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Biosafety and Biosecurity: Government Regulations to Protect Dual Use Technology

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Introduction

Biosafety and biosecurity are two sides of the same coin. According to the Centers for Disease Control and Prevention (CDC), "Biosafety and biosecurity are related, but not identical concepts." Biosafety has been defined as early as 1984 by the CDC as referring to the "discipline addressing the safe handling and containment of infectious microorganisms and hazardous biological materials." This definition was described in Biosafety in Microbiological and Biomedical Laboratories (BMBL) published by the CDC (CDC, 2007).

Biosafety's goal is to protect the individual laboratory worker from exposure to microorganisms while biosecurity's goal is to protect dangerous pathogens from inadvertent or intentional release to the community or environment. The main objective of biosecurity is to prevent theft, loss or misuse of hazardous biological materials (SEMP, 2009).

Current and refresher training is an important aspect of biosafety for laboratory personnel who handle pathogens such as bacteria and viruses (ABSA, 2010). In general, laboratory personnel and maintenance personnel are trained by biosafety personnel in their own institutions. The training has to be documented and up to date as required by the CDC for high containment facilities. The BMBL is a good reference for designing laboratories for biosafety levels from 1 to 4. It provides guidelines for personnel protection and training to handle various biological agents for each of the four biosafety levels. Biosafety level 1 (BSL-1) encompasses research involving "well-characterized biological agents" not known to cause any disease in any healthy adult humans and which present a minimal hazard to personnel and the environment. Biosafety level 2 (BSL-2) involves research on biological agents that may be a moderate hazard to the health of laboratory personnel and the environment. Biosafety level 3 (BSL-3) includes clinical, diagnostic, teaching, research, or production facilities where research is conducted on unknown or exotic biological agents that may cause serious harm or a potentially lethal disease through the inhalation route. This level requires that laboratory personnel receive special training in handling pathogenic agents, and be supervised by personnel competent in handling infectious agents and associated procedures. Biosafety level 4 (BSL-4) is the highest containment level and involves research with dangerous biological agents that pose a highly significant risk of life-threatening

disease, aerosol transmission, or a related agent with an unknown risk of transmission. BSL-3 laboratories working on select agents must be registered with the CDC. Most public health facilities have BSL-3 laboratories to protect the laboratory personnel from accidental exposure and prevent release of pathogens to the environment (ABSA, 2010).

Biosecurity should be implemented at the institution or laboratory to prevent loss, theft or misuse of microorganisms that pose a biohazard to humans and animals. The risk could be minimized by limiting access to the facility where these biological agents are stored.

There is no zero risk. However, it is essential to minimize the risk of bioterrorism on a global scale. In order to achieve this goal, the US government has enacted regulations for domestic controls on the possession, use and transfer of "select agents," such as microorganisms and toxins that could be used as bioweapons e.g. anthrax and the bubonic plague.

Select Agent Program

The US government introduced the Select Agent and Biosafety Improvement Act in 2009 to amend the Public Health Service Act and the Agricultural Bioterrorism Protection Act of 2002 to reauthorize appropriations for the Select Agent Program (Open Congress). One of the provisions of the Act calls for the development of minimum standards for laboratory safety and biosecurity training of responsible personnel at high-containment laboratories.

The Department of Health and Human Services and the US Department of Agriculture have the primary responsibility for administering the Select Agent Program. Any institution having select agents on the premises needs to be in compliance with the safety and security standards for these agents. All individuals working with select agents must have an approved security risk assessment (SRA). In addition the laboratory must have a safety and security plan that establishes the policy and standard protocols to ensure the security of areas within.

Information on the select agent regulations (42 CFR Part 73, 9 CFR Part 121, and 7 CFR Part 331) is located at the national select agent website (www.selectagents.gov). Laboratories handling the select agents have to be registered with the Centers for Disease Control (CDC, 2011) or US Department of Agriculture (USDA) Animal Plant Health Inspection Service (APHIS, 2011). The law applies to any entity that possesses, uses, or transfers select agents or toxins. Any individual or laboratory that is not registered with either CDC or APHIS will be subject to a heavy penalty of $500,000 for the entity and $250,000 and/or imprisonment for up to 5 years for an individual.

Export Regulations on Dual Use Technology

The rapid advancement of biotechnology and nanotechnology in the 21st century will generate challenges for many governments and multi-lateral regimes. Export controls currently do not cover the current commercial applications of nanotechnology because the products that incorporate nanotechnology are not listed as dual-use items. The US government aims to promote research and advancing the technology and at the same time minimize the risk of misuse or diversion for nefarious purposes. The basic research and tools essential to fighting disease, protecting the environment, and improving agriculture are the same for producing biological weapons. Emerging new technologies pose a conundrum for many countries that are concerned

about bioterrorism and preventing these sensitive technologies from being used by terrorist groups.

