The Security Threat from Producers of Counterfeit Botulinum Toxin
Phase 1: Scoping out the Problem

Written By:
Kenneth D. Coleman, M.B.A., Ph.D.
Raymond A. Zilinskas, Ph.D.
James Martin Center for Nonproliferation Studies

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Defense Threat Reduction Agency  
Advanced Systems and Concepts Office  
8725 John J. Kingman Road  
Ft. Belvoir, VA 22060-6201

ASCOInfo@dtra.mil
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PHASE 1: SCOPING OUT THE PROBLEM

Kenneth D. Coleman, M.B.A., Ph.D.
Raymond A. Zilinskas, Ph.D.
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Introduction, Background, and Study Methodology

Because of the utility of botulinum neurotoxin (BoNT) for a large number of cosmetic and therapeutic applications (see Table 1; all tables are to be found at the end of this report), the global market for legally produced and distributed BoNT has grown at a rapid pace, and it currently exceeds $1.5 billion in annual sales. Similar to what has occurred with other high-value pharmaceuticals, criminal organizations are mounting increasingly large efforts to profit from the huge BoNT market by offering “counterfeit” BoNT to doctors, clinics, and even beauty salons at much lower prices than legitimately produced BoNT.

Broadly speaking, there are two types of counterfeit BoNT. The first type is actual BoNT packaged in vials whose labels are designed to resemble those sold by legitimate pharmaceutical companies. The second is not botulinum toxin, but an unknown substance of undetermined origin that is packaged in a vial bearing a label resembling that of a legitimate pharmaceutical company. For the purposes of this study, we address only the first type because of its biological weapons proliferation potential. Accordingly, when reference is made to counterfeit BT, we mean real botulinum toxin that has been packaged so it resembles a legitimate pharmaceutical product but in fact is the product of a criminal enterprise.

As far as we now know, there are two sources for counterfeit BoNT: (1) legitimate producers of BoNT whose product is diverted into illicit distribution channels, and (2) illicit manufacturers of BoNT. With regard to the first source, legitimate pharmaceutical and chemical companies produce BoNT under conditions approved by their home nations. The legitimately manufactured BoNT then is sold in bulk or diluted form to criminal middlemen who appear to be bona fide business men, but who package the purchased BoNT in vials bearing counterfeit labels and then sell these vials to end-users, such as clinics or individual doctors. (See Photograph 1 for examples of vials bearing labels of Chinese-manufactured BoNT that can be purchased via the internet). The contents of these vials are reconstituted by the end-users and administered to patients the same way as is done with legitimate BoNT. However, due to poor or no quality control over packaging, these vials can contain more or less than the amount of BoNT stated on the label. The main hazard to which patients are exposed if the amount of BoNT they receive exceeds the amount specified on the label is that they could experience symptoms of botulism. Conversely, if the amount of BoNT is less than the specified amount, its administration will have little or no cosmetic or therapeutic effect, which means that the patient will suffer no direct physical harm but will have been cheated, since he will not achieve the cosmetic results for which he has paid. Further, regardless of the amount of BoNT present in a vial, the middleman’s diluent may be contaminated by microorganisms or chemicals that can cause infection or toxic reactions among recipients.

The second source of counterfeit BoNT is illicit production laboratories that have been set up in China and India, and possibly in other Asian countries and Russia.
understandable reasons, there are no regulatory or quality controls over the substances produced by these laboratories. The operators of these secret laboratories can sell their undiluted products to criminal middlemen or spuriously labeled vials to unethical end-users. Recipients of BoNT produced in illicit laboratories face even greater dangers than those who receive legitimately produced BoNT diluted by criminal middlemen because the illicitly manufactured products probably have been manufactured under poorly controlled and unhygienic non-pharmaceutical conditions, leading to more possibilities of recipients being infected, poisoned, or both.

Our hypothesis is that those who operate illicit bulk BoNT manufacturing facilities or who illicitly distribute BoNT from legitimate or illicit sources are willing to sell their product to anyone willing to pay the asking price, be they suppliers to cosmetic treatment facilities, criminal gangs that black-market the toxin, or terrorist organizations. Figure 1 illustrates the structure of the counterfeit BoNT industry that might enable terrorist organizations or national biological weapon (BW) programs to obtain this material.

![Figure 1. Structure of the Counterfeit Botulinum Neurotoxin (BoNT) Threat](image)

The illicit manufacture and distribution of BoNT presents three types of security threats:

1. The threat from the product, itself: i.e., BoNT can itself be used for military or terrorist purposes;
2. The threat from the dual-use technology for manufacturing BoNT: i.e., the know-how, equipment, and supplies possessed by BoNT producers, which may be transferred to support national or terrorist biological weapons programs; and
3. The threat from the illicitly acquired profits from BoNT sales: i.e., funds a terrorist organization that acquired a BoNT manufacturing capability might obtain from sale of the product and use to advance its cause, whether or not it sought to exploit the BoNT as a BW agent.

This project’s objective was to assess the threats that may be posed to U.S. security by legitimate and illicit producers and criminal distributors of BoNT that currently fuel the international trade in counterfeit botulinum toxin. This report contains the information that allowed us to make the assessment and its findings presented below.

To accomplish the project’s objective, we undertook four activities, each of which is addressed in the sections that follow. The first section provides information on BoNT production methods, paying particular attention to those that may be utilized by hidden and less well-equipped laboratories. In the second section, the known producers of BoNT in the United States and foreign countries are identified and described, and information about their markets and estimates of their total BoNT sales volume are made. In the third section, we present the results from interviews conducted with legitimate BoNT producers about the trade in counterfeit BoNT and what is being done to stop it. This information was supplemented by observations made by our consultant in Russia. In the fourth section, Conclusion and Follow-Up, we analyze the information presented in the preceding sections and delineate our findings. Specifically, (1) we present findings on the security implications of what we have learned and outline strategies for limiting the proliferation of clandestine BoNT production facilities; (2) based, in part, on our analysis of the supplier to middleman to end-user supply process, we present ideas on methods for stopping supply and/or diminishing demand; and (3) we present suggestions on follow-up activities to this scoping study. Section five contains endnotes and references.

1. Botulinum Toxin and Methods of Production

BoNT is the protein product of the anaerobic bacterium, Clostridium botulinum (C. botulinum). Seven BoNT serotypes exist and are identified by the letters A – G. As is explained further below, so far only serotypes A and B have human applications, although serotypes C and E have been clinically tested in humans. All BoNT serotypes can cause the disease commonly called “botulism.” In the United States the most common form of botulism is infant botulism. The second most frequent form is wound botulism, which occurs after drug addicts infect themselves with C. botulinum while injecting heroin (black tar) and other illegal substances by intramuscular routes. The incidence of food-borne botulism was high in the United States in the past, but has decreased over the last few decades to a few cases per year. However, it remains the most prevalent form of botulism in many developing countries, including China.

The toxin molecule itself is a large, reasonably stable protein and is the most potent poison known to science. BoNT has a remarkable affinity for nerve cells and is so toxic that a single molecule of toxin is capable of incapacitating one nerve cell completely. The nerve cells controlling ocular and respiratory function are particularly vulnerable targets due to this affinity,
and thus toxin exposure often leads to diplopia (double vision) and respiratory failure, with subsequent need for ventilation support through the recovery period. However, the toxin appears to have no effect on the heart muscle.\textsuperscript{5}

Six agents have been designated by the U.S. Centers for Disease Control and Prevention (CDC) as Category A Select Agents. They are described as follows: “Agents in Category A have the greatest potential for adverse public health impact with mass casualties, and most require broad-based public health preparedness efforts (e.g., improved surveillance and laboratory diagnosis and stockpiling of specific medications). Category A agents also have a moderate to high potential for large-scale dissemination or a heightened general public awareness that could cause mass public fear and civil disruption, which are the highest-rated threats to humans from biological sources.”\textsuperscript{6} BoNT is one of these six.

Most \textit{C. botulinum} strains isolated from natural sources are efficient BoNT producers, but not all. For example, in the early 1990s the Aum Shinrikyo sect attempted to produce BoNT and use it in aerosol attacks against Japanese population centers, but the cult failed because its scientists mistakenly cultured a low toxin-producing strain. However, when properly cultured in fluid or solid media of many different types, and in the absence of oxygen (since the organism is an anaerobe), toxigenic strains of \textit{C. botulinum} will produce toxin. The bacterial strains used for industrial purposes are naturally occurring hyper-producers of BoNT. These hyper-productive strains (such as Hall A) have over the last 50 years been procured by applied microbiological institutions throughout the world and thus probably are stored in most national culture collections.

Traditionally, BoNT is produced in fermenters set up to grow the bacterium under anaerobic conditions. This is the preferred method for growth of the microorganism because a technician can precisely control the various fermenter parameters, such as temperature, pH, and rates of agitation.\textsuperscript{7} Simple media, consisting of commonly found laboratory ingredients, such as yeast extract, hydrolyzed casein, and glucose, are used for the broth.\textsuperscript{8} An inoculum of bacteria is typically seeded into a small flask, and this starter or seed culture is transferred after about 24 hours to a larger fermenter. After an additional 72 hours or more of fermentation, the toxin-containing liquid is separated from the broth by centrifugation; however, lower-tech methods, such as settling and filtration, will also work. The toxin-containing liquid is then subjected to concentration and purification by acid precipitation.\textsuperscript{9,10} This method consists of slowly adding a common acid (such as sulfuric acid) to the toxin-containing liquid, refrigerating the mixture, and allowing the resulting slurry to settle.\textsuperscript{11,12} The (clear) liquid on top is poured off, and the thick, toxin-containing slurry remains. A buffering solution containing water and a neutral salt is added to the slurry and serves to dissolve it. This process is repeated once or twice. (Sometimes, another common precipitating chemical, ammonium sulphate, is used to further concentrate the toxin.) These simple procedures, which require no sophisticated equipment or training, takes less than a week to complete and result in a 20- to 50-fold concentration of the toxin. Acid precipitation also substantially reduces the number of contaminants within the toxin mixture.\textsuperscript{13} (At this point, BoNT is sufficiently concentrated that it can be used for a targeted, small-scale biological attack.)
Of course, the pharmaceutical industry does not stop at this point but continues with additional purification steps to ensure the quality and stability of the product. These steps include the use of specialized but readily available laboratory supplies and techniques, such as ion exchange and affinity chromatography. But criminals and terrorists do not necessarily require highly purified BoNT.

If the final product is to resemble a therapeutic product, it must be packaged in a vial as a dry powder. To do this, the producer has to lyophilize (freeze-dry) or vacuum-dry the solution containing the BoNT. Simply put, lyophilization or vacuum drying is a method of removing water from the formulation to provide long-term stability. Either method is used for extending the toxin’s shelf life and preserving its biological activity. By preparing aliquots of the dilute BT solution, dispensing the aliquots into vials, and then lyophilizing or vacuum drying them, it is possible to reproducibly distribute minute quantities of BoNT into thousands of vials with minimal vial-to-vial variation. Several legitimate manufacturers worldwide manufacture and market systems that allows for the preparation of batch samples in vials and their stoppering under vacuum. Once the vials are stoppered, labels that look like the genuine therapeutic products can be affixed to them.

Importantly, *C. botulinum* can be grown, and the toxin produced, in much simpler ways than the industrial process described above. For instance, studies have shows that *C. botulinum* grows well in pasteurized milk and will produce toxin under those conditions. Indeed, toxin-producing *C. botulinum* has been shown to grow well in substances as common as tomato juice and a slurry made from grass clippings. However, these more primitive production methods have their drawbacks. Toxin production rates will not be as high as in standard growth media, and unwanted proteins are likely to be introduced into the final product. Nevertheless, it is important to recognize that basic methods of BoNT production are available and can achieve potencies close to those achievable in a legitimate manufacturing setting. In any case, when dealing with counterfeit BoNT, the package’s appearance is more important than what it contains; i.e., from the counterfeiter’s perspective, the closer the package resembles the genuine therapeutic product, the better.

