should be required to:

A. meet strict requirements for the management and handling of raw agents;
B. ensure stringent controls over the possession, management, and shipment of finished product; and
C. undergo an additional and rigorous review by FDA, CDC, and the Department of Homeland Security to ensure that oversight over both raw agents and finished product are maintained from cradle to grave and that the firms handling these agents and products are both legitimate and competent.

[54] IMS Health, *IMS National Sales Perspective,* February 2006.

[55] *Access to Life-Saving Medicine Act*, H.R. 1038, introduced on 14 February 2007.

[56] *Generics First Act of 2007*, S. 28, introduced on 4 January 2007.

A component of these requirements is that follow-on products must be appropriately coded—particularly those derived from select agents. An increase in the number of comparable products which are manufactured from the same raw material, but which do not have proper identifying and tracking mechanisms, complicates the ability to identify and prevent a public health crisis, whether caused intentionally or unintentionally.

VACCINE SUPPLY CONTAMINATION

Vaccines are another example of products derived from select agents. A revised coding system could prove useful in reducing panic and delaying a public health crisis should a contamination of the vaccine supply occur. First, the scenario which creates the need for nationwide distribution of vaccine could trigger panic. Second, if the supply of vaccine to counter the effects of an outbreak were contaminated, it is not currently possible to determine at what point this may have occurred. Anxiety would thus be created based on a series of unsettling unknowns: how has a highly toxic/communicable substance entered the environment? Who is the perpetrator? How can its damaging effects be stemmed? Improving the product coding system could provide the answers to such questions immediately, help coordinate an appropriate response and investigation, and keep public anxieties and fears in proportion to the actual threat. The intended consequences of a terrorism event could be mitigated.

THE TYLENOL POISONINGS

In the fall of 1982, seven Chicago area residents fatally ingested Extra-Strength Tylenol capsules laced with cyanide. Each capsule was laced with 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.[57] 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 11 May 2006, company and FDA investigators were able to confirm that the actual product, not the generic brands, were the source of contamination.[58]

Similarly, in the case of the Tylenol poisonings, because authorities were able to trace the laced

[57] 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', *New York Times*, 2 October 1982.

[58] FDA Statement, 'Bausch & Lomb global recall of ReNu with MoistureLoc contact lens cleaning solution', 15 May 2006; 'Maker says not to use contact lens solution', 14 April 2006, www.cnn.com; 'CDC: Most infected lens wearers used same cleaner', 10 May 2006, www.cnn.com.

Tylenol to shipments from the plants to the Chicago area, they concluded that any tampering must have occurred once the Tylenol reached Illinois—not at the manufacturing plants. 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 (31) million bottles of the product, with a retail value of more than one hundred (100) 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 which read 'Extra Strength Tylenol'. In comparison, the J-code system does not make distinctions among similar products. In the event of a bioterrorism incident using a CMS coded product, this would be analogous to having contaminated Tylenol, but all similar products in the drug store are labeled as 'pain reliever'. 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, this scenario could be averted.

Given the deficiencies in current tracking systems in the US and the emerging threat posed by pharmaceuticals derived from biological agents and toxins, a need for a multi-tiered solution is clear. Below is the primary recommendation for upgrading the coding system.

RECOMMENDATIONS FOR THE US GOVERNMENT

RECOMMENDATION	RATIONALE
REVISE THE CURRENT MEDICARE DRUG CODING SYSTEM, AND THE REIMBURSEMENT STRUCTURE THAT FLOWS FROM THIS SYSTEM, IN ORDER TO MAINTAIN UNIQUE NOMENCLATURE IDENTITIES.	This measure would support above-mentioned recommendations for standardized pedigree requirements. It is particularly important for disparate types of products which are manufactured from the same raw material, both brand-name and generic. For instance, at present there are two products which use botulinum toxin. As more products using the various types of botulinum toxins come on the market, they should have distinct product codes within the medical system for claims processing to reflect appropriately their dosages and uses, and allow for an assessment of their efficacies. A new system could contribute significantly to our national security by facilitating the accurate tracking and tracing of products with health security implications and bioterrorist potential.