How does the Federal government regulate dual use technology? The Export Administration Regulations (EAR) cover the export and re-export of dual-use items and technologies and is another way the Federal government has for minimizing risks for misuse. The primary agency for dual use export controls in the United States is the Bureau of Industry and Security at the U.S. Department of Commerce (BIS, 2011). Many microorganisms and toxins on the Select Agent List are also on the Commerce Control List (CCL). The CCL is a list that includes nuclear, biological and chemical controls for dual use commodities and technology. There are 10 categories that cover electronics, telecommunications, information technology, marine, aerospace industries as well as the chemical and biotechnology industries.

The CCL is found in Supplement No. 1 to part 774 of the EAR (EAR 2011).Dual-use biological agents, toxins and related technology are listed in Category 1 of the CCL, while biological, chemical processing equipment and related technology are listed in Category 2 of the CCL. The Commerce Country Chart is found in Supplement No. 1 to part 738, which explains the licensing requirements based on destination and reasons for control (Orr and Lee, 2009).

Most biological processing equipment including fermenters, cross-flow filtration devices, Class III biological safety cabinets, freeze-drying equipment and aerosol testing chambers are listed as controlled dual-use items on the CCL. Complete containment facilities at the biosafety level (BSL) 3 or 4 are also controlled. Pharmaceutical and biotechnology industries that manufacture vaccines and therapeutics rely on the bioprocessing equipment for their manufacturing processes (Lee, 2010). The same biological processing equipment could also be used by bioterrorists to produce bioweapons.

Many developed countries have export controls on certain types of designated dual-use technologies, and they are required by a number of treaties as well. These controls restrict the export of certain commodities and technologies without the permission of the government.

The Australia Group (AG) is a multi-lateral regime which consists of 41 members. The first meeting of the group was held in Brussels in June 1984 with subsequent annual meetings held in Paris. The AG is an informal forum of countries which seeks to ensure that exports do not contribute to the development of chemical or biological weapons. The main objective of AG members is to use export controls to ensure that exports of certain chemicals, biological agents, and dual-use chemical and biological manufacturing facilities and equipment, do not contribute to the spread of chemical and biological weapons (CBW). The AG maintains a control list of dual-use biological equipment, related technology and software (AG 2011). The control lists developed by the AG include equipment and technologies which can be used in the manufacturing or disposal of biological and chemical weapons. Export licenses of these items are required for most countries. The member countries of the AG maintain common control lists that are evaluated on a periodic basis to evaluate their effectiveness in promoting non-proliferation of chemical and biological weapons.

Member countries of the AG are parties to the Chemical Weapons Convention (CWC) and the Biological Weapons Convention (BWC) (AG 2011). The BWC was formed in 1975. The objective is to prohibit nations from developing, producing, stockpiling or acquiring biological weapons. There are currently 170 signatory countries to the BWC. Due to the nature of

biowarfare agents, the difficulties of evaluating compliance to the BWC are numerous (Grotto and Tucker, 2006). The AG aims to support the objectives of the BWC by enhancing the effectiveness of national export licensing measures. The scope of the export controls encompasses emerging threats and challenges posed by these threats. The AG's activities are limited to non-proliferation measures and do not help the commercial development of industries in member countries or to obstruct the legitimate economic development in other countries.

Synthetic Biology Challenges

The power of synthetic biology to synthesize whole genomes of microorganisms is impressive. Within the last few years, this emerging technology has had a wide ranging impact on society for revolutionizing medicine, biotechnology, pharmaceutical industry and environmental science at a breath-taking pace. The multidisciplinary nature of the technology also has the potential for misuse. The ease of synthesizing a pathogen or designing a new virus could be manipulated by bioterrorists to launch a biowarfare on an unsuspecting population. Accidental release of novel organisms could have devastating effects on the environment and agriculture as well.

The advent of gene synthesizing technology that is able to synthesize whole genomes in a short span of time poses a conundrum. This technology is available to amateur biologists as well as academic scientists. Complete sequences of bacteria and viruses are published and stored in publicly available databases. Anyone could order DNA sequences from these companies to create novel and synthetic organisms that may produce biofuels or recombinant therapeutic proteins for diseases that currently have no known remedies.

Currently, there are only a few companies that have the capability to synthesize genomes. The industry has two groups, International Gene Synthesis Consortium (IGSC, 2008) and the Industry Association Synthetic Biology (IASB, 2008), which have similar and overlapping recommendations to screen synthetic DNA orders for suspicious orders and self-governance. The IASB report emphasized that, "legislation for domestic orders is much more relaxed—both in the USA and the EU. Such legislation is much more focused on biosafety than biosecurity" (IASB, 2008). In addition, the harmonization of such guidelines is pursued through the formulation of a code of conduct by the IASB for the whole industry.