2. Legitimate Producers of Botulinum Toxin Worldwide

BoNT is produced for two legitimate purposes: for human uses that include therapeutic and cosmetic treatments, and for non-human applications, including industrial and research uses. As can be seen from the two lists below, there are relatively few legitimate producers of BoNT in the world.

i. Producers of Botulinum Toxin for Human Uses

As far as we can discern, there are eight companies producing BoNT for human use; three in the United States, two in Europe, one in China, one in South Korea, and one in India. (See Table 2 for a listing of BoNT products used in North America and Europe.) Each of these...
companies is capable of producing gram-quantities of pure BoNT. The actual production capability of each of these legitimate companies is a closely held secret, but we estimate that the total amount of BoNT sold throughout the world is less than ten grams per year. The companies in the United States and Europe operate under stringent regulations and continuous oversight by governmental agencies. In the United States, the CDC, the Food and Drug Administration (FDA), the Occupational Safety and Health Administration (OSHA), and the U.S. Department of Agriculture (USDA) scrutinize the activities of these companies. In addition, the Federal Bureau of Investigation (FBI) must clear all persons who actually work with BoNT because it is a Select Agent.

a. Allergan Incorporated, Irvine, California, U.S.A. Allergan manufactures and sells Botox® (hereafter Botox), which is a sterile vacuum-dried form of botulinum toxin type A. Botox generated sales of over $1.37 billion worldwide in 2007, most of which came from cosmetic applications. It is produced from one of the Hall strains of \textit{C. botulinum} and purified by a series of acid precipitations to a crystalline complex containing the toxin and other stabilizing proteins of the toxin complex that are made by the production organism at the same time as the neurotoxin core. Botox is distributed in 10 milliliter vials that are marked as containing 100 Botox units, which is equivalent to 4.8 nanograms. Botox’s major excipient (an inactive substance used as a carrier for the active ingredients of a medication) is human albumin, and the toxin is stored at refrigeration temperature. The FDA first approved Botox in December 1989 as an “orphan drug” for the treatment of two neurological disorders, strabismus and blepharospasm. BoNT was approved for cosmetic use in 2002, and branded as Botox Cosmetic in the United States. Other indications, such as the treatment of hyperhidrosis (excess sweating), have also been approved by the FDA. In other countries, the product is branded as Vistabel and sold as a 50 Botox-unit vial for cosmetic purposes. Allergan owns in excess of 400 world logo and trademark registrations for the Botox brand in 110 countries or regions throughout the world. Allergan has sales representatives in over 100 countries. In order to fulfill the demands of its huge customer base, Allergan has become the largest legitimate producer and seller of BoNT in the world. The authors have had close contact with a senior Allergan scientist.

Allergan’s representative in Russia is called “Family Health” in Russian. Botox was approved for therapeutic purposes by the Russian government in 1995 and for cosmetic purposes in 2003. Family Health has what is considered an effective sales promotion department made up of seven persons whose major responsibilities are to conduct seminars for doctors and communicate with clinics throughout Russia.

b. Mentor Corporation, Santa Barbara, California U.S.A.

Founded in 1969, Mentor Corporation is a leading supplier of medical products for the global healthcare market. Over the years, Mentor has specialized in the development,
manufacturing, and marketing of innovative, science-based products for the aesthetics, urologic specialties, and clinical and consumer healthcare markets around the world.

Mentor established its BoNT R&D program through an exclusive licensing agreement with the Wisconsin Alumni Research Foundation (WARF) in December 2003. Under terms of the agreement, Mentor obtained the exclusive rights to the proprietary BoNT technology developed at the University of Wisconsin-Madison, one of the few world centers of toxin expertise. The University has been a pioneer in the development of BoNT toxins for over 30 years and has developed intellectual property that includes the composition, preparation, purification, and characterization of all seven BoNT serotypes. In November 2004, Mentor announced that it was constructing a state-of-the-art BoNT manufacturing facility in Madison, Wisconsin.

At the time of this writing, Mentor was evaluating its product in a series of clinical trials but only results of Phase I trials have been published. Mentor will market its product under the tradename PurTox and, according to Mentor, the product is considerably purer than other currently available BoNT formulations, therefore providing a reduced dosage administration with fewer adverse reactions. It is uncertain whether these claims will prove to be correct since an alternative purified BT product Xeomin® (see below) is administered at similar doses and has a similar adverse event profile as Botox, which contains the toxin complex. It appears that PurTox has no excipients but is dissolved in preservative-free saline. The authors have had no contact with Mentor.

c. Solstice Neurosciences Incorporated, Malvern, Pennsylvania, U.S.A.

Solstice Neurosciences focuses on the development, manufacturing, sales, and marketing of specialty biopharmaceutical products. Originally formed by four investor groups, in July 1994 the company acquired the intellectual property, world-wide marketing rights, manufacturing facility, and licensing applications for Myobloc® (BoNT type B) Injectable Solution (called NeuroBloc in Europe). Solstice’s product is the only BoNT type B formulation that is approved for human use in many countries. For example, Myobloc is approved in the United States, Canada, and 26 European countries to treat cervical dystonia, and is being readied for the Japanese market. Solstice operates a state-of-the-art manufacturing facility in South San Francisco, California, but its global headquarters is located in Malvern, Pennsylvania. The authors have had discussions with several ex-Solstice employees and found that they are interested in cooperating with any of our future anti-counterfeiting efforts.

d. Ipsen Group, Paris, France

Ipsen is an innovation-driven international specialty pharmaceutical group with over 20 products on the world market and a total worldwide staff of nearly 4,000. Of direct relevance to this report, Ipsen produces Dysport® (hereafter Dysport), which is also a BoNT serotype A in complexed form in a lyophilized preparation with the major excipient human albumin. Dysport
was originally launched in the United Kingdom in early 1991, and in 2008 had marketing authorizations in over 70 countries. On January 31, 2008, the FDA accepted a filing by Ipsen of a license application for treating patients suffering from cervical dystonia with Dysport. This acceptance signifies the start of the review process of the Dysport dossier in the United States. Later information reported by the company indicates that the FDA will complete its review by the end of 2008. A separate filing with the FDA for cosmetic use of the product, under the brand name Reloxin, was also made in 2008 by Ipsen’s partner Medicis, which has marketing rights for this product in all of North America and Japan. Ipsen has also partnered with the aesthetic European company Galderma for the rights to distribute and market Dysport in countries outside of Medicis’ territory. We have had contact with one of Ipsen’s senior managers.

Dysport is prepared using a different purification technique from that used by Botox and is distributed in 500-unit vials, each containing 4.35 nanograms of toxin complex proteins, which are stored at refrigeration temperature.

Botox and Dysport are quite distinct from one another. In particular, the potency assay used for each product is different, meaning that the potency units for each product are not interchangeable. Therefore, clinicians must use approximately 2-3 times the number of Dysport units as Botox units to obtain a similar clinical effect, due to a simple number difference only. Differences in these toxins may relate to variations in the strain of bacterium and the production and subsequent purification of the toxin complex.

Dysport was registered for therapeutic purposes in Russia in 1994 and for cosmetic purposes in 2005. It is the only officially registered BoNT serotype A product in Kazakhstan and Iran.

e. Merz Pharma, Frankfurt, Germany

Merz Pharma is an innovative international healthcare company with several subsidiaries, of which one, Merz Pharmaceuticals, is active in the production of botulinum toxin Type A. Merz Pharmaceuticals concentrates on developing medications for neurological conditions such as Alzheimer's Disease and Parkinson's Disease, and neuro-muscular disorders. Xeomin® (hereafter Xeomin) is a formulation of BoNT serotype A that was developed to treat dystonia (chronic movement disorders consisting of involuntary muscle spasms). Merz Pharma claims to have applied its own innovative production and purification process in developing Xeomin. The product is supposedly free of other proteins of the toxin complex. Therefore, Merz claim patients are less likely to suffer from allergic reactions to Xeomin compared to Botox or Dysport. In 2006, Merz Pharma won a significant ruling against Allergan in a patent dispute related to Xeomin. In effect, the United Kingdom’s High Court of Justice invalidated the grant of a patent to Allergan relating to the use in the UK of a neurotoxic component of BoNT for treating pain related to muscle activities.

Xeomin contains the highest concentration of human albumin per vial of the licensed BoNT products. Sucrose is also present. Both of these excipients stabilize the toxin in the vial,
which is necessary because the normal stabilizing components of the toxin complex are not present. Xeomin is stored at room temperature, again a feature of the stabilizers in the vial.

The authors have so far been unable to learn more technical details about Xeomin because when attempting to access the Xeomin.com website, one reads the message “On this website healthcare professionals find detailed information on botulinum neurotoxin type A. According to German law, only healthcare professionals can be given access to this specific information.”

Originally, Merz was the German distributor of Botox for 15 years. Currently, the company competes directly with Allergan, Ipsen, and Solstice in several markets. For example, Xeomin is licensed in several Latin American countries (e.g., Mexico and Brazil) and Merz currently is seeking approval for Xeomin in Russia. The authors have had no contact with Merz Pharma.

f. Lanzhou Institute of Biological Products, Beijing, China

As of 2005, the Lanzhou Institute of Biological Products (LIBP) site covered 430,000 square meters and its capital asset was 797 million yuan (approximately $120 million). It is a state-owned enterprise under China National Biotec Corporation. LIBP employs approximately 1,500 persons, including 400 specialists and senior technicians. The company manufacturers more than 100 biological products, including vaccines, antitoxins, toxoids, blood products, immunoregulators, diagnostic reagents and other health care products. LIBP claims to have developed 27 new biological products between 1995 and 2005, but it is not clear if they are only for the Chinese market.

A C. botulinum research laboratory was set up in LIBP in 1960 for developing BoNT preparations and antitoxin. At that time, the development of an injectable formulation of BoNT serotype A was initiated by a team of scientists led by Dr. Yinchun Wang. By the 1970s, several products used for diagnosis, treatment, and prevention of botulism were researched and developed by the laboratory, and the laboratory became the national research centre for C. botulinum and BoNT. To this day, LIBP is the only manufacturer in China that is authorized to produce, supply, and store botulinum anti-toxins.

The development of BoNT serotype A for therapeutic and cosmetic purposes began after one of the C. botulinum Hall strains was donated to LIBP by the Food Research Institute of University of Wisconsin in 1984. Four years after receiving the strain, Wang and his colleagues succeeded in developing a crystalline form of BoNT with high toxicity, purity, and stability. In February 1989, this product was evaluated by China’s National New Drug Evaluation Committee (NDEC) and permitted to enter Phase I and II clinical testing. After the toxin had been proven safe and effective for the treatment of blepharospasm, hemifacial spasm, and partial strabismus, a New Drug Certificate and Trial Production License were issued in October 1993 by the Ministry of Health, permitting Phase III clinical testing to proceed. (See Figure 2 for drug approval process in China.) Based on the positive results of three years’ trial production and clinical Phase III observations organized by the China Medical Association and involving 500

CNS MAIN OFFICE
460 Pierce Street
Monterey, CA, 93940
Tel: 831-647-4154 | Fax: 831-647-3519

CNS Washington, DC, Office
1400 K Street, NW | Suite 450 | Washington, DC 20005
Tel: 202.842-3100 | Fax: 202.842.0556
http://www.cns.miis.edu
patients, the product was approved by the NDEC for commercial use in December 1996. A Formal Production License was issued by the Ministry of Health in February 1997, and the product was registered under the trade name BTXA. In 1997, BTXA was approved with a Free Sale Certificate by the Chinese State Drug Administration. The Bacterial Toxin Department for BTXA production was awarded the Good Manufacturing Practice (GMP) Certificate in 2001. BTXA’s excipients are bovine gelatin, sucrose, and dextran. LIBP claims that its research has demonstrated that BTXA loses less toxicity during lyophilization than other BoNT formulations. There is, however, no possibility that LIBP could substantiate since, to perform such studies, LIBP would have needed access to the other BoNT toxin products prior to formulation and preparation in vials, which would not have been possible. As of this writing, BTXA is the only brand of BoNT serotype A that has been legally approved by the Ministry of Health for human use in China. BTXA’s Chinese name is Hengli (衡力). BTXA’s license number is: Guo Yao Zhun Zi S10970037.31

Since its commercial launch in 1997 in Hong Kong by its subsidiary company Hugh Source (see below), BTXA has been used throughout China, so thousands of patients have benefited from treatments for a vast range of medical conditions and for cosmetic purposes. In 2002, India and South Korea were the second and third foreign countries to license BTXA for medical uses (Hong Kong was the first). Since then, an additional ten countries have approved the product for sale and use. Post-marketing surveillance studies undertaken in several countries since 1997 to monitor the safety of BTXA have shown no untoward effects.

One major difference between BTXA and other BoNT products is that a bovine gelatin protein is added to the vial in order to prevent the BTXA from sticking to the wall of the vial, the syringe, etc. Two Canadian scientists have warned that since the gelatin utilized is of bovine derivation, it has the potential to induce allergic reactions or, possibly, bovine spongiform encephalopathy, a neurological disease commonly known as “mad cow disease.”32 A second difference is the addition of dextran as a second stabilizer.

BTXA has been marketed internationally since 1997 through a company called Hugh Source (International) Limited, which is headquartered in Hong Kong. Hugh Source utilizes a broad network of consultants and scientists to identify potentially useful pharmaceutical products from different parts of Asia, including Mainland China, and then acts to export these products to global markets.33 BTXA is marketed in Brazil as Prosigné®. It bears noting that a team of Brazilian scientists compared the biological activity of Prosigné with that of Botox and found: “Our results suggest that Prosigné and Botox are comparable with respect to efficacy and safety for the short-term treatment of blepharospasm and hemifacial spasm.”34 The Brazilian company Cristália in Itapira SP offers to sell 100 units of Prosigné for $200, which it claims compares to the more than the $400 cost for Botox. We do not know if this seller screens buyers.35

BTXA is marketed in Russia under the name Lantox,36 and in Ukraine as Estetox.37 Its representative in Russia is said to be Nike-Med, which is a cosmetic clinic in Moscow. Oddly enough, BTXA is not licensed in Russia, but Lantox is. It is probable that BTXA is marketed in other countries under local brand names.
It is important to note that the U.S. Department of State specifically mentioned LIBP in its 2005 compliance report to Congress, conveying its suspicion that the company may be involved in activities that violate the Biological and Toxin Weapons Convention. The following quote is taken from the section dealing with LIBP:

China has a number of civilian and military facilities that could be associated with an offensive BW program. For example:

- The Chinese Ministry of Defense’s Academy of Military Medical Sciences (AMMS) Institute of Microbiology and Epidemiology (IME) in Beijing is acknowledged as a biodefense research facility.
- The Lanzhou Institute of Biological Products (LIBP) has been identified as a vaccine producer. We believe that LIBP has several BL-3 laboratories and dual-use capabilities.

