Mitigating Security Issues in the Evolving DNA Synthesis Industry

by

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B.A. Economics
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Submitted to the Engineering Systems Division in Partial Fulfillment
of the Requirements for the Degree of

Master of Science in Technology and Policy

at the

MASSACHUSETTS INSTITUTE OF TECHNOLOGY

June 2013

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ABSTRACT

DNA synthesis technologies are advancing at exponential rates, with production of ever longer, more complex, and less expensive sequences of double stranded DNA. This has fostered development of industrial scale design, construction, and sale of synthetic DNA. The tools and methods of synthesis used to create beneficial genetic material can also be used to construct dangerous pathogens.

To prevent unknown actors from ordering potentially dangerous genetic material, the largest DNA synthesis firms formed two industry associations that require members to screen the DNA sequences ordered and the customers ordering sequences. The firms also worked with the U.S. Health and Human Services to formulate voluntary screening guidelines for synthetic double stranded DNA. As DNA synthesis technology advances and diffuses, this centralized voluntary approach may become less effective.

This thesis identifies strengths and weakness in the current voluntary regime and offers recommendations to improve security in the DNA synthesis industry. It describes the origins and current status of DNA synthesis technologies and the structure of the DNA synthesis industry. Then, it describes the formation of voluntary screening consortia and the U.S. and international guidelines that address security issues in DNA synthesis. Finally, this thesis compares DNA synthesis with other potentially “dual use” technologies, concludes that regulatory approaches may not enhance security in this area, and suggests that governments should focus on education and outreach.

Thesis Supervisor: Kenneth A. Oye

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Acknowledgements

This two-year journey, culminating with this thesis, would not have been possible alone. I would especially like to thank:

My research sponsors, the Synthetic Biology Engineering Research Center, the National Science Foundation, and the Alfred P. Sloan Foundation: You have allowed me to study, perform research, and live the graduate student lifestyle here at MIT. This work would not have been possible without your generous support.

My research supervisor and mentor, Ken: Thank you for all of the support and guidance you have given to me over the past two years. The opportunity to work with you and your research group has been an honor.

Shlomiya Bar-Yam, Kelly Drinkwater, Julie McNamara, and Robert Reardon: Thank you for being such great teammates in our working group, and for offering invaluable assistance with my thesis. Your contributions and willingness to discuss and brainstorm have made this a much higher quality project.

Melanie: Thank you for your love, support, and the many revisions to this and other projects over these past two years.

My mother and father for all of the support and love you have given me. This education would not have been possible without you. I hope my life choices will make you proud.

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1. Introduction

Deoxyribonucleic acid (DNA) can be considered the instruction manual for all life on earth. Francis Crick, James Watson, and Maurice Wilkins discovered its structure in 1951, the double helix. DNA is naturally formed, created, and replicated in living cells. It is composed of specific base nucleotides[1] that can create genetic information when placed in certain sequences and lengths. This genetic information is linked together as genes. These genes code for different amino acid sequences that, in turn, combine together in different ways to form different proteins. Genes also include DNA sequences that notify the cell when and when not to code proteins. Proteins transfer the information stored in the DNA to actual actions by the cell and its components. In the human body, there are an estimated 150,000 individual genes that code for a specific amino acid sequence (Human Genome Project, 2013).

The chemical synthesis of DNA began in the early 1950s. In the mid 1980s, genes that code for DNA replication proteins were isolated from natural bacteria living near thermal vents. The isolated genes allowed for the rapid replication of DNA in high temperatures. This led to the creation of a process known as Polymerase Chain Reaction (PCR) (Baker, 1992). PCR allowed for a very small amount of genetic material to be quickly and accurately copied millions of times. While the DNA created by PCR was not completely synthetic, the ability to replicate millions of copies of a very small amount of DNA allowed for the creation of more powerful, completely automated synthesizers.

Today, DNA that is not isolated from a living cell, but is created through the use of modern DNA synthesizers, is termed synthetic DNA. This DNA is often created by large DNA synthesis companies and is often synthesized with its base pairs following an exact order that a researcher requests. A computer can now build specific DNA sequences of varying lengths (Gibson, 2010). To supply

[1] There are only four nucleic acids in DNA: adenine, guanine, thymine, and cytosine.

researchers and companies with synthetic DNA, an industry has been created that is constantly producing faster, more automated, and more complex synthesis machines.

