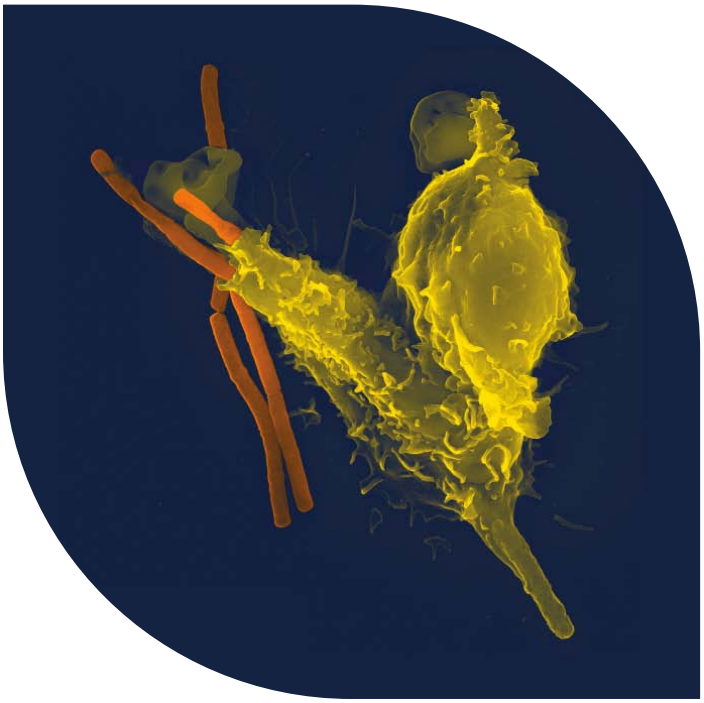
PHARMACEUTICAL TERROR

GETTING HEALTH CARE REFORM RIGHT

BRIAN D. FINLAY

STIMSON



President Obama has made comprehensive health reform a key priority for his Administration. According to the President, his goal is to control rising health care costs, guarantee the free choice of doctors, and assure high-quality, affordable health care for all Americans. While their preferred options may differ, Democrats and Republicans in Congress are rightly focused and equally committed to changing the way we operate the healthcare enterprise in this country.

From a public health perspective, there is much to celebrate among the many competing health care reform proposals that have been offered on Capitol Hill. Yet one underlying and potentially worrisome subtext to almost all existing reform options is a continued lack of recognition of the growing link between public health and national security. Legislative decisions being made today on health care reform could have a deleterious impact on US efforts to address the growing threat of bioterrorism.

Without a doubt, biotechnological innovation has yielded incomparable benefits to humanity. In many ways, the world is a better place to live than it has ever been: life expectancy has doubled in the past 100 years; the technology-driven revolution has created astonishing new capabilities to diagnose and treat illnesses once thought incurable; and new technologies are being applied to bolster food production for a growing and increasingly hungry world. As a result of globalization, these technologies have spread to more entities, in more countries, in more regions of the world than

ever before. Yet a formidable challenge in the age of globalization is governments' inability to effectively monitor and regulate these emerging technologies—and the growing commitment and wherewithal of terrorist organizations to exploit these advances for hostile purposes.

Terror Warnings: The 9/11 and WMD Commissions

In 2004, the 9/11 Commission warned that "the greatest danger of another catastrophic attack in the United States will materialize if the world's most dangerous terrorists acquire the world's most dangerous weapons." Despite expanded efforts at prevention, US national security and intelligence agencies have warned that since 9/11, the threat has grown rather than receded. Writing in a Congressionally-mandated report last year, Chairman Bob Graham and Vice-Chairman Jim Talent of the Commission on the Prevention of Weapons of Mass Destruction Proliferation and Terrorism said, "The Commission believes that unless the world community acts decisively and with great urgency, it is more likely than not that a weapon of mass destruction will be used in a terrorist attack somewhere in the world by the end of 2013." They further asserted that "terrorists are more likely to be able to obtain and use a biological weapon than a nuclear weapon," and that "the US government needs to move more aggressively to limit the proliferation of biological weapons and reduce the prospect of a bioterror attack."