From 1993 to the present, military scientists have published the results of studies of aerosol stability of bacteria, models of infectious virus aerosols, and detection of aerosolized viruses using polymerase chain reaction technology in the open literature. Such advanced biotechnology techniques could be applicable to development of offensive BW agents and weapons.

Other facilities in China that may have legitimate public health and commercial uses and could also offer access to additional BW-enabling capabilities.38

g. Medy-Tox, Inc., Seoul, South Korea39

Throughout the 1980s and 1990s, C. botulinum was intensively studied by a group of scientists in South Korea. In May 2000, some of them established a biotechnology venture and named it “Medy-Tox, Incorporated.” Since its founding, this company has focused on biopharmaceuticals and other products based on C. botulinum. For this purpose, in July 2001 Medy-Tox established the Microbial Toxin Research Institute in Chungnam, which has been officially certified by the Korea Industrial Technology Association. Medy-Tox’s primary business goal is to use its science and technology expertise to establish itself as a premier biopharmaceutical firm providing BoNT-related pharmaceuticals and therapeutic/diagnostic antibodies. Specifically, its vision is:

… to be "A Supreme Specialty Biopharmaceutical Company" in the world. Our specialty will be "Technology for Toxins as Therapeutics." By 2007, we will be "The Largest Bio-venture in Korea" in terms of market capitalization. By 2010, we will be "A Worldwide Recognized Biotech Company." We strive to be a top-tier biotech company for all people, including customers, shareholders, and employees. In addition, we want to become the most valued company to our society through economic contribution.40
Following much research on biological, biochemical, immunological, and toxicity aspects, Medy-Tox scientists developed a BoNT serotype A formulation called Neuronox for cosmetic uses. In December 2002, Medy-Tox completed the construction of a South Korean Good Manufacturing Practice (GMP)-compliant plant in Ochang. Then, in March 2004, it completed the Phase III clinical trial of Neuronox and the product was licensed by South Korea for human use that year. Medy-Tox claims that as of 2007, customers and partners in more than 50 countries were using Neuronox for cosmetic purposes (see Table 3 for comparisons between Neuronox and other BoNT products). On its homepage, it reproduces letters of appreciation for the product from Egypt, Italy, Japan, Lebanon, Russia, South Africa, and Thailand.

During 2004 and 2005, Medy-Tox claims that Neuronox was licensed to several international pharmaceutical companies, including the giant Indian company Ranbaxy. Ranbaxy supposedly will invest significant resources to market Neuronox in India and other countries. Also, South Korea’s largest food company, CJ Corporation, has licensed the marketing and sales rights to market Neuronox in Latin American countries. In 2007, Medy-Tox made an agreement with the Swedish company Q-Med AB to collaborate on marketing Neuronox in India, Thailand, Singapore, and South Korea.41 We do not know how this agreement meshes with the earlier agreements.

In addition to Neuronox, Medy-Tox is conducting R&D along the following lines:

- BoNT serotypes A, B, and E biopharmaceuticals;
- Environmental rapid detection kits for BoNT;
- Therapeutic neutralizing antibodies against BoNT;
- Functional cosmetics.

h. Bio-Med Private Limited, Ghaziabad, India

Bio-Med was established in 1972 for the purpose of developing and producing animal vaccines. It has expanded considerably since that time and now produces a wide range of both veterinary and human vaccines. More to the point of this report, Bio-Med claims to have launched India's first indigenously manufactured drug BoNT serotype A under the brand name BOTOGenie in January 2007.42 Bio-Med describes its product as a biologically active and highly purified preparation of BoNT serotype A. The company claims that since BOTOGenie is in a highly purified form of the toxin that is used in minute quantities, it does not induce any immunological response even after several treatments in most subjects. BOTOGenie is available as a lyophilized powder in 100-unit or 50-unit vials that include 5 milligrams of lactose as stabilizer. The powder is reconstituted with 10 milliliters of normal saline. The shelf life of unreconstituted BOTOGenie is 36 months, but it must be used within four hours after being reconstituted.43

Although Bio-Med provides information on certifications and good manufacturing practices accorded to its veterinary and human vaccines, there is no such information about BOTOGenie. Further, Bio-Med’s website provides information on how this product may be used
for both human therapeutic and cosmetic applications, but there is no reference to any country having issued permission or certification for such applications. The site does not list the cost of the products, but persons interested in purchasing them are invited to submit an inquiry form to the sales department. It seems to us that this company is very flexible about selling all of its products, including BOTOGenie. There is no mention on its web site of a procedure for screening buyers.

ii. Producers of Reagent-Grade Botulinum Toxin for Non-Human Uses

Because of its potency and potential use as a vaccine, an antigen for the development of anti-botulinum antibodies, and a reagent in other biochemical tests, BoNT is a useful reagent that is sought-after by researchers. With little expertise needed to produce and purify the toxin, it is a profitable product for several biochemical manufacturers. (See Table 4). However, the problem with these "reagent grade producers" is that they are mostly unregulated (especially when compared to the extensive regulation imposed on pharmaceutical manufacturers) and therefore they are considered the "cowboys" of the toxin production industry. We had hoped to list all legitimate producers of BoNT for non-human applications but found that this task was impossible to accomplish with our limited resources and time.

In the following sections, we list three groupings of BoNT “reagent-grade producers.” The first grouping consists of legitimate BoNT producers in industrialized countries, primarily the United States. The second group is comprised of companies in countries other than China, and the third group consists of Chinese companies. We identify a few of these companies that we sense are producers, but these identifications should be considered tentative. To repeat, our lists should not be considered comprehensive.

a. BBTech, Inc., Dartmouth, Massachusetts

BBTech is an offshoot of an Indian company variously called BBTech Harbal Ltd. or Bishoushadhi Biotechnology, Inc., which has its headquarters in New Delhi and was founded by Dr. Bal Ram Singh. According to its homepage, “The word ‘Bishoushadhi’ was coined by Dr. Singh to reflect the medicinal (oushadhi) nature of botulinum neurotoxins (Bish). Thus Bishoushadhi Biotechnology, Inc. was established in 1998 to promote the idea of converting poisonous substances – be they natural products, human thoughts or disease-causing chemicals produced in the human body – into therapeutic medicines.” BBTech Harbal has subsidiaries in Sultanpur and Lucknow, India. It “…strides [sic] to become one of the best Ayurvedic Company [sic] in India.” There is no indication on its homepage that BBTech Harbal produces or sells BoNT.

BBTech was incorporated in the United States in 1998, and opened for business in 2000 in Dartmouth, Mass. Its R&D focuses on the production and sale of BoNT, BoNT derivative products such as antitoxins and detection kits, and other neurological products. BBTech has
partnered with the nearby National Botulinum Research Center at the University of Massachusetts for the purpose of being able to provide large-scale production of BoNT serotypes A, B, and E to customers. BBTech is one of the lowest-cost manufacturers of the pure toxin, advertising rates of $500 per microgram of purified BoNT serotype A.

The U.S. company divulges almost no information about itself on its website but does notify perspective customers as follows: “BBTech products are intended for research purpose only, and are not for use in humans. Within the United States, CDC registration is required for all customers purchasing botulinum related products, except for recombinant light, heavy chains, toxoids or antibodies.”

b. List Biological Laboratories Incorporated, Campbell, California

According to its website, List is the world leader in the production of bacterial toxins, including BoNT, for research. Between 2000 and 2007, List was awarded at least $259,848 worth of defense contracts, many for the production of bacterial toxins. The company came under intense public scrutiny in 2004 after it became known that a Florida chiropractor, Bach McComb, injected himself and three others with reagent grade BoNT supplied by List. We do not need to consider this case here other than note that because of the difficulties List experienced as a result of this case, its representatives have refused to talk to us.

c. Calbiochem Biochemicals, San Diego, California

Calbiochem Biochemicals has broad expertise in the production and purification of numerous proteins, and offers a wide range of biochemicals, as well as kits for the detection and assay of many of these proteins, including reagent grade BoNT. Calbiochem is a part of EMD Chemicals Inc. It is interesting to note that the company charges $382 for 10 micrograms of BoNT serotype B.

d. Accurate Chemical & Scientific Corporation, Westbury, New York

Another company offering reagent grade BoNT is Accurate Chemical & Scientific Corporation. Accurate specializes in products for basic and R&D research, as well as routine laboratory work. Accurate's market covers a broad range of customers and applications, serving government labs, university research centers, pharmaceutical laboratories, as well as hospitals, clinical and industrial centers. Accurate publishes a 570-page "Incomplete" catalog, offering nearly 33,000 entries, including various types of reagent-grade BoNT products. Thus, a search of its product line using the search term “botulinum” yielded 46 hits, including toxins, toxoids, antibodies, and others.

e. Metabiologics Incorporated, Madison, Wisconsin
Located in the University of Wisconsin Research Park, Metabiologics currently manufactures and sells all seven serotypes of BoNT to accredited researchers on a worldwide basis. Metabiologics claims to manufacture toxins and related products, such as antibodies to BoNT, to the highest industry standard for purity and specific activity. Further, Metabiologics is developing novel, rapid, and sensitive BoNT detection systems.\textsuperscript{53}

f. Ilongen Company, Warminster, Pennsylvania

This is a mysterious company we found when seeking information about the Shandong Ilongen Bio Technology Co. Ltd. in China. Since Ilongen sells the Chinese BoNT product Beauteous, it could be a subsidiary of the Chinese company. Ilongen makes the following pitch: “Botulinum toxin type A is the main ingredient [sic] of the American product botox. It is used for temporarily removing facial wrinkles by injecting into facial muscles. We offer private labeling for companies with their own brand name. We also sell in bulk.”\textsuperscript{54} Ilongen claims that it was established in 2000, has a workforce of between 11 and 50 persons, and has an annual sales volume of $5-10 million.

g. Ghandour For Medical and Chemicals, Hama, Syria\textsuperscript{55}

Ghandour was established in 2005, employs between 11 and 50 persons, and has annual revenues of between $1 and 2 million. It claims that, “Our office in China offers the best quality and prices regarding to botulinum toxine [sic] type A and Hyaluronic acid injections. We are willing to produce the customers' private label," Ghandour states.\textsuperscript{56} The company claims to be manufacturing a BoNT Type A product called “Maxitox Cosmetic” and asserts that it is made in a GMP pharmaceutical factory in accordance with the strictest international quality-control standards.\textsuperscript{57} As with other BoNT products we have described, Maxitox Cosmetic is said to be a highly purified protein produced by the \textit{C. botulinum} bacterium. Despite Ghandour's claims that appear to indicate that it is a producer, we think it merely distributes Beauteous. (See below.)