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CONCLUSION

This report examines the role of the growing biologics industry in future opportunities for bioterrorism. There has been extensive research on controlling dual-use pathogens and toxins up through the research and development stages. But there has been far less scrutiny on the vulnerabilities associated with the use of such agents in pharmaceutical products, including counterfeiting, diversion or misuse—all of which could pose severe public health and national security threats. The potential use of biological agents and toxins to incite panic in the United States should motivate government regulators to utilize all means available to close oversight loopholes and ensure the ability to track the movement of both raw toxin and finished product. In an effort to enhance national security as it relates to the proliferation and potential use of biological pathogens and toxins, the authors recommend the following upgrades to existing precautionary practices:

1. Ensure effective domestic and international measures for the oversight of the storage, transfer, and research of select agents;
2. Develop greater awareness among the public, policy community, private industry and the international community about the potential health and security threats posed by the development and distribution of therapeutic products derived from select agents;
3. Ensure rapid implementation of federal standards against counterfeiting, misuse and diversion;
4. Implement a standardized system of advanced pedigree requirements for select agent and product distribution to prevent groups and businesses from 'opportunity shopping' and diversion;
5. Amend the current drug nomenclature and coding system to achieve new levels of public health safety and bioterrorism preparedness.

The infrastructure to enhance existing mechanisms is already in place, and some improvements are already underway. The nation and the international community now only need the initiative and momentum to transform it.

ANNEX 1

REGULATING SELECT AGENTS*

DEPARTMENT OF HEALTH AND HUMAN SERVICES	
	**Centers for Disease Control and Prevention (CDC)** Charged with the implementation of the Select Agent Program, as laid out in the Public Health Security and Bioterrorism Preparedness and Response Act of 2002.
	**Food and Drug Administration (FDA)** Oversees product safety and reviews the safety of imported drugs. Also has established an interagency task force on counterfeit drugs.
DEPARTMENT OF HOMELAND SECURITY	
	**Customs and Border Protection (CBP)** Responsible for seizing counterfeit products at the border and enforcing anti-counterfeiting and defrauding laws.
DEPARTMENT OF COMMERCE	
	**Bureau of Industry and Security (BIS)** Responsible for implementing and enforcing the Export Administration Regulations (EAR), which regulate the export and re-export of most commercial items, including biological toxins, in accordance with domestic and international nonproliferation objectives.

The list of agencies presented here is not exhaustive.

ANNEX 2

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 Senior Associates, Dr. Elizabeth Turpen and Brian Finlay, and was supported full-time by a Research Associate, Rita Grossman-Vermaas. The team brings to the table a considerable breadth of knowledge over 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. We also hold a keen interest in the intersection of national security and the biotechnology sector. See below for full biographies of the authors.

Rita Grossman-Vermaas is a Research Associate with the Cooperative Nonproliferation Program at the Henry L. Stimson Center. Prior to joining the Center in February 2006, Rita spent four years in Ottawa, Canada where she worked on WMD verification and compliance issues. Most recently, she was the lead researcher and program administrator at the Canadian Centre for Treaty Compliance, Norman Paterson School of International Affairs. Her prior work also includes positions as fellow and research associate at the International Security Research and Outreach Program, Foreign Affairs Canada; Senior Consultant to the Subcommittee on Bioterrorism Response and the Canadian Public Health Laboratory Network (Health Canada); and Senior Consultant to the CBRN Research & Technology Initiative (DRDC Canada). Prior to her work in Canada, Rita was a researcher at the Center for Biosecurity at the University of Pittsburgh Medical Center.

Rita holds an MA in International Relations from the University of Chicago and a BA (Honors) in International Studies from Johns Hopkins University.

Brian Finlay is a Senior Associate at the Henry L. Stimson Center, where he works on issues of weapons proliferation, global health and development, scientist redirection and private sector engagement in the former Soviet Union. Brian currently serves as co-director of the Cooperative Nonproliferation Program, a multifaceted program designed to accelerate existing efforts, and design innovative new initiatives aimed at more rapidly and sustainably securing dangerous nuclear and biological weapons, materials and expertise while leveraging resources to address other issues of global concern such as international public health and global economic development. Prior to joining the Stimson Center in January 2005, Brian served as Director of the Nuclear Threat Reduction Initiative and as a Senior Researcher at the Brookings Institution. Before emigrating from Canada, he was a Project Manager for the Laboratory Center for Disease Control in Ottawa. He has also served as a consultant to Foreign Affairs Canada, where he worked on the Ottawa Treaty on Landmines and the Comprehensive Nuclear Test Ban Treaty. Brian is author of numerous articles on national

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Elizabeth received her PhD from the Fletcher School of Law and Diplomacy at Tufts University.

ABOUT THE COOPERATIVE NONPROLIFERATION PROGRAM

The Cooperative Nonproliferation Program 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.

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