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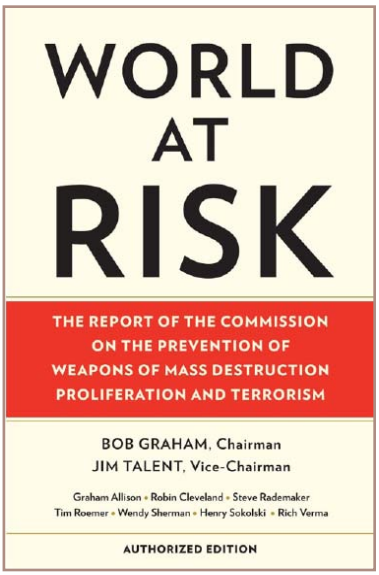

Traditionally, efforts to manage the biological weapons threat have been confined to those in the military, diplomatic, law enforcement, and intelligence communities. But today, two trends have rendered this approach anachronistic:

- First, as a result of the biotechnological revolution and the very nature of the bioweapons threat, it has become increasingly difficult to distinguish between legitimate pharmaceutical research and offensive bioweapons development. What is a legitimate biotech enterprise one day might easily become an offensive bioweapons research and development facility the next.

- Second, according to a recent study by Ernst and Young, more than 90% of biotechnological and pharmaceutical innovation occurs in the private

sector, making government control increasingly difficult to exercise. Thus, any successful effort to curb the threat of biological terrorism must necessarily involve, at its core, private industry.

At present, US public health agencies seldom consider the national security implications of their decisions. As the biotechnological revolution continues to generate innovative new medicines, this has opened a window of opportunity to individuals and terrorist groups intent on harnessing biology for mass destruction. As the President and Congress undertake serious reforms to the health care system of the United States, it is critical that new policies recognize the potential implications for US national security. Ultimately, this will mean new restrictions; as importantly, it will necessitate deep collaboration with the public health community, private biopharmaceutical firms, and life sciences organizations throughout the country and around the world.

A Brave New World: Pharmaceutical Terrorism

In 2008, the Stimson Center, a Washington-based public policy think tank, published a study entitled, Old Plagues, New Threats: The Biotech Revolution and its Impact on US National Security. The study was part of a broader program on the respective roles of government and the private sector in preventing the proliferation of biological weapons. Perhaps the most striking finding of this particular study was the discovery of a growing interest in R&D into so-called "select agents" due to: (1) the market success of existing products bearing or containing select agents, and (2) the use of toxins and other potentially dangerous agents as non-addictive pain relievers. The emergence of these innovative medicines is a case study in how biotechnologies could be used for terrorist purposes, and how poorly equipped the US government is to engage in meaningful prevention.

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"Select agents" are defined as pathogens or biological toxins which have been declared by the US Department of Health and Human Services or by the US Department of Agriculture to have the "potential to pose a severe threat to public health and safety." The Centers for Disease Control and Prevention (CDC) administer the Select Agent Program, which regulates the laboratories which may possess, use, or transfer specified agents within the United States.

In the United States, the use of these agents for pharmaceutical benefit was popularized by the brand BOTOX®, which uses as an active ingredient

Sample List of Select Agents as Regulated by the Department of Health and Human Services (DHHS)

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

Source: HHS and USDA Select Agents and Toxins, 7 CFR Part 331, 9 CFR Part 121, and 42 CFR Part 73, accessed at: http://www.SelectAgents.gov/Select Agents and Toxins.html

botulinum toxin Type A—a CDC regulated select agent. The drug is approved to treat an array of orphan diseases such as cervical dystonia (head tilting, neck pain, and neck muscle spasms), blepharospasm (eyelid spasms), and strabismus (crossed eyes).

While clearly the most renowned—particularly after receiving approval for cosmetic uses years after its introduction—BOTOX® is not the only product in the US or global marketplace, which itself is dwarfed by the wide number of similar products in the drug development pipeline. Other existing products in development or on the market contain, for instance, botulinum toxin, ricin, tetradotoxin, and conotoxin—all CDC-defined select agents. These substances have remarkable promise for a broad array of pharmaceutical uses, from pain management to the treatment of cancerous tumors.

These positive developments for patients have also resulted in a significant growth in the number of companies around the world experimenting with and marketing products that could be diverted by a committed bioterrorist. In all cases, governments have been slow to recognize the potential for bioterrorism a poorly regulated industry creates, and in some cases, private companies have not proven sufficiently responsible by exercising strict command and control over dual-use research and product distribution. While the producer of BOTOX® has proven to be especially diligent in controlling its research and