We need to make note of some general characteristics of Chinese companies involved in BoNT production for non-human applications:

- There are a relatively large number of Chinese companies that offer some version of BoNT (often branded as “Botox”) through their Internet sites. Although many of them claim that their products have been approved and/or are regulated by Chinese governmental agencies, such claims are of doubtful worth and certainly cannot be verified by outsiders.
- Although some Chinese companies state that their products are for human use, we group them along with the "reagent grade" producers because it is unlikely that they meet the high standards one would associate with human pharmaceuticals.
For each company it is impossible for an outsider to determine whether it is a producer, producer, and distributor, or distributor only of the BoNT products it offers. Most claim on their web sites to be producers, but when one examines the products that are advertised, it appears as if only one or a few BoNT products are being repeatedly featured. In particular, the name “Beauteous” reappears with high frequency. Also, the claims made by each company about the contents of the vials they sell cannot be checked, so we cannot know if they contain actual BoNT and, if so, in what concentrations. This being the case, in each capsule description presented below, the wording provided by the companies is of uncertain veracity. Lastly, some companies that we identified during mid-2008 as BoNT distributors have disappeared by the time this report was being finished, while new entities have appeared. We do not know the reason for this phenomenon – perhaps they have gone bankrupt, changed their name, were driven out of business, or some other reason. (The sale of BoNT for cosmetic purposes is, however, a highly profitable business and these companies only need to sell limited quantities in order to make exceptional profits, especially if the products do not in fact contain the most expensive element, BoNT. A rapid turnover of different companies could therefore be considered a good way of avoiding detection and potential prosecution by authorities, while maintaining a continuing revenue stream.)

h. Aima Business Co., Ltd., Guangzhou

Aima Business Co., Ltd. states that it is a professional international trade company, founded in 1992. It claims to import and export medical equipment, beauty equipment, and beauty products. It sells “biotin,” about which it claims: “Biotin is a sulfur content of water-soluble vitamins, it also call [sic] botulinum toxin, BTX.” The company also markets a product it calls “Botulinum Toxin Anti-wrinkle Cream,” whose main ingredient is “botulinum toxin type A gene protein component.” Since biotin actually is a water-soluble B-complex vitamin and the ingredient called “botulinum toxin type A gene protein component” is unidentifiable, we believe that this company is attempting to sell two BoNT serotype A look-alike products that actually contain no BoNT.

i. Beijing Bt Biotechnology, Beijing

This company appears to have just one product for sale, its own formulation of BoNT serotype A. The photograph provided of its products depicts two vials, one with a blue label and the second with a brownish label. The text on the labels is illegible. Other than providing a contact name on its web site, there is no other information about the company.

j. Beijing Candacy Medical Beauty Co Ltd. (also Beijing Candacy Science & Technology Co.)
Beijing Candacy states that it sells “Beautious-a,” which is BoNT serotype A, for cosmetic purposes. It claims that this product is: “...a sterile, vacuum-dried purified botulinum toxin type a, produced from fermentation of hall strain clostridium botulinum type a grown in a medium containing casein hydrolysate, glucose and yeast extract. It is purified from the culture solution by dialysis and a series of acid precipitations to a complex consisting of the neurotoxin, and several accessory proteins. The complex is dissolved in sterile sodium chloride solution containing albumin human and is sterile filtered (0.2 microns) prior to filling and vacuum-drying. One unit (u) of beautious-a equal one unit (u) of botox (allergan)” [as stated in the original]. The company’s profile states that it was established in 1998 and employs between 26 and 50 persons. There is no information about its capabilities or facilities. We believe it to be a mere distributor of “Beauteous.”

k. Hunan Hormones Pharmaceuticals (also Hunan Steroid Chemicals Co., Ltd; possibly also DBA Shanxi SteroidsFarma Co.), Shanghai

The company offers for sale Botox 50 unit vial[s] and Botox 100 unit vial[s]. These products are of course not genuine Botox. While Hunan blatantly infringes on the Allergan trademark, it makes no attempt to replicate the packaging. Thus, the product name is likely used to draw customers familiar with the Allergan brand who may be seeking an imitation. One of its trade sites indicates that the company is a government-approved manufacturer, but there is no accompanying certificate or reference to any regulatory body.

l. Jingmen Kaitai Pharmaceutical Co., Hubei

This company describes itself as a high-level scientific and technical pharmaceutical ingredient manufacturer and marketing enterprise. The company description indicates that Botox (and snake venom) were developed by cooperating with [a] Chinese national-level biomedical research institute, but does not name it. Jingmen claims also that the quality of Botox satisfies the standard of [the] National Institute for the [C]ontrol of [P]harmaceutical and [B]iological [P]roducts (NICPBP), the official regulatory body for pharmaceuticals in China. However, whether the company is actually licensed to sell its products online is not specified and it is unclear what type of selling practices or security measures it employs. Jingmen most likely is a mere distributor of “Beauteous,” a photograph of which appears on the web site.

m. Merrystone Medicine Science and Technology Development Company Ltd., Shijiazhuang Hebei

Merrystone specializes in selling cosmetic products such as BoNT, hyaluronic acid, polyacrylamide hydrogel, as well as anti-aging products such as human placenta succus, stem cells, injections for removing pouches under the eyes, pimple remover injections, and fat-
dissolving products. The company was established in 2004, employs between 11 and 50 persons, and claims annual revenues of between $500,000 and 1 million. It markets a BoNT serotype A product named CNBTXA, which probably is the same product as is produced by the Nanfeng Medical Science and Technology Development Company Ltd. If so, then Merrystone is merely a distributor.

n. Nanfeng Medical Science and Technology Development Company Ltd., Shijiazhuang

Nanfeng Medical claims to specialize in cosmetic medical products, such as those used for wrinkle removal, breast augmentation, body shaping, and weight loss. Included in its product line is CNBoNTX-A, a formulation of BoNT serotype A used for eliminating wrinkles on the face, forehead, back of the neck, and so forth. (CNBoNTX-A probably is an acronym for Chinese botulinum toxin Type A.) According to Nanfeng Medical, 100 units of CNBoNTX-A are equivalent to 100 units of Botox. However, the potency of CNBoNTX-A was recently investigated and found to contain significantly higher levels of BoNT than are listed on the product’s label, which could pose a severe health risk for patients. We are not aware of any additional details about this preparation.

As far as we are aware, CNBoNTX-A is neither licensed nor approved in any country. Nevertheless, orders for this product may be placed directly with the company via the Internet. We do not know if the company screens the orders it receives in any way. Our sense is that Nanfeng Medical is a producer of BoNT and, although it sells it for cosmetic use, it probably does not have the certification to do so.

o. Phenix Medical Company Ltd., Guangzhou City

Phenix was established in 1999 with a investment of nearly $3 million made by Phenix Medical Ltd. in the United Kingdom. Phenix states that it is dedicated to the discovery, development, and manufacture of medicines for cosmetic purposes. Its main product is Phenix BoNT serotype A, which was first offered for sale on the Chinese domestic market in 2004 and for the export market in 2005. The company claims that this product is produced according to United Kingdom quality standards but sold at Chinese prices. The company states that it produces its BoNT serotype A product in two sizes, 50 and 100 units. On one of its pages, the company states that its product is “Botulinum Toxin Type A (botox dysport).” This implies that its source of BoNT is Ipsen, but that would be odd; why would a Chinese company import Dysport? More likely, the statement is made to suggest that the Phenix product resembles Dysport. If that is the case, we do not know the source of Phenix’s BoNT. Prominently featured on the BoNT product page is the seal of the Chinese Certification Committee for Drugs, but there is no assertion to the effect that the BoNT product actually has been certified by this committee. We have subsequently confirmed through our contacts that this certification is false; no such certification has been issued by the Chinese regulatory authorities.
p. Shandong Biogen (or Shandong Biogen Tech Limited or Shandong Ilongen), Yantai

Shandong Biogen claims to market several BoNT formulations, including “cnbotox, cbxa (we also work as oem) beauteous, bts” [as specified in the original]. The company states that its BoNT development technique has been licensed in China. Several contact names and emails are available on its various web sites, suggesting that its practices may well be approved in China. One site advertises its “broad network of consultants and collaborating scientists,” although it does not specify from which government agency or sector of the pharmaceutical industry their expertise has been sought.

The company offers rapid delivery of its products, as follows: “Express delivery: UPS, EMS, TNT. Packed with ice bags or dry ice (dry CO2) to ensure the low temperature in three days. it will take 2 or 3 days for South America and East Asia, 3 or 4 days for Europe and South Asia, 4 or 6 days for West Asia, Africa and South America.” Apparently, it will not deliver to the United States.

q. Shandong Biomedicine Company, Shandong

Similar to other Chinese companies, Shandong advertises “Botox” on its web site as one of its main products, but it actually displays vials with the brand name “Beauteous.” Interestingly, on one of its web sites, Shandong goes into specific detail about its toxin production process, at one point describing the “series of purifying procedures” leading to the crystallizing complex of the toxin protein. This would suggest that the company either has direct ties with a producer or is producing the toxin itself. Another possibility is that this information is copied from a site owned by a real producer of BoNT or plagiarized from the many references on BoNT production that have been published in the open scientific literature for over 60 years.

r. Shanxi SteroidsFarma Company, Shanghai

Shanxi claims that it is one of China’s leading manufacturers of hormones, steroids, and other pharmaceuticals. It has a very confusing BoNT product information page, as follows:

Jintropin somatropin goldprep HGH Products
Botox
botulinum toxin type A
Restylane
Beauteous
BoNTS-A
We are offering high quality Jintropin HGH Injectable (Human Growth Hormone) and somatropin goldprep HGH Botoxat very low prices.
It is difficult to make sense of Shanxi’s offerings, especially since an accompanying photograph depicts two vials that are labeled “MedBotox,” a name that is owned by Allergan. Further, Restylane is a formulation of hyaluronic acid that has no chemical relationship to BoNT. We believe that Shanxi is actually selling Beauteous, but we are not certain of this.

s. Sinocos Eastcos Medical Technology Development Ltd., Hong Kong

Claiming approval by the SFDA [Chinese State Food and Drug Administration] and the Chinese Ministry of Health, Sinocos Eastcos’ website states that its brand “Beautox” is made in a GMP standard pharmaceutical factory in accordance with the strictest international quality-control standards. We cannot verify this statement. On its homepage, Sinocos also describes the production process for its BoNT formulation and asserts that it is in accord with U.S. FDA and the Chinese standards of production. The company does not specify with which regulations it complies, but claims that it uses the same “main effective ingredients.” We believe that this company is both a producer and distributor of BoNT.

3. The Trade in Counterfeit Botulinum Toxin and Current Monitoring Efforts

The market value of BoNT products produced by Allergan is approximately $1.5 billion and that of other manufacturers' products, such as Dysport, Myobloc, Vistabel, and NeuroBloc, is in the hundreds of millions of dollars. While the latter products are also targets for counterfeiters, our investigation to date suggests that Botox is most often copied or counterfeited, so henceforth we use its name as shorthand to describe all counterfeit BoNT products used for cosmetic and health purposes. With consumers throughout the world demanding this product, and their willingness to pay considerable sums to obtain treatment with the drug, there is clear financial incentive for criminals to capture some of this market by selling counterfeit BoNT. Below are our findings with regards to counterfeit BoNT producers and/or distributors in China, India, and elsewhere.

i. China

While India and the United Arab Emirates (UAE) are listed by the European Commission as the world’s top exporters of counterfeit medicines, our research makes clear that China is the most important country of origin for illicitly produced BoNT, particularly for medical uses. The Chinese government recognizes the problem, as evidenced by the following government statement:

In order to strengthen the supervision of botulinum toxin type A, the Ministry of Health and the State Food and Drug Administration decided to regulate botulinum toxin type A
and its preparations as medicinal toxic drugs, and recently issued a notice on further strengthening the management of the production, distribution and use of botulinum toxin type A and its preparations.\textsuperscript{79}

Information for our research on Chinese BoNT producers and distributors was derived from two sources: the Internet and the two companies Allergan and Ipsen. The Internet certainly provided fertile ground for our research on China. Our research uncovered numerous suppliers offering in both English and Chinese to sell BoNT. In fact, all the producers and distributors described in Section 2 have some sort of Internet presence. It is interesting that most do not have their own web sites but instead depend on something called B2B (business-to-business) electronic services to provide platforms for advertising their wares. The B2B service we found most useful for our research is called EC21 Global, based in South Korea, which asserts that it is “a global B2B marketplace where trading companies post products, or trade leads information, and exchange offers…. We catalyze the active exchange of inquiries, and provide high rate of business trading.”\textsuperscript{80} Other B2B companies are Alibaba.com (www.alibaba.com) established in 1999 in China; All Products Online Corporation (allproducts.com) established in 1999 in Taiwan; and Tootoo.com, which is Ninetowns Internet Technology Group Company Ltd.’s B2B, established in 1995 in China.

As a readily accessible resource for most any product, the World Wide Web allows those interested in purchasing BoNT, legitimate BoNT products, or counterfeit Botox to buy what they need from a surfeit of sites. Providing only a name, mailing address, and credit card information, a potential buyer can locate and purchase a vial of BoNT for a fraction of the Allergan price. The inexpensive vial may contain actual toxin, poorly purified toxin, poorly diluted and stabilized toxin, or no biologically active compounds at all. For example, in July 2008, a woman living in Marina del Rey, California, was arrested for selling human growth hormone and counterfeit Botox she had ordered from China by mail. The parcels mailed to her from China were mislabeled, purporting that they contained “synthetic hair pieces, plastic molds, and sample iron oxide.”\textsuperscript{81} While the analysis of the human growth hormone vials found that they did indeed contain the hormone, the vials labeled as Botox contained no toxin at all. In this case, one type of criminal defrauded another.

Nevertheless, we hypothesize that customers anywhere in the world can purchase counterfeit Botox from suppliers in China or their agents in other countries via the Internet in any desired quantity. To prove or disprove this hypothesis it will be necessary to set up a system for purchasing the Botox offered by purveyors on Internet and then analyze the purchased product, something we propose below in the Conclusion. Further, some sort of mechanism must be set up to attempt to purchase bulk BoNT from Chinese and other distributors, which might require an alternative purchase and transmittal system than that needed for the purchase of Botox vials.

From our interviews with a senior Allergan manager, we learned that the company takes the counterfeit Botox problem very seriously and has established an internal system to deal with illegitimate producers abroad. Its main concern is not counterfeiting per se, but rather that products packaged in vials bearing the counterfeit Botox label will harm patients and adversely
affect the legitimate Botox market because end-users will be afraid to purchase the real product and patients will be reluctant to be treated with it. The Allergan executive revealed to us some information about the company’s attempts to shut down counterfeit Botox producers in China.