This automated synthesis accelerated development of different biotechnologies. Many leading supporters and practitioners of genetic engineering and synthetic biology, including George Church, Drew Endy, and Bill Gates, believe that biofuels, medical advances, bioremediation, and other applications are the next frontier in genetic engineering. Biotechnology could be the defining technology of the 21st century, much like microchips and computers were for the 20th century.

1.1 The Challenge of DNA Synthesis as a Dual Use Technology

For all of the benefits DNA synthesis may provide, there are security issues in the global DNA synthesis industry. DNA synthesis is a dual use technology. A dual use technology refers to materials, hardware, and knowledge that have peaceful applications but could also be exploited for harmful purposes (Tucker, 2012). Other examples of dual use technologies include nuclear technologies that are able to produce both nuclear power and nuclear weapons, chemical technologies that are able to provide for a chemical industry and chemical weapons, and missile technologies that are able to launch satellites into space, and send warheads to targets around the world.

There are several similarities and differences between DNA synthesis technology and the technologies listed above. With advances in the automation and accuracy of DNA synthesis since the 1980s, it is now possible to construct entire genes and microbial genomes[2] from off-the-shelf chemicals. This raises a number of security concerns. Someone could order a gene sequence coding for a dangerous pathogen and then perform a few low skilled steps to create a dangerous, self-replicating microbe. This ability to create a dangerous pathogen

[2] Bacteria and other microscopic organisms and their associated DNA.

with little training in genetic engineering has been improved with the use of computers to forward design[3] genetic components. This ability to forward design has led to the creation of the commercial suppliers we see today. These commercial suppliers exist not only in the U.S., Europe, and Japan, but also in the developing world, including countries in Asia, South America, and the Middle East. Many of the current major suppliers in this emerging field are based in the U.S. and Western Europe, where much of the biotechnology boom started. However, both China and India, along with other developing countries, are investing heavily in their own biotechnology sectors (Larson, 2013).

As the industry currently exists, the largest U.S. and European companies belong to one of two voluntary consortia. These organizations set standards and protocols for screening synthetic DNA orders. The screening seeks out dangerous DNA sequences, which can include parts that can code for dangerous genetic parts. These dangerous parts would include the genetic sequences that make microbes like smallpox, plague, and Ebola virus so virulent. Many of the largest U.S. and European synthesis companies have voluntarily incorporated these safety precautions into their business practices. In addition, members of these consortia also screen their customers. This screening attempts to prevent shipments to customers that should not be working with synthetic DNA.

Currently, emerging economies that are developing DNA synthesis industries are not always taking strong precautions to screen potential customers. This is a negative security externality that is not accounted for in existing markets. This externality leads to a lowered level of security for everyone. Any single synthesis company that does not screen its orders could allow an unknown and potentially dangerous order to be created and shipped. This would make all of the precautionary practices by other companies nearly irrelevant, as a nefarious

[3] Forward design: the ability to engineer a system from the ground up by designing all the components before you begin to build them.

actor could simply order dangerous genetic elements from a company that does not screen orders.

Tools and strategies that have been used for other dual use technologies may be studied as a starting point for addressing this externality. However, these tools and strategies may face issues when directly applied to DNA synthesis technology. Many of today's existing security measures were created before a synthetic DNA industry had developed, so security efforts need improvement.

1.2 Research Questions

This thesis addresses the following questions:

- What is DNA synthesis?
- What is the DNA synthesis industry and how did it develop?
- What are current national and international security measures and how did they come to exist?
- What are some technologies that DNA synthesis can be compared and contrasted to?
- Where is the DNA synthesis industry headed?
- What are some policies to encourage the secure development of DNA synthesis technologies?

1.3 Thesis Structure and Organization

This thesis seeks to study how the DNA synthesis industry developed, examine the current standards for security in the DNA synthesis industry, and suggest a number of different policies that would allow the international DNA synthesis industry to develop while mitigating its associated security issues.

This framework will consider the many sides of the DNA synthesis industry and its industrial structure, including the current state of safety and security practices, the growth of DNA synthesis companies in emerging economies, and where the

DNA synthesis industry is headed. In addition, this thesis will examine how the current industry players could possibly use regulations to capture more of the market and prevent new players from entering the market and increasing competition.

To achieve its objective, this thesis will:

Provide a background on DNA synthesis and the current DNA synthesis industry. DNA synthesis has become increasingly automated since the mid-1980s. This rise in the automation of DNA synthesis was coupled with a rise in genetic engineering. This thesis will describe the history of DNA synthesis technology and its current capabilities. It will also describe how the technology's development led to the establishment of a multi-company network of large DNA synthesizers.