Drug Development Pipeline

Agent	Company	Product	Country of Origin	On Market	In Pipeline
BOTULINUM TOXIN	Allergan (USA)	BOTOX®	USA	•	
	Ipsen Group (France)	Dysport®	France	•	
	Metabiologics Inc. (USA)	production/distribution of all 7 serotypes of botulinum toxin	USA	•	
	Merz Pharmaceuticals GmbH	Xeomin®	Germany	•	
	Mentor Corporation	PurTox® Botulinum Toxin	USA		•
	Solstice Neurosciences, Inc.	Myobloc® (Type B Toxin)	USA	•	
	Mody-Tox	Neuronox®	South Korea	•	
TETRODOTOXIN	WEX Pharmaceuticals, Inc.	Tectin®	Canada		•
RICIN	Twinstrand Therapeutics	TST10088	Canada		•
CONOTOXIN	Metabolic Pharmaceuticals	ACV1	Australia		•
	Xenome, Ltd.	conopeptides for pain	Australia		•
	AMRAD Operations	AM336	Australia		•
	Elan Pharmaceuticals	Prialt®	USA	•	
	Cognetx Inc.	CGX-1160, CGX-1007, CGX-100	USA		•

finished product, growing evidence suggests that other firms have been far less security conscious. In one case, a European manufacturer has transferred raw toxins and potentially sensitive know-how to Iran. Another Western firm was fined by the US Commerce Department for sending vaccines that contained the Newcastle disease virus to Syria.

Of course, the threat goes beyond products that bear or contain select agents. Last year, a large state-owned Chinese pharmaceutical company that exports products to dozens of countries, including the United States, was at the center of a nationwide drug scandal after nearly 200 Chinese cancer patients were paralyzed by contaminated leukemia drugs.

As more companies in more regions of the world begin experimenting with dangerous or potentially dangerous substances, the likelihood that they may be diverted for nefarious uses grows exponentially. And even once converted to packaged pharmaceuticals, these products, while unlikely to be used as mass-casualty biological weapons, still contain pathogens that pose a grave concern for national security because of their potential to do physical harm and to incite panic.

We find a growing number of cases of legitimate companies acting recklessly out of ignorance rather than deliberate malfeasance.

While governments around the world should avoid interfering needlessly in legitimate R&D or drug distribution, a growing number of cases suggest that legitimate companies often act recklessly out of ignorance rather than deliberate malfeasance. As a result, sensitive research, know-how, and perhaps biological agents themselves may have fallen into the hands of those who would act contrary to the national security interests of the United States.

Existing Government Efforts

At present, the system used by the US government—as with other Western governments—to track especially dangerous pathogens and toxins and subsets of pharmaceutical products that are, bear, or contain these agents is inadequate and encumbered by stovepipes in both the policymaking and policy execution phases. Governments' ability to effectively regulate the booming pharmaceutical industry is complicated by the growth of the market itself, as well as by an increasing number of companies involved in the research, development, and sale of products that capitalize on both legitimate market forces and illicit opportunities.

In 1996, recognizing the potential for misapplication of biological agents and toxins, Congress passed and the President signed the Antiterrorism and Effective Death Penalty Act. The bill established the Select Agent Program and created the first list of biological agents whose possession and transfer between laboratories was to be regulated by the CDC. Subsequent actions by Congress, including the USA Patriot Act, have mandated additional restrictions on access to these dangerous agents.

Despite these actions, however, a patchwork of agencies with differing missions has led to incoherence in ensuring both patient safety and national security. For example, once a select agent becomes part of a pharmaceutical product, it leaves the regulatory purview of the CDC. The Food and Drug Administration (FDA), which is responsible for product safety from a public health standpoint, then takes over, but lacks a specific mandate for national security. Regardless of the product's potential for proliferation or the pharmaceutical firm's compliance with reasonable nonproliferation standards, provided the product is safe and effective, it will enter the US marketplace. Similarly, as these products cross borders into the United States, Customs and Border Patrol (CBP) may work to identify counterfeits and adulterated products, but again has no specific mandate to identify potential risks stemming from the importation of select agents contained therein.

Recently, Senators Joseph Lieberman (I-CT) and Susan Collins (R-ME) introduced S. 1649, the WMD Prevention and Preparedness Act of 2009. The proposed measure amends the Public Health Service Act (PHSA) to direct the Secretary of Health and Human Services, in coordination with the Secretary of Homeland Security, to designate as "Tier I agents" those agents and toxins which have significant potential to be used effectively in a biological attack and for which the DHS Secretary has issued a Material Threat Determination, with exceptions. The bill further amends the Homeland Security Act to direct the Secretary of Homeland Security to establish enhanced biosecurity measures for registered entities to use in handling such agents

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While S. 1649 could go far to help bridge critical gaps, in its current form, the bill perpetuates the agency stovepipes that have opened wide the windows of opportunity for terrorists to exploit legitimate pharmaceutical research and biologics for nefarious purposes. In short, both the Select Agent Program and the proposed Lieberman-Collins legislation treat dangerous pathogens strictly as a national security challenge, without sufficient recognition

that they are increasingly a pharmaceutical/public health issue. Particularly in the midst of the dramatic changes being proposed to the current health care enterprise in the United States, Congress must be especially attuned to the potential proliferation and national security consequences of this subset of pharmaceutical line.