Allergan has come to realize that most counterfeit Botox is produced in China. In response, some years ago Allergan hired a Chinese law firm, which it declined to name, and with its assistance developed a strategy for dealing with the counterfeit problem locally. As part of this strategy, Allergan representatives gathered information about counterfeit products, as well as their producers and distributors, and passed this information to Chinese regulatory and police agencies. In particular, Allergan has over time developed a close and trusting relationship with China’s State Food and Drug Administration (SFDA). In early 2008, this relationship bore fruit when the Chinese authorities, acting on the basis of information supplied by Allergan, shut down one of the major manufacturers of counterfeit Botox. The Allergan manager stressed to us the importance of keeping a low profile in these dealings; accordingly, the company insists on keeping its arrangements with Chinese agencies and details of ongoing efforts secret. Allergan has no equivalent relationship with any other government.

Ipsen has been cooperative in our efforts to gain further information about counterfeit BoNT. Although Ipsen has fewer problems with counterfeiters than Allergan, Ipsen does take this problem very seriously and has a senior manager assigned to oversee it from a worldwide perspective. Analysis of the counterfeit Ipsen BoNT products their representatives have collected from Brazil, Iran, and Russia indicates that their origin was almost exclusively Chinese. Chinese BoNT products often contain higher concentrations of the toxin than is indicated on the label, but occasionally have less. Toxin assays from samples of counterfeit and look-alike products indicate that there probably are several production facilities in the country, in addition to Lanzhou. The Ipsen representative would be receptive to an ongoing collaboration, especially with regards to the molecular fingerprinting and cataloging of counterfeit samples.

ii. India

According to the European Commission, India accounted for 31% of the illegal flow of counterfeit drugs across European borders in 2006 (the UAE also accounted for 31% and China for 20%). The percentage of the drugs that were BoNT products was not revealed in this report; however, in the conclusion the Commission noted the implications for the pharmaceutical industry and for public health and security: “The emergence of India in this sector reflects the developing industrial capacity of this nation and highlights the reality that counterfeiting is carried out on an industrial scale, in all sectors where a potential profit is perceived.”

While information on counterfeit BoNT production is not currently available through Internet sources and vendors, the vast counterfeit drug trade in India suggests that counterfeit Botox would constitute some proportion of this black-market industry. Indeed, as noted in Section 2, the Indian BoNT product BotoGenie has relatively recently entered the market, and it might already be sold by some distributors as a counterfeit BoNT product. It should be noted that India already has a market in place for BoNT products in both the medical and cosmetic
areas, so has a domestic market for these products as well as established trade routes for counterfeit pharmaceuticals that could easily assimilate counterfeit BoNT products.

India has noted and reacted to its position as one of the top exporters of counterfeit medicines. As the Indian government becomes increasingly concerned about its inability to contain this trade, and as the size of the illicit market increases, drastic control and punishment measures have been suggested. For example, an expert committee in 2003 recommended that the death penalty be imposed on those peddling counterfeits. This suggestion has not been acted on and is not likely to be instituted. As an Indian reporter wrote in July 2007, “The call for death penalty for makers of spurious drugs has long been given a silent burial.”

The problem, as pointed out in an earlier James Martin Center for Nonproliferation Studies (CNS) report to DTRA, is that although India appears to have sufficiently tough regulations for controlling its industry and exports, its government systems for monitoring and ensuring compliance with these regulations, as well as policing actual and would-be law breakers, are exceedingly poor. According to an article in the Indian press, “The Drug-Controller General of India has only 700 inspectors countrywide. The regulatory body has about 600 vacancies, an official source said. Drug inspectors were last recruited in 1993. While the pharmaceutical industry has increased several-fold since, the number of drug inspectors has dwindled, the source observed.”

Because India is such a large producer of counterfeit drugs, this information is startling and should serve as a call to action to both India and its international pharmaceutical partners. In particular, the exports of Bio-Med (P) Limited, which already claims to be selling its vaccines to African and South American countries, should be monitored to make certain that BotoGenie, or relabeled variations of it, are not sold without proper export controls. Further, since a BoNT-related industry is very likely to emerge in India, its products must be closely monitored to prevent a situation similar to the illicit production of BoNT in China.

iii. Russia and Kazakhstan

There is evidence that several criminal entities are pursuing profits in the illicit trade of counterfeit Botox in this region. The practice of selling counterfeit products is so common that an estimated 90% of doctors providing Botox procedures in Russia knowingly use counterfeits, mostly identified by low fees that would be unprofitable with legitimate products. One source has provided us with direct information on an operation that has been established for over two years:

The Family Health representative could name one representative of an illegal distributor and/or manufacturer located somewhere in Chechnya. This individual, named Ruslan, personally transports suitcases full of vials with labels almost identical to the legitimate Botox by airplane to St. Petersburg. According to the preliminary investigation by Family Health, Ruslan has been coming to St. Petersburg for the last two years and selling his product to beauty salons. Asked about the quantity he could provide, he answered that
any quantity can be supplied, as much as 500 or 1000 vials. There has been no move against Ruslan or the entity he represents because both end-user and authorities are afraid of taking on a Chechen criminal organization.92

In Kazakhstan, one operation is known to authorities and is believed to have the capabilities to produce the toxin. The company is called “Time Medical.” The local Ipsen representative expressed his strong concern regarding this company. Although he did not know the precise source of their counterfeit Botox, he assumed that they could produce it themselves since they have their own production facility.93

4. Conclusions and Follow-up

In the foregoing sections, we have made clear that production facilities of real BoNT have been established in various parts of the world, but especially in China. It is reasonable to assume that as the worldwide market for legitimate BoNT products increases, the profit motive for cheap counterfeit versions of these drugs will also increase. The security implications posed by multiple illicit BoNT production facilities, which can supply criminal groups with a powerful BW agent, must be regarded as a serious threat to the security of U.S. and other countries. In this section we analyze the security implications of the growing phenomenon, consider strategies for stopping or limiting the proliferation of BoNT and relevant know-how, and recommend follow-up activities to the project reported here.

i. Security Implications

Many authors and agencies have considered the various ways that BoNT could be used for biological weapons purposes by military forces, terrorist groups, or individuals, so there is no reason for us to delve into this subject in any depth. It is sufficient at this point to note that BoNT is classified by the CDC as a Category A threat agent94 and is featured on the Department of Health and Human Services’ list of “select agents,”95 which indicates that it is one of the most dangerous toxins for terrorist purposes. However, for reasons that are made clear below, it is important to note that BoNT quantities of less than 0.5 milligrams are excluded from the select agent list; in other words, if the quantity of BoNT in question is less than 0.5 milligrams, it does not have to be handled, packaged, and shipped according to the strict rules that regulate select agents generally.96 Thus a package containing up to 100,000 vials of Botox, each of which contains 4.8 nanograms (0.0000048 milligrams), can be shipped without special packaging and through ordinary surface mail.97

In view of the small quantities of BoNT present in Botox vials, neither they nor vials marketed by other legitimate BoNT producers present serious security threats because they cannot be applied in such a way as to generate mass casualties. (See Chart 1.) To illustrate, it would take the contents of approximately 100 Botox vials injected intravenously to kill just one adult human.98
Conversely, we have developed two troubling scenarios in which a small, easy-to-produce quantity of BoNT could generate a substantial number of casualties, overwhelming local and regional healthcare systems. In the first scenario, a terrorist (or group of terrorists) visits all of the Starbucks' coffee houses within 10 miles of downtown Washington, D.C., and uses a small dropper bottle to put several drops of a BoNT formulation into each creamer container. This type of attack would be simple to carry out, efficient in generating casualties, require little expertise, and be almost undetectable. Within 24 hours, thousands of people would present with labored breathing and each one would need to be hooked up to an artificial breathing device. According to a CDC scientist, approximately 4,000 artificial breathing devices would be available to any locality in the United States within 24 hours, but this number would be quickly exceeded by the number of casualties. Once there were no more respirators, widespread panic and disorder might follow. Although most of those maintained on respirators would probably survive, each victim would require a 30-60 day course of treatment before his or her body was clear of the toxin and would require intensive care for much of that period. Approximately 80% of those who ingested the toxin and did not have access to a respirator would die.

The second scenario is even more frightening because a variation of it has already been used by terrorists. In 1984, the religious sect called Rajneeshees contaminated 11 salad bars in The Dalles, Oregon, with a formulation that contained Salmonella bacteria. As a result, at least 751 persons contracted gastrointestinal illness. This type of food-borne attack could be carried out relatively easily in any American urban center. A variation of the "salad bar scenario" would be for a terrorist group to contaminate salad dressing tubs in open salad bars with a BoNT formulation. Because BoNT is stable in a cool environment that is mildly acidic, these tubs would serve as excellent carriers of the toxin. A casualty rate similar to the one described above in the creamers scenario would result.

While pharmaceutical-grade BoNT producers and products pose only a slight threat to U.S. security, we believe that the gray- and black-market producers of high-grade BoNT are of high proliferation concern. This concern takes two forms. First, the potential sale of bulk BoNT to criminal or terrorist buyers could present a clear danger to U.S. national security because they could employ the product in various types of attacks that would generate mass casualties. A second type of proliferation is even more threatening: criminals or terrorists could acquire the capability to manufacture bulk BoNT, which would allow them to carry out biological attacks at the time and place of their choosing, with no worry about having sufficient BoNT to accomplish their objectives.

By what process would criminals and terrorists acquire such a capability? Our thinking is that there is a stepwise process by which a criminal entering the counterfeit BoNT field would advance from being a dilettante to becoming a serious operators and, potentially, a proliferation threat. For the purposes of this report, we assume that criminals would operate in a less restrictive legal and regulatory environment than that of the United States, which, in effect, means most of the developing and newly industrialized world. In this freer environment, the entry step would be that criminals (possibly including members of organized crime syndicates or terrorist groups) would recognize the size of the local cosmetic market for BoNT products and

CNS MAIN OFFICE
460 Pierce Street
Monterey, CA, 93940
Tel: 831-647-4154 | Fax: 831-647-3519
CNS Washington, DC, Office
1400 K Street, NW | Suite 450 | Washington, DC 20005
Tel: 202.842-3100 | Fax: 202.842.0556
http://www.cns.miis.edu
look for an opportunity to “wedge into” it. Most likely they would learn that purchasing legitimate BoNT products such as Botox is difficult without using a dishonest doctor or clinic as a front, which is expensive because the product itself is costly and profits would have to be shared with the front person.

Alternatively, a cursory examination of the overall supply situation would quickly reveal that there are two possible sources outside legitimate pharmaceutical suppliers – legitimate bulk manufacturers and illicit manufacturers of BoNT products. The advantages for a criminal of dealing with an existing bulk manufacturer would be that a steady supply of a product of known composition and strength would be assured, but the cost of the product would nevertheless be high. (See Table 4.) Moreover, if the manufacturer is subject to government regulation, it is possible that he would recognize a criminal purchaser and refuse to do business with him. The advantage of dealing with an illicit supplier is that his product would be cheap; the supplier would not be concerned about the identity of the purchaser or the purpose for which the product would be used. Rather, since the supplier would not wish to attract the attention of regulatory and police agencies, as he protected himself, he would also safeguard the purchaser. The purchaser, in turn, would not require a middleman to sell and convey the product to the end-user but could do this himself. The disadvantages of dealing with an illicit producer are that he might disappear at any time, making continuity of supply uncertain; the product is not quality-controlled so it could be anything or, if it is BoNT, of unknown concentration; and if harm came to recipients of the product, not only the end-user but also his supplier would probably become targets for inquiry and arrest. Based on the likely cost-benefit calculations performed by criminals, however, we believe that most of them would probably seek to acquire BoNT products from illicit producers.

Once the criminal purveyor has enough paying customers to secure a high income, he could take one of two paths. The first would be to maintain the status quo and continue to buy already diluted and packaged counterfeit BoNT from a dependable outside source. Alternatively, he might learn that producers of counterfeit BoNT are willing to deal with him directly and realize that additional profits could be generated if he were to dilute and package the toxin himself. By selecting the second option, the next step for him would be “backward integration,” that is, he would buy the counterfeit BoNT in bulk from the illicit manufacturer and hire someone with minimal technical skills to dilute the bulk toxin, package it in vials, and affix what appear to be genuine labels to the vials. He probably would assume that his clientele would not know the difference between his packaged product and the genuine article and would purchase what he supplied them, believing that it was a legitimate product being sold at a discount.

A third step in the “backward integration” would be for the criminal purveyor to not only eliminate the middleman, but also the bulk manufacturer. To do so, he or the people he hires would have to become fully versed in the manufacture of BoNT; he would also need to have the financial resources to purchase the requisite manufacturing equipment and to rent or purchase a building where the BoNT could be produced. From what we have learned about the manufacture of BoNT and its packaging, as explained above, we estimate that if the criminal purveyor were to hire a Master's-level microbiologist, that person would be able to set up a BoNT manufacturing
facility capable of producing gram quantities of the toxin in less than a month's time and at a cost of less than $30,000. If the criminal sought to produce a final product that appeared similar to a legitimate product such as Botox or Dysport, he would need to purchase lyophilization and packaging equipment costing an additional $5,000 to $6,000. After achieving the third step, the criminal would become capable of manufacturing actual bulk BoNT. He could then dilute the product so the final concentration is approximately 480 nanograms per liter, filling vials so that each contains 10 milliliters of the product, lyophilizing (or just drying) the contents of each vial so it resembles powder, stoppering each vial, printing and affixing labels that look much like the genuine Botox or Dysport label to the filled vials, and selling the final product through the established marketing network. The advantage for the criminal of setting up and operating his own manufacturing plant would be that the supply of the product would be assured, an adequate level of quality control could be maintained, and profits would be higher because all middlemen had been eliminated. Further, it might be possible for the new manufacturer to sell his product to other criminals, generating additional profits.