In March 2004, the US government set up the National Science Advisory Board for Biosecurity (NSABB) (NIH Office of Science Policy, 2011). One of the working groups of the NSABB focused on synthetic biology. In recognition of the risks posed by this emerging field of synthetic biology, an interagency group composed of various agencies of the Federal Government proposed a set of guidance for synthetic DNA providers.

In the case of synthetic biology, the government has recently published guidelines for the companies that are involved in this promising area of science. The Guidance report was released on Oct. 13, 2010, by the U.S. Department of Health and Human Services (FAS Blog, 2010). The primary goal in the guidance for synthetic dsDNA providers is to minimize the risk that persons with malicious intent will gain access to synthetic pathogenic organisms because they were created or modified with nucleic acid synthesis technologies, while at the same time minimizing any negative effects on the conduct of research and business operations. In the document, sequences of concern are identified as those unique to Select Agents and Toxins (CDC SAP, 2011). Sequences unique to pathogens and toxins on the Commerce Control List are also cause for concern in the case of international orders (EAR, 2011). The draft document offers guidance

to providers of synthetic DNA regarding the screening of orders so that these orders are filled in compliance with current U.S. regulations and to encourage best practices in addressing potential biosecurity concerns.

Synthetic biology provides significant benefits to scientific advancements. However, it is important for governments to work with industries in developing guidelines to help obviate the potential dual use capabilities of this technology. “This guidance is an important step in ensuring that synthetic DNA is used to promote, not threaten, public health,” HHS Assistant Secretary Nicole Lurie said in released remarks (FAS Blog, 2010).

The Synthetic dsDNA Screening Framework is a three-part screening process when a customer places an order to a synthetic DNA provider: sequence screening, customer screening, *and* follow-up screening*:*

a. Sequence screening will identify orders with “sequences of concern.” These sequences are whole or parts of whole sequences derived from the Select Agents and Toxins.

b. Customer screening is one of the primary step which verifies the individual or organization where the order originates. This step will identify potential “red flags” of suspicious individuals. Both sequence and customer screening could be done simultaneously.

c. Follow-up screening is strongly recommended if customer screening and/or sequence screening raises a reason for concern. It is recommended for verifying the legitimacy of the customer and stated end-use purpose.

The Guidance is adaptable to international usage. Although it is not possible to completely prevent misuse, the Guidance will minimize the potential risks posed by bioterrorists. Synthetic DNA providers are encouraged to use screening procedures when they received any orders from customers (FAS Blog, 2010). The process provides another mechanism of oversight for this promising dual use technology.

In May 2010, President Obama called for a bioethics commission to study the potentials and risks of synthetic biology, after researchers from the Craig Venter Institute reported in the journal *Science* that they had inserted a man-made genetic sequence into a bacteria, which then reproduced with the new genes (PCSBI, 2010). On requesting this review, Obama said "It is vital that we as a society consider, in a thoughtful manner, the significance of this kind of scientific development." The report makes 18 recommendations, 12 of them recommending White House coordination of "vigilant" monitoring and oversight of the field in various ways, starting with a funding review by 2012 (USA Today, 2010).

Conclusions

In summary, the US government is recommending a graded implementation of protection based on a risk management assessment (Salerno, 2006). Research with pathogens will involve some level of biosafety and biosecurity risk. Regulations should be balanced to minimize the inherent risks and not prevent legitimate research in infectious disease or vaccine development.

In the case of biosafety, physical protection includes the four biosafety levels appropriate for each pathogen to prevent accidental release of the biological agent. Where biosecurity is

concerned, physical protection includes graded protection from theft and misuse by limiting access to areas such as secured areas, exclusion areas and personal property areas. Both biosafety and biosecurity require material control and personnel reliability. In addition, transfer of pathogens domestically and internationally has to conform to Federal regulations such as the CDC's SAP and Commerce's EAR.

Multilateral regimes, such as the AG, have export controls in place for dual use technologies that have legitimate uses but could be misused for biowarfare purposes. The same biological processing equipment and technology used in the production of a vaccine or therapeutic protein could be used to grow a novel pathogen to terrorize an unsuspecting population. The consequences could be disastrous if the human or animal population has no immunity. With the rapid advance of biotechnology, nations have to be vigilant and regulate dual use technologies.

Similarly, it is essential for life science research that any regulations should be balanced so as not to hinder the free exchange of knowledge and innovation due to the global nature of science. Therefore, educating the scientific community and the public about the promise and dangers of dual use technology is an important outreach activity that the US government should encourage.

(Disclaimer: *The views and opinions of the author expressed herein do not necessarily state or reflect those of the United States Government.*)

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