The Terrorist Window of Opportunity:

(i) Threats of R&D Diversion: Iran and Biological Weapons

The biotechnological revolution has stimulated dramatic worldwide growth in biological R&D and pharmaceutical sectors. In 2006 for instance, the Iranian drug market reached an estimated $1.58 billion, and it is expected to grow by 50 percent to $2.44 billion by 2011. Some of this is internally-generated organic growth. However, Tehran has also made a concerted effort to encourage foreign multinationals to enter the Iranian market, introducing new technologies and capacities into that country to service its public health needs. However, those same technologies and capacities can also be diverted to more nefarious uses.

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As with other countries suspected of bioweapons development, the evidence against Tehran is significant, but far from conclusive. In 1989, Iran was accused of trying to purchase pathogenic strains from Canada and the Netherlands that could be used to develop T-2 mycotoxin—a key component of "yellow rain." The collapse of the Soviet Union led Iranian headhunters on successful missions to lure former Soviet bio-weaponeers to work for Tehran. European biotech firms have been regularly targeted by Iranians for dual-use technology and equipment. Some experts allege that Iran may have started to develop small quantities of bioweapon agents, such as ricin, botulinum toxin, and the smallpox virus. And various reports have also indicated possible Iranian research interest in plague, anthrax, and tularemia.

In 2006, Tehran inexplicably announced that it had succeeded in developing an anti-botulinum serum whose civilian application is unclear. While perhaps unrelated, Iran has opened its doors to a British pharmaceutical company to conduct clinical trials on a product containing botulinum toxin. The company's decision to conduct trials may have involved the sharing of critical dual-use information. The willingness of legitimate foreign companies to share

sensitive data with state sponsors of terrorism raises serious questions about our capacities to control sensitive biological agents, toxins, and know-how.

As with Iran's nuclear development program, Tehran's "peaceful uses" of biotechnology could either be a cover for harmful intent or an aspiration to compete and succeed in a globalized world. Regardless, the questions surrounding Iran's biotech innovation, and the willingness of allied governments to transfer sensitive materials and know-how to Tehran are representative of the challenges faced by an international community committed to preventing the proliferation of biological weapons.

Taken altogether, more than 20 years of incidents feed suspicions that Tehran is quietly continuing the development of an offensive biological weapons capacity. But the work of proving—or disproving—these fears is far more difficult than on the nuclear side of the WMD equation. A formidable challenge of globalization is governments' inability to effectively monitor and regulate emerging biotechnologies, thereby separating their peaceful from their potentially hostile uses.

As determined proliferators continue to seek new opportunities, the number of companies that are experimenting with potentially dangerous substances is growing exponentially. Meanwhile, no protocol is in place to prevent the nefarious diversion of these products and the research behind them. The US Congress must redouble its efforts to ensure that decisions made in the context of health care reform do not open additional exploitative opportunities for determined proliferators.

(ii) FDA/CDC Coordination: Skirting US Regulations

While the Iran case indicates that the United States is being challenged by lax regulations among even our closest allies, further evidence reveals that poor coordination between our own agencies is failing to curtail these same biotech and pharmaceutical firms from skirting US law, then capitalizing upon the US market. For instance, the lack of coordination between the FDA and the CDC Select Agent program allows foreign firms to conduct research abroad that would otherwise be proscribed by US law, then apply to FDA for market approval without fear of reprisal.

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At present, under the CDC Select Agent Transfer regulations, companies located in

the United States cannot undertake research involving recombinant DNA (rDNA) technology to generate functional forms of select toxins as delineated in the regulations. Regardless, one prominent pharmaceutical firm based in South Korea is undertaking such research not only using recombinant DNA to generate a functional form of botulinum toxin, but is using rDNA technology to generate a longer duration toxin—an experiment of significant concern to both the CDC and the National Science Advisory Board for Biosecurity (NSABB). Meanwhile, the firm has stated its intent to seek FDA approval for this product upon successful completion of its research and development.