Achievement of a BoNT production capability by a criminal would not present a proliferation threat as long as he supplied BoNT to only greedy doctors and clinics for cosmetic procedures. Most criminals probably would be satisfied with having reached this operational level. But it is conceivable that a criminal has other objectives in mind that go beyond making money. Two such objectives would pose security threats. The first would be for the criminal to supply bulk, genuine BoNT to terrorists. We believe that an illicit manufacturer would not differentiate among customers, meaning that anyone who is able to pay and does not appear to be undercover police would be sold whatever quantity of BoNT he orders. If a supposedly legitimate company offers to sell BoNT in bulk and offers “private labeling for companies with their own brand name,” it is reasonable to assume that illegitimate producers of BoNT would not only be willing to do the same, but would sell their products without screening customers.

Do we possess some evidence for the existence of criminals somewhere in the world who produce and/or distribute BoNT? The answer is a conditional yes. As the information presented in Section 3 demonstrates, counterfeit BoNT products are being distributed in several countries, and the large majority of them appear to have originated in China.

A second troubling possibility is that the criminal in the scenario above is a terrorist group that has, from the start, been intent on acquiring biological weapons. Thus, the group has come to recognize that while it learns the techniques of industrial microbiology that may be applied for terrorist purposes, a handsome profit can be derived from the production and sale of counterfeit BoNT that funds its operations. Although we have no evidence that such a scenario has been realized, the potential for terrorists acquiring a BoNT capability should not be underestimated. At a two-day meeting in 2004 that attracted drug regulators from 40 countries, an Interpol representative stated, “…emerging evidence shows that counterfeiting [BoNT products] is linked to organized crime and terrorist organizations, including al Qaeda.” If this statement is correct, it suggests that a highly organized terrorist group intent on attacking the United States was seeking to acquire a toxin that could be used to generate income and, when the time was right, employed as a biological weapon. Thus, BoNT is a unique terrorist option
because it can be acquired for use in a weapon of mass destruction while simultaneously generating high profits by being sold as counterfeit Botox or Dysport in civilian markets.

**ii. Strategies for Stopping or Limiting the Proliferation of Botulinum Toxin and Relevant Know-how**

After we completed gathering data for this scoping study, one basic question we asked was whether activities to stop or limit the proliferation of BoNT and relevant know-how should be aimed at shutting down its supply or curtailing the demand for this product. We first regarded the supply side and looked for examples from nuclear nonproliferation to ask the following question: Is there a piece of equipment, like a specialized centrifuge in the nuclear field, that if somehow was made unavailable to would-be proliferants would stop them from acquiring BoNT production capabilities? After having analyzed the possibilities for doing so, we reached an unequivocal conclusion: in the case of BoNT, the answer is "no." The reasons for our conclusion are:

1. the bacterial strains used for toxin production probably are stored in most if not all national cell culture collections (which, unlike U.S. culture collections, are still open providers of such bacteria), and they also can be relatively easily isolated from natural soil;
2. the culture media required for propagating the bacterium are in common usage and are easily obtained;
3. the fermenters used for anaerobic fermentation are in common usage throughout the world and can be easily purchased;
4. the chemicals required for toxin purification are widely available for restriction-free purchase;
5. the lyophilizers required to dry BoNT formulations for packaging are freely and inexpensively available on eBay and other second-hand suppliers.

Therefore, at this time, the supply side of the BoNT-acquisition equation does not appear susceptible to effective interdiction, foreclosing this approach to curbing counterfeit BoNT production.

As for limiting demand for counterfeit BoNT, we found that some inroads have already been made in the form of public awareness campaigns that have helped alert consumers and health professionals to the dangers of counterfeit Botox. In general, local and state authorities have been supportive of these campaigns, which have increased awareness of the problem among both candidate clients and end-users. Patients are better educated and have learned to ask about the source of the product they are using. An example of the value of this type of activity is provided in a report from our Russian consultant:

CNS MAIN OFFICE
460 Pierce Street
Monterey, CA, 93940
Tel: 831-647-4154 | Fax: 831-647-3519
CNS Washington, DC, Office
1400 K Street, NW | Suite 450 | Washington, DC 20005
Tel: 202.842-3100 | Fax: 202.842.0556
http://www.cns.miis.edu
Previously, Family Health offered a “blacklist” of medical clinics offering illegal/counterfeit botox procedures. A negative reaction from the black market, including threats and blackmailing, forced these companies to eliminate the blacklist and redesign the website. Now Family Health offers a list of “reliable” clinics on its redesigned website, rather than exposing clinics that use illegal botox.

At the same time, the representative of the Family Health noted that the clinics have been more responsible lately and choose not to jeopardize their reputation. Clinics have also become the best informers on illegal botox. They often call the Family Health office to verify the origin of botox shipments. Typically, low prices or non-standard packaging raise their suspicions. Family Health receives such calls at least once a week.106

Legitimate pharmaceutical BoNT producers have been the leaders in these education efforts, as they help these producers maintain the value of their franchises, while helping potential patients of injectable cosmetic products to make informed choices. Special advanced labeling technologies, such as holograms and known serial numbers to identify genuine packages containing BoNT products, have been widely applied by these manufacturers. Thus, some diminution of the counterfeit BoNT trade has been achieved, but these are small victories in a market that is likely to grow as the demand for lower-priced injectable cosmetic products will increase among both the female and male populations, especially in developing countries with rising incomes.

Our conclusion is that to suppress the counterfeit BoNT supply, it is best for regulators and/or police to detect and then shut down illegal manufacturers and their distribution channels. To this end, one can learn from the success in stopping the production and distribution of other types of counterfeit pharmaceuticals, although there are only a few relevant examples. One model of international cooperation that led to the suppression of a counterfeit drug and may serve as a roadmap for similar future international BoNT control efforts was published in early 2008.107 This case involved the anti-malarial drug artemesunate, which when administered to malaria victims in combination with mefloquine is effective in treating this difficult infection. As a result of the high therapeutic value and limited availability of artemesunate, a large and vibrant counterfeit drug market grew rapidly. Today, an estimated 33-53% of all drugs sold as artemesunate in mainland South East Asia are actually counterfeit products and hence are useless.108 Malaria sufferers who ingest the counterfeit substance will remain sick (or die) from untreated malaria, and may also be inadvertent sources of the malaria parasite that are transported by mosquitoes to infect others. Accordingly, the sale of this particular counterfeit drug represented a public health hazard in the Southeast Asia region. As a result of the widespread sale of counterfeit artemesunate, malaria outbreaks worsened locally and regionally, malaria sufferers lost confidence in the real drug, buyers experienced large economic losses, and legitimate artemesunate manufacturers had their reputations smeared and lost substantial income.

An international initiative, called the Jupiter Operation, was launched for the purpose of shutting off the supply of illegal artemesunate. To conduct this operation, an international team was established, including representatives from the Welcome Trust, Interpol, Royal Canadian
Mounted Police, Australian Therapeutic Goods Administration, Intellectual Property Division at the Chinese Ministry of Public Security, WHO, CDC, and others. As a result of a complex operation that included securing 391 samples from five different sites in Cambodia, Laos, Myanmar, Thailand, and Vietnam, and analyzing them for their contents, the team discovered that “at least some of the counterfeits were manufactured in southeast People’s Republic of China. This evidence prompted the Chinese Government to act quickly against the criminal traders with arrests and seizures.”

In this case study, a "molecular fingerprint" was made of each sample. The physical characteristics of the packages containing the counterfeit artesunate were noted and recorded. Intelligence was gathered from end-users on who sold them the products. By analyzing and comparing the “fingerprints” and package characteristics, it was possible for Jupiter Operation analysts to deduce how many different illicit producers were manufacturing counterfeit artesunate. Once the number of laboratories was determined, information from sellers was used to purchase more samples, which allowed the authorities to learn about distribution channels. In the end, the main distribution channel was disrupted after distributors were arrested, although it is unclear whether all counterfeit artesunate trade routes were discovered and closed down. The Jupiter Operation’s report concluded with what we believe is a recommendation relevant to this study: "International cross-disciplinary collaborations may be appropriate in the investigation of other serious counterfeit medicine public health problems elsewhere, but strengthening of international collaborations and forensic and drug regulatory authority capacity will be required." In other words, what the Jupiter Operation did on a relatively small scale in addressing one special counterfeit drug needs to be institutionalized on a larger scale and be prepared to address a panoply of counterfeit drugs.

To date, nothing like the Jupiter Operation has been attempted to address the counterfeit BoNT problem. Currently this problem is being addressed on two levels, the individual company and the organization, but neither is comprehensive or well supported. On the individual company level, the most focused and effective efforts have been led by each of the two major BoNT producers, Allergan and Ipsen. Through their representatives in many countries, they obtain vials that carry their counterfeit labels and unknown contents. These vials are sent to the respective companies’ analytical or reference laboratories and the contents are analyzed and reported internally. As mentioned above, in only one case, however, was Allergan successful in closing down a counterfeit BoNT operation in China. Outside of that incident, it appears that legitimate companies try to learn what they are dealing with, but they make little effort to go after counterfeiters. Of course, this is understandable; they are not police or security agencies, and broader biosecurity issues are not their primary concern. In reality, the issue is one of regulatory monitoring that should be carried out by the respective authorities in countries where these products are identified. In addition, as the number of counterfeit laboratories increases, these companies do not have the international expertise or resources needed to track down and prosecute these criminals.

On the organizational level, there are at least 22 non-governmental and intergovernmental organizations throughout the world whose mission is to counteract the widespread
and lucrative trade in counterfeit drugs. (See Table 5.) However, each of these organizations has its own distinctive objectives, working methods, and levels of expertise in often esoteric disciplines. From what we have observed, there appears to be little exchange of information among these organizations, and few if any of them are knowledgeable about terrorism and terrorists. This being the case, were BoNT to become an acquisition objective for terrorist groups, it is doubtful whether any existing international organization, including Interpol, would be well prepared to address the resultant threat.

iii. Recommended Follow-up to the Present Project

We have developed two sets of recommendations; one that DTRA, with assistance from the CNS, can implement immediately to begin addressing the counterfeit BoNT problem, and one that DTRA can consider for follow-up activities to be undertaken by CNS in partnership with the Lawrence Livermore National Laboratory (LLNL) and the FBI.

a. Immediate Actions by DTRA

We have found that at present, no agency or organization is gathering information from the companies and organizations directly involved in producing, marketing, and distributing licensed BoNT products. Such entities have the highest interest in stopping the illicit BoNT trade. However, each discovery of a new counterfeit BoNT product is handled on an ad hoc basis by the discoverer, and the associated findings and experience are not shared with others. This being the case, we recommend that DTRA and CNS immediately organize a meeting that brings together representatives from regulatory and law enforcement agencies, as well as the Interagency Botulism Research Coordinating Committee,112 with the aim of accomplishing two goals:

♦ Establish an interagency committee whose mission would be to allow the parent organizations to share on a continuous basis all information they receive on licensed and illicit BoNT production and distribution. It would be important to invite the two main BoNT production companies, Allergan and Ipsen, to join this committee, even if only as “permanent advisors”;

♦ Establish a confidential reporting site at DTRA or CNS to which private industry and individuals could convey information about illicit BoNT activities by email, fax, or telephone. Instructions on how to report should be provided immediately to all companies listed in this report and as possible to companies that will be identified in the future.

b. Follow-Up Activities by CNS.