In such cases, poor coordination between FDA, the CDC, and the US national security agencies continues to allow foreign companies that have undertaken research which is expressly prohibited in the US to benefit from the US market. Because FDA lacks a national security mandate, the Agency cannot know to be critical of such research. The United States Government should be working to ensure that there is at least some oversight given to the biosafety and biosecurity standards that foreign companies have in place when attempting to enter the country.

(iii) Exploiting the Follow-on Market: Promoting a Culture of Security

As the implications of the biotechnological revolution continue to evolve, enhanced coordination between national public health authorities and national security agencies is essential. The current debate over follow-on biologics is indicative of the inadequate coordination between these constituencies. This is especially true when considering the rapid growth of entities expected to enter the biopharmaceutical market once follow-on biologics are provided an abbreviated regulatory pathway in the United States. With an established regulatory pathway for follow-on biologics in place, the number of entities interested in entering the market will grow, and new companies will pursue FDA licensure for follow-on products containing a select agent. Many of these new companies will not have the resources to sufficiently mitigate the national security risks associated with the handling of select agents. This could prove to be a serious loophole in the US government's ability to manage potentially dangerous biological agents and research.

Any relaxation of standards governing the acquisition, handling, and use of select agents in the United States or abroad should be discouraged.

It is important that as this aspect of the biologics industry develops, the government recognizes this threat and puts in place appropriate safeguards to ensure that companies developing follow-

on products are capable of meeting rigorous security standards. The 2008 Stimson Center study concludes that any company pursuing FDA licensure or approval for a follow-on biologic that is, bears, or contains a select agent should be required to undergo a thorough product and safety competence review and abide by a standardized and stringent set of controls over the possession, management, and use of select agents to protect public health and safety. While the goal of reducing costs is laudable, encouraging companies that have not fully considered the security implications of their research and product distribution is not in the best interest of our national security. Any relaxation of standards governing the acquisition, handling, and use of select agents in the United States or abroad must be discouraged.

An early success story: Eshoo-Barton legislation

Recently, Representatives Anna Eshoo (D-CA) and Joe Barton (R-TX) introduced an important measure as part of their plan to promote a follow-on biologics industry in the United States. The measure was ultimately incorporated as part of H.R. 3962, the House-passed Affordable Health Care for America Act (Title V, Subtitle C, Part 2, Section 2575). It stated in part:

> `(D) RESTRICTIONS ON BIOLOGICAL PRODUCTS CONTAINING DANGEROUS INGREDIENTS- If information in an application submitted under this subsection, in a supplement to such an application, or otherwise available to the Secretary shows that a biological product—
>
> > `(i) is, bears, or contains a select agent or toxin listed in section 73.3 or 73.4 of title 42, section 121.3 or 121.4 of title 9, or section 331.3 of title 7, Code of Federal Regulations (or any successor regulations); or
> >
> > `(ii) is, bears, or contains a controlled substance in schedule I or II of section 202 of the Controlled Substances Act, as listed in part 1308 of title 21, Code of Federal Regulations (or any successor regulations);

the Secretary shall not license the biological product under this subsection unless the Secretary determines, after consultation with appropriate national security and drug enforcement agencies, that there would be no increased risk to the security or health of the public from licensing such biological product under this subsection.

The Eshoo-Barton provision is a good example of how national public health authorities can and should be required to work more seamlessly with national security agencies to ensure good public policy. The provision should be replicated across all areas of the health care reform effort in order to ensure that the biotechnological revolution helps rather than hinders efforts to ensure the safety and security of Americans.

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In short, the public health agencies of the United States must be given an express role in the national security of our country, particularly as the line between peaceful biotechnological research and offensive biological weapons intent becomes increasingly blurred.

The benefits of biotechnology have brought unprecedented advances in global development. In many ways, the world is a better place to live than it has ever been: life expectancy has doubled in the past 100 years; the technology-driven revolution has created astonishing new capabilities to diagnose and treat illnesses; and new technologies are being applied to bolster food production across the developing world.

A formidable challenge of globalization is governments' inability to effectively monitor and regulate these emerging technologies—and the increasing commitment and wherewithal of non-state actors to use these advances for hostile purposes.

This report uses as a case study industry's growing interest in dangerous pathogens and toxins as therapeutic pharmaceuticals. It illustrates the full life-cycle of threats and opportunities from research to distribution to injection into patient of products derived from select agents.

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The Stimson Center
1111 19th Street, NW, 12th Floor
Washington, DC 20036
Phone: 202-223-5956 | Fax: 202.238.9604
www.stimson.org