CNS MAIN OFFICE
460 Pierce Street
Monterey, CA, 93940
Tel: 831-647-4154 | Fax: 831-647-3519
CNS Washington, DC, Office
1400 K Street, NW | Suite 450 | Washington, DC 20005
Tel: 202.842-3100 | Fax: 202.842.0556
http://www.cns.miis.edu
We recommend that DTRA and the FBI support two activities for the purpose of gaining control over the counterfeit BoNT trade and thus preventing BoNT producers and distributors from becoming proliferation threats: (1) establishing a Botulinum Toxin Nonproliferation Network (BotNet), and (2) setting up a Botulinum Toxin Investigative Team (BoNTIT).

i. Establishment of the Botulinum Toxin Nonproliferation Network (BotNet). One of the main weaknesses of the status quo is the lack of cooperation between international agencies and the major pharmaceutical and "reagent-grade" BoNT producers in the United States and abroad. The substantive information that these companies could provide about illicit BoNT activities in the countries where they are represented would greatly increase the effectiveness of the work of international law-enforcement agencies. However, this proposed collaboration poses a delicate problem. Pharmaceutical companies are not inclined to reveal sensitive information that could harm their business, and providing such information to international agencies over which they have no control appears inconsistent with their interests. This is where an impartial and trusted party could benefit these efforts by serving as a bridge between the companies and an international clearinghouse. CNS would take on this responsibility for being the impartial and trusted party. To enable it to be successful in this role, CNS will establish and operate the Botulinum Toxin Nonproliferation Network (BotNet), which would aim to be an information clearinghouse and would, in addition, have an analytical capability that would enable it to provide actionable information to the interagency committee.

ii. Setting up the Botulinum Toxin Investigative Team (BoNTIT). We recommend that DTRA support the setting up of a Botulinum Toxin Investigative Team (BoNTIT), which would be an analytical cooperative effort to be undertaken by CNS staff and scientists working at LLNL’s Biosciences and Biotechnology Division. CNS’ role in the BoNTIT would be to continue the effort begun as part of the scoping study reported here, but on a broader scale and with a more intense effort. CNS would expand on the research already performed by utilizing analysts who are fluent in at least the eight languages taught at the Monterey Institute of International Studies (MIIS), as well as local languages in Southeast Asia and the former Soviet republics. In addition, close relations would be established with the personnel of the FBI, the U.S. Department of Homeland Security (DHS), Interpol’s Anti-terrorism Unit and Intellectual Property Crime Unit, WHO’s International Medical Products Anti-counterfeiting Task Force (IMPACT), the U.S. Food and Drug Administration, and other agencies and organizations as appropriate. Having the FBI and DHS on the team would be particularly important because they would have the legal authority to act on information to pursue criminals and protect public health.

One of the BoNTIT’s major activities would be to collect samples for analysis. In other words, since there is the necessity to discover how many illicit BoNT production facilities are operating in China, India, and elsewhere, vials containing real or purported BoNT must be collected and analyzed using advanced molecular fingerprinting and chemical analysis using mass spectrometers. There are two preferred method for collecting these samples. First, CNS will use its contacts at Allergan, Ipsen, and other companies as possible to request them to submit the
samples they already possess and samples they will collect in the future. These samples will be conveyed to LLNL, as described below. Second, the FBI can set up an operation to collect samples by, for example, setting up phony clinics in foreign countries that order purported Botox and other marketed BoNT via Internet. These samples would be conveyed to LLNL. As of this writing, the counterterrorism unit at FBI’s San Francisco branch has submitted a project proposal to FBI headquarters to undertake such a project and is awaiting a decision.

As for LLNL’s Biosciences and Biotechnology Division, it would perform either open or classified studies on BoNT samples, as appropriate. As part of a concerted effort to identify and, as possible, quantify the illicit laboratories in the world capable of producing BoNT, the collected samples would be carefully documented and then transported to LLNL for molecular fingerprinting of proteins they may contain and mass spectrometry analysis of excipients and chemical contaminants. The information derived from analysis will be entered into the Botulism Molecular Fingerprint Database (BMFD). This procedure would allow a profile to be built of all counterfeit and legitimate samples, and the matching of new samples to those previously analyzed. It bears mentioning that samples containing counterfeit material would not need to be handled as hazardous biological substances until it had been determined that a sample contained a hazardous substance. Further, any sample that contains less than 0.5 milligrams of BoNTd would not fall under the Select Agent Rules and thus can be transported freely.

An analytical group made up of staff from CNS and LLNL would periodically analyze the information collected from both efforts and its findings would be conveyed to DTRA and other agencies as appropriate. In case actionable information on threatening situations involving BoNT is generated by the project, this information would immediately be conveyed to DTRA and, as appropriate, FBI and intelligence agencies. Substantial efforts would be made to make certain that the information collected in the course of activities noted above would be secure. (There is potentially a role in this group for the two main BoNT companies as well, due to their experience in dealing with BoNT issues for over 25 years.)

It can be seen from the foregoing that a unique partnership will be developed between policy analysts, biomedical scientists, and an enforcement agency, where each partner brings needed expertise. CNS has the policy expertise and academic credibility to move this project forward, will be the hub of the network that is created, and can easily connect the elements of industry, government, and academe into a working unit. Further, were there to be involvement of foreign companies and government agencies, CNS would be in a fine position to smooth their entry into the network and set up a user-friendly reporting mechanism in their languages. The LLNL has the scientific expertise to perform the analysis required for the molecular and chemical fingerprinting of samples that will enable the quantification of BoNT producers and, eventually, give an idea of where they might be located. The FBI is best suited for collecting samples in what might be inhospitable environs and transporting them safely to LLNL. Further, were actionable intelligence to be generated by the project, it would be best placed to take the needed enforcement action.
Table 1: Cosmetic and Therapeutic Applications of Botulinum Toxin

**Cosmetic Applications**
- Botulinum Toxin Irons Out Facial Wrinkles
- Botulinum Toxin Lessens Facial Scarring
- Botulinum Toxin Might Prevent Baldness

**Therapeutic Applications**
- Botulinum Toxin Provides Temporal Symptom Relief from Dystonia
- Botulinum Toxin is Beneficial for Cervical Dystonia
- Botulinum Toxin Provides Temporal Symptom Relief from Laryngeal Dystonia
- Botulinum Toxin Eases Writer's Cramp
- Botulinum Toxin is Beneficial for Oromandibular Dystonia
- Botulinum Toxin Eases or Cures Tics
- Botulinum Toxin Eases or Cures Tremors
- Botulinum Toxin Eases Parkinson's Disease
- Botulinum Toxin Treats Hemifacial Spasm
- Botulinum Toxin Treats Blepharospasm
- Botulinum Toxin Treats Strabismus
- Botulinum Toxin Eases Spasticity
- Botulinum Toxin Eases Stroke Effects
- Botulinum Toxin Eases Traumatic Brain Injury
- Botulinum Toxin Eases Cerebral Palsy
- Botulinum Toxin Eases Multiple Sclerosis
- Botulinum Toxin Relieves Various Intractable Pain
- Botulinum Provides Temporal Symptom Relief from Hypertonic Disorders
- Botulinum Toxin Eases Rigid Spine Syndrome
- Botulinum Toxin Eases Bladder Dysfunctions
- Botulinum Toxin Eases Tinnitus
- Botulinum Toxin Might Assist Healing of Anal Fissures
- Botulinum Toxin Might Ease Refractory Vaginismus
- Botulinum Toxin Helps to Provides Temporal Symptom Relief from Dysphagia
- Botulinum Toxin Eases Migraine Headaches
- Botulinum Eases Severe Facial Pain
- Botulinum Provides Relief from Pelvic Floor Pain
- Botulinum Toxin Eases Symptoms of Children with Non-Neurogenic, Neurogenic Bladder
- Botulinum Toxin is Finding Applications in Cancer Treatment
- Botulinum Toxin Reduces Pain and Itching of Hand Eczema
- Botulinum Toxin Eases Plantar Fasciitis Pain
Botulinum Toxin Treats Carpal Tunnel Syndrome
Botulinum Toxin Reduces Auxiliary, Palmar, and Plantar Hyperhidrosis
Table 2: Botulinum Toxin Products Used in North American and Europe in 2008

<table>
<thead>
<tr>
<th>Company</th>
<th>Allergan Inc.</th>
<th>Allergan Inc.</th>
<th>Ipsen Inc./Medicis Inc.</th>
<th>Ipsen Inc./Medicis Inc.</th>
<th>Solstice Neurosciences Inc.</th>
<th>Merz Pharmaceuticals</th>
<th>Mentor Corporation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type</td>
<td>Type A-Hall strain</td>
<td>Type A-Hall strain</td>
<td>Type A</td>
<td>Type A</td>
<td>Type A</td>
<td>Type A-Hall strain</td>
<td>Type A-Hall strain</td>
</tr>
<tr>
<td>Approvals</td>
<td>In over 75 countries worldwide, including US and Canada</td>
<td>In over 16 countries, including US, Canada, Italy, France</td>
<td>Germany, other European countries</td>
<td>Some European countries, US, Canada</td>
<td>Germany, other European countries, Mexico, Argentina</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>Active Substance (molecular weight)</td>
<td>Botulinum toxin type A complex (500kD)</td>
<td>Botulinum toxin type A complex (900kD)*</td>
<td>Botulinum toxin type A complex (900kD)*</td>
<td>Botulinum toxin type B complex (70kD)</td>
<td>Botulinum toxin type A, free from complexing proteins (150kD)</td>
<td>Botulinum toxin type A, free from complexing proteins (150kD)</td>
<td></td>
</tr>
<tr>
<td>Strength of Action (BTX-A/Product)</td>
<td>1:1</td>
<td>1:1</td>
<td>1.2 - 1.4 (approximate)</td>
<td>1.2 - 1.4 (approximate)</td>
<td>1.50 - 1.00</td>
<td>1:1</td>
<td>1:1.5?</td>
</tr>
<tr>
<td>Indications</td>
<td>Blepharospasm; cervical dystonia; glabellar lines; hyperhidrosis</td>
<td>Glabellar lines</td>
<td>Blepharospasm; cervical dystonia</td>
<td>Glabellar lines</td>
<td>Cervical dystonia</td>
<td>Blepharospasm; cervical dystonia; glabellar lines in Argentina</td>
<td>Phase 3 for glabellar lines; Phase 1 for spasmodic torticollis/cervical dystonia</td>
</tr>
<tr>
<td>Pharmaceutical Form</td>
<td>Powder dissolved in solution for injection</td>
<td>Powder dissolved in solution for injection</td>
<td>Powder dissolved in solution for injection</td>
<td>Solution</td>
<td>Powder dissolved in solution for injection</td>
<td>?</td>
<td></td>
</tr>
<tr>
<td>Units/wial</td>
<td>100</td>
<td>50</td>
<td>500</td>
<td>300 or 500</td>
<td>2,500; 5,000; 10,000</td>
<td>100</td>
<td>?</td>
</tr>
<tr>
<td>Volume</td>
<td>10mL maximum</td>
<td>1.25mL or 2.5mL recommended</td>
<td>2.5mL recommended</td>
<td>5mL maximum</td>
<td>0.5mL; 1mL; 2mL</td>
<td>8mL maximum</td>
<td>?</td>
</tr>
<tr>
<td>Reconstitution</td>
<td>0.9% NaCl solution</td>
<td>0.9% NaCl solution</td>
<td>0.9% NaCl solution</td>
<td>0.9% NaCl solution</td>
<td>Prepared solution, dilutable</td>
<td>0.9% NaCl solution</td>
<td>0.9% NaCl solution</td>
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</tbody>
</table>

Notes about Table 2 provided by our reviewers:
1. The strength of action data presented in the table is speculative and ranges can be identified for all products mentioned.
2. The Ipsen Inc /Medicis first column indications are incorrect; the word “Blepharospasm” should be deleted.
Table 3: Comparisons Between Neuronox, Botox, and BTXA

<table>
<thead>
<tr>
<th>Subject</th>
<th>Neuronox®</th>
<th>Botox®</th>
<th>BTXA®</th>
</tr>
</thead>
<tbody>
<tr>
<td>Manufacturer</td>
<td>Medy-Tox Inc, South Korea</td>
<td>Allergan The U.S.A</td>
<td>Lanzhou Institute China</td>
</tr>
<tr>
<td>Appearance</td>
<td>white flat freeze-dried cake</td>
<td>white flat vacuum-dried cake</td>
<td>white volumetric freeze-dried cake</td>
</tr>
<tr>
<td>Identity</td>
<td>positive</td>
<td>positive</td>
<td>positive</td>
</tr>
<tr>
<td>Visual clarity</td>
<td>no foreign matter present</td>
<td>no foreign matter present</td>
<td>no foreign matter present</td>
</tr>
<tr>
<td>pH</td>
<td>6.8 ± 0.5</td>
<td>6.8 ± 0.5</td>
<td>6.0 ± 0.4</td>
</tr>
<tr>
<td>Bacterial Endotoxin</td>
<td>≤ 1 EU/vial</td>
<td>≤ 1 EU/vial</td>
<td>≤ 1.5 EU/vial</td>
</tr>
<tr>
<td>Potency</td>
<td>100 units/vial ± 10%</td>
<td>100 units/vial ± 10%</td>
<td>100 units/vial ± 30%</td>
</tr>
<tr>
<td>Moisture</td>
<td>≤ 3%</td>
<td>≤ 3%</td>
<td>≤ 3%</td>
</tr>
<tr>
<td>Composition</td>
<td>100 units of botulinum toxin type A 0.5 mg of human serum albumin 0.9 mg of sodium chloride</td>
<td>100 units of botulinum toxin type A 0.5 mg of human serum albumin 0.9 mg of sodium chloride</td>
<td>100 units of botulinum toxin type A 5mg of gelatin 25mg of dextran 25 mg of sucrose</td>
</tr>
</tbody>
</table>

Table 4: Pricing of Botulinum Toxin Types Manufactured for Research Purposes

<table>
<thead>
<tr>
<th>Botulinum Toxin Type</th>
<th>Quantity</th>
<th>Price in Dollars</th>
</tr>
</thead>
<tbody>
<tr>
<td>Botulinum Neurotoxin Type A</td>
<td>100 micrograms</td>
<td>500</td>
</tr>
<tr>
<td>Botulinum Neurotoxin Type B</td>
<td>100 micrograms</td>
<td>500</td>
</tr>
<tr>
<td>Botulinum Neurotoxin Type C</td>
<td>100 micrograms</td>
<td>1500</td>
</tr>
<tr>
<td>Botulinum Neurotoxin Type D</td>
<td>100 micrograms</td>
<td>1000</td>
</tr>
<tr>
<td>Botulinum Neurotoxin Type E</td>
<td>100 micrograms</td>
<td>1000</td>
</tr>
<tr>
<td>Neurotoxin Type</td>
<td>Quantity</td>
<td>Rate</td>
</tr>
<tr>
<td>------------------</td>
<td>-----------</td>
<td>-------</td>
</tr>
<tr>
<td>Type F</td>
<td>100 micrograms</td>
<td>1500</td>
</tr>
<tr>
<td>Type G</td>
<td>100 micrograms</td>
<td>1500</td>
</tr>
</tbody>
</table>

(For larger quantities, the customer can expect discounts.)
Table 5. Examples of Non-governmental and Inter-governmental Organizations Involved in Countering the International Counterfeit Drug Trade

Interpol
Interpol is attempting to combat the spread and sale of counterfeit antiretroviral, anti-tuberculosis, and anti-malaria drugs in Africa. It is also engaged in the prevention of trafficking in counterfeit drugs in general, as it poses an international health and security risk. Interpol is a stakeholder in IMPACT and has indicated great concern about the potential for terrorist involvement in counterfeit operations.

Pharmaceutical Security Institute
The Pharmaceutical Security Institute (PSI) is a not-for-profit, membership organization supported by 26 pharmaceutical manufacturers. Its headquarters is in Alexandria, Virginia. It has committed to sharing information on the counterfeiting of pharmaceuticals and initiating enforcement actions through appropriate authorities throughout the world. The PSI has not issued information on whether it is combating the counterfeit BoNT problem.

State Food and Drug Administration (SFDA) of China
The SFDA, sometimes called the Chinese FDA, has been aware of the problem of counterfeit BoNT for some time, and has been active in tracking some of the counterfeit activities uncovered by Allergan. Recently, it issued the following statement, indicating its focus on preventing the spread of counterfeit BoNT:

In order to strengthen the supervision of botulinum toxin type A, the Ministry of Health and the State Food and Drug Administration decided to regulate botulinum toxin type A and its preparations as medicinal toxic drugs, and recently issued a notice on further strengthening the management of the production, distribution and use of botulinum toxin type A and its preparations.\textsuperscript{116}

The responsibilities of the SFDA in regards to counterfeit drugs are as follows:

In China, SFDA is responsible for administrative punishment on counterfeit drug including to investigate and penalize illegal activities of manufacturing, selling, using counterfeit drugs. But SFDA is not responsible for criminal punishment on counterfeiting. In order to meet the gaps, SFDA cooperates with other government bodies:

\begin{itemize}
\item working with the Public Security Ministry for criminal punishment for manufacturing and selling counterfeit drugs,
\item working with Postal Office for eliminating, closing of mail orders and mail boxes of counterfeit drugs.
\item working with the Customs Office to control of smuggling counterfeit drug.\textsuperscript{117}
\end{itemize}
U.S. Food and Drug Administration (FDA)

The FDA, in acknowledgement of the serious problems posed by counterfeit drugs has formed an internal taskforce to focus on it and also is a member of IMPACT. The FDA is dedicated to ensuring the safety of the nation’s drug supply. The agency maintains an excellent website where consumers are able to report suspected counterfeit drugs.\(^{118}\) It has been instrumental in efforts within the U.S. to prevent reagent grade BoNT products from getting into the nations legitimate drug supply. In an extraordinary step to safeguard the U.S. food supply, it has recently opened three offices in as many Chinese cities to monitor suppliers of food items exported to the U.S.\(^{119}\) It would appear as if the mandate of these offices could easily be expanded to include counterfeit drugs, if the necessary human resources were made available.

World Health Organization (WHO)

One of the main pioneering efforts undertaken by the WHO includes the formation of the International Medicinal Products Anti-Counterfeiting Taskforce (IMPACT) in 2006. WHO established IMPACT with the goal to "build coordinated networks across and between countries in order to halt the production, trading and selling of fake medicines around the globe."\(^{120}\) While IMPACT has made some advances against counterfeit pharmaceuticals trafficking, it has not had the broad impact hoped for in its charter. We have interviewed one of IMPACT’s founding members and although he expressed interest in our efforts, he made known that IMPACT does not appear to be aware of the counterfeit BoNT problem. Members of IMPACT that we are aware of include:

- ASEAN
- Commonwealth Secretariat
- Council of Europe
- European Association of Pharmaceutical Full-Line Wholesalers (GIRP)
- European Communities
- European Directorate for the Quality of Medicines and HealthCare (EDOM)
- German Pharma Health Fund
- International Alliance of Patients’ Organizations
- International Council of Nurses
- International Federation of Pharmaceutical Manufacturers and Associations (IFPMA)
- International Federation of Pharmaceutical Wholesalers
- International Generic Pharmaceutical Alliance
- International Pharmaceutical Federation
- Interpol
- Organisation for Economic Cooperation and Development
- Pharmaceutical Security Institute
- United States Pharmacopeia
- World Customs Organization
- World Intellectual Property Organization

CNS MAIN OFFICE
460 Pierce Street
Monterey, CA, 93940
Tel: 831-647-4154 | Fax: 831-647-3519
CNS Washington, DC, Office
1400 K Street, NW | Suite 450 | Washington, DC 20005
Tel: 202.842-3100 | Fax: 202.842.0556
http://www.cns.miis.edu
World Medical Association (WMA)
World Self-Medication Industry
World Trade Organization
Photograph 1. Vials from China Bearing Labels of BoNT Products
Figure 2. Schema of the Drug Approval Process in China
Chart 1: Botulinum Toxin Potency Comparisons

<table>
<thead>
<tr>
<th>Subject Type</th>
<th>Amount (nanograms)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LD One mouse (injection)</td>
<td>0.02</td>
</tr>
<tr>
<td>One vial of Botox®</td>
<td>5.00</td>
</tr>
<tr>
<td>LD One human (intravenous)</td>
<td>90.00</td>
</tr>
<tr>
<td>LD(50) in one human (orally)</td>
<td>370.00</td>
</tr>
<tr>
<td>LD One human with Botox® injection (100 vials of Botox®)</td>
<td>500.00</td>
</tr>
<tr>
<td>LD One human (inhalation)</td>
<td>700.00</td>
</tr>
<tr>
<td>LD One human (orally)</td>
<td>70,000.00</td>
</tr>
<tr>
<td>LD Every Person on Earth</td>
<td>1,000,000,000.00</td>
</tr>
</tbody>
</table>
5. Endnotes and References

1 The authors wish to thank CNS graduate research assistants Paula Humphrey and Josh Newman for their contributions to this project and report. In addition, we are grateful to reviewers from inside and outside the CNS whose careful readings of this report gave rise to many fine suggestions for improving its contents and clarity, and correcting technical errors. Some of these reviewers have requested anonymity, which we respect, but they should know from this acknowledgement how grateful we are to them. The reviewers we would like to openly acknowledge are Dr. Stephen Arnon, Dr. Paul Jackson, Dr. Jonathan Tucker, and Mr. Leonard Spector.

2 When used in conjunction with pharmaceuticals, the word “counterfeit” may have different meanings. For the purposes of this report, “counterfeit” refers to a product that is represented as being legitimate and even trade marked, but in fact is being distributed by a criminal enterprise. In some cases, a criminal enterprise is also the producer of the counterfeit product, but for an outsider to determine this usually is difficult or impossible.

3 When dealing with BoNT, “bulk” is measured in grams or even fractions of grams.

4 In this report, “China” means only the People’s Republic of China.


9 Peter F. Bonventre and Lloyd L. Kempe, “Physiology of Toxin Production by *Clostridium botulinum* Types A and B: Effect of Carbohydrate Source on Growth, Autolysis, and Toxin Production,” *Journal of Applied Microbiology* 7:373 (November 1959).

10 Siegel, “Toxin Production.”

11 Ibid.


13 Bonventre and Kempe, “Physiology of Toxin Production by *Clostridium botulinum* Types A and B.”


For the purposes of this report, legitimate producers are those that are licensed and overseen by competent national agencies akin to the U.S. Centers for Disease Control and Prevention and the Food and Drug Administration.

We extrapolated this estimate from annual revenue numbers, the price of an individual vial, and the amount of toxin in each vial.

The USDA has a remit since the toxin can be an agent of disease in animals. USDA and/or CDC are responsible for granting various permits, for example to deal with transport of toxin into the United States and also the transport of strains within the United States.


The China National Biotec Corporation is China’s largest bioengineering corporation. It supervises the China National Scientific Instruments and Materials Import/Export Corporation, China National Medical Equipment & Supplies I&E Corporation, six biological product research institutes formerly under the Ministry of Health located in Beijing, Changchun, Chengdu, Lanzhou, Shanghai, and Wuhan, as well as the Beijing Tiantan Biological Products Co., Ltd., which is a listed company. In the coming years, the CNBC will be focusing its efforts on the development and production of generic drugs and the group's own proprietary products, which it aims to market on both domestic and international markets. Source: China National Biotec Corporation homepage at http://www.cnbg.com.cn/ (2007).


41 Q-Med, “Welcome to Q-Med,” 2007; http://www.q-med.com/. (We have heard that this agreement has recently been terminated by the Swedes.)
44 We have had no contact with any of the listed companies.
67 Carruthers and Carruthers, “Botulinum Toxin Products Overview.”
69 Company Profile, Phenix Medical Co. Ltd., http://phenixmedical.en.ecplaza.net/1/profile.asp.
82 Pickett and Mewies, “Counterfeit botulinum toxins – a serious risk to patient safety.”

CNS MAIN OFFICE
460 Pierce Street
Monterey, CA, 93940
Tel: 831-647-4154 | Fax: 831-647-3519
CNS Washington, DC, Office
1400 K Street, NW | Suite 450 | Washington, DC 20005
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http://www.cns.miis.edu
83 Ibid.
84 European Commission, Taxation and Customs Union, Summary of Community Customs Activities...
85 Ibid.
87 Ganapati Mudur, “India to introduce death penalty for peddling fake drugs,” British Medical Journal 327(7412):414 (August 23, 2003); http://www.bmj.com/cgi/content/full/327/7412/414-b.
90 Datta, “Fake drugs issue in focus after three-year gap.”
91 This estimate was derived from interviews with officials in Russia who do not want to be identified so it should be used with caution.
93 Ibid.
97 There may be U.S. legislation applying to pharmaceutical/medicinal products containing toxin that may be relevant in this regard, but due to time limitations we have not been able to research this legal area.
98 Chemical and Biological Arms Control Institute, “An Assessment of the Proliferation Potential of the Pharmaceutical Product Marketed as BOTOX®” (Alexandria, VA, 1998); Chemical and Biological Arms Control Institute, “Updated Assessment of Proliferation Potential of the Pharmaceutical Product Marketed as BOTOX®” (Alexandria, VA 2001).
101 One of our reviewers believes that high grade BoNT is not necessarily needed for terrorist purposes, that very low grade material is all that is needed for their purposes. Even BoNT industry chemists have as yet no idea of the quality of BoNT in the counterfeit or look-alike toxin products. His suggestion therefore is that this issue should be discussed more thoroughly and consideration given as to the higher likelihood of such material being far more readily available than the high grade BoNT. If he is correct, the proliferation problem posed by producers of counterfeit BoNT is greater than what we describe in this report.
102 See endnote 3.
One reviewer notes, however, that there is very little to stop anyone in the United States from manufacturing low grade BoNT in a rudimentary laboratory located at a home or garage and transporting it undetected to any site in the U.S.

Ilongen Company, “Skin Care, Others, and More.”

Liza Gibson, “News extra: Drug regulators study global treaty to tackle counterfeit drugs,” British Medical Journal 486 (February 28, 2004); http://www.bmj.com/cgi/content/full/328/7438/486-c.

Voronova, “Report to the CNS…”


Artesunate is a Chinese formulation of the generic anti-malarial drug artemisinin.


Ibid.

The LIBP devotes substantial space on its web site to the counterfeiting problem, but it does not state whether it is actively involved in suppressing it.

The IBRCC is a group of U.S. governmental agencies that have mandated responsibilities for the detection, surveillance, prevention, treatment, and advancement of knowledge of human and animal botulism. The agencies that comprise the IBRCC are CDC, NIH, U.S. Army, USDA, FDA, U.S. Geological Survey (National Wildlife Health Service), and California Department of Public Health. In addition, members of the BoNT industry attend the IBRCC’s meetings.

Carruthers and Carruthers, “Botulinum Toxin Products Overview.”

Chart copied from the Medy-Tox, Inc. website; http://www.medy-tox.co.kr/new_site/products/neuronox_01.htm.