Describe the industrial structure of the DNA synthesis industry. The current DNA synthesis industry is dominated by a few large players based mostly in the U.S. and Western Europe. However, large companies from emerging economics are entering the industry, along with start-up companies in the U.S. whose new technologies threaten to change the existing industry. These large players will be compared to smaller players that can process less complex orders with a faster turnaround time.

Describe the current DNA synthesis security regime and how it was established. A series of public incidents motivated the largest DNA synthesis companies to join together and establish a voluntary consortium. However, not all companies joined this consortium and a handful of very large companies established their own consortium with similar standards. The actions that led to industry and regulatory reflection and the creation of the two competing screening consortia are described in this chapter.

Describe existing U.S. and international frameworks for biological security. There are a series of existing international agreements that are designed to inhibit the production of dangerous biological pathogens. These existing agreements include the United Nations Biological Weapons Convention, the Australia Group, and the United Nations Resolution 1540. In addition, there are a series of U.S. guidelines established after the the September 11 terrorist attacks, and the 2001 Anthrax attacks that attempt to provide guidance to suppliers of synthetic DNA.

Describe the dual use nature of DNA synthesis technologies in relation to other dual use technologies. DNA synthesis is similar in many respects to other industries that have great benefits, but it can also be manipulated to serve militant and dangerous goals. By comparing and contrasting DNA synthesis to these other technologies, we will be able to better predict where DNA synthesis technology may go in the future and study the effectiveness of security policies.

Predict where DNA synthesis technology and the DNA synthesis industry are going. In recent years, smaller and cheaper synthesizers gained speed and accuracy while decreasing costs. This has led to the advent of the powerful desktop synthesizer. This dispersion of synthesis ability will require further study on how more centralized regulatory policies will affect security in the DNA synthesis industry. With the advancement of these technologies, some firms and laboratories are bringing their DNA synthesis in house. This means that they will create the synthetic DNA themselves instead of sending orders to the large existing DNA synthesis companies. This could be done for a number of reasons including projected cost savings and quality control (Miklos et al., 2012). This chapter will provide an introduction to what these technological and industrial shifts may mean and how they will affect current and future security policies.

Discuss the International Genetically Engineered Machine Competition (iGEM) as a case study in adaptive security management. The iGEM

competition began with five U.S. based teams in 2003. In 2013, it had participants from over 200 countries. The competition is open source, and has devoted resources to its safety and security procedures and outreach programs. The iGEM Safety Committee has found gaps in the existing security structure, and has worked to address the gaps quickly and in an open manner. iGEM's Safety Committee's recommendations serve as a case study to successful adaptation regarding safety and security gaps.

Describe several policy recommendations and their possible implications. This thesis will conclude with several policy recommendations to mitigate the emerging security concerns in the international DNA synthesis industry. This will include the use of the International Genetically Engineered Machine Competition as an example of a voluntary and international system that uses adaptive regulation in response to changing technology.

2. DNA Synthesis and DNA Synthesis Industry

This chapter explores the development of DNA synthesis, focusing on the period since the 1980s where the merging of advanced synthesis techniques and computer aided design allowed for rapid advancement in the length and complexity of the synthesized DNA. The decreasing costs and increasing abilities of DNA synthesis will be examined. In addition, the DNA synthesis industry will be described with a focus on the development of the current system.

2.1 Overview of DNA

"DNA is like a computer program but far, far more advanced than any software ever created." – Bill Gates, co-creator of Microsoft

DNA is a long, stable molecule in the form of a chain polymer. It consists of four different units called nucleotides. All four nucleotides have sugar and phosphate groups that are shown in the red boxes in Figure 2. The other part of the nucleotide structure, known as the base, is shown in the blue boxes in Figure 2. These bases are divided into two groups with two nucleotides in each group. The pyrimidines (thymine and cytosine) have one six-membered ring containing a nitrogen atom. The other group called purines (adenine and guanine) has a double ring instead (Berg, et al., 2006). These nucleotides line up as pairs: as shown in Figures 1 and 2, adenine (A) pairs with thymine (T), and cytosine (C) pairs with guanine (G). Together, these groups form a ladder-like structure with the bases forming rungs on the inside and the sugar and phosphate groups forming the vertical shell on the outside. This ladder naturally twists, forming the double helix of DNA, as shown in Figure 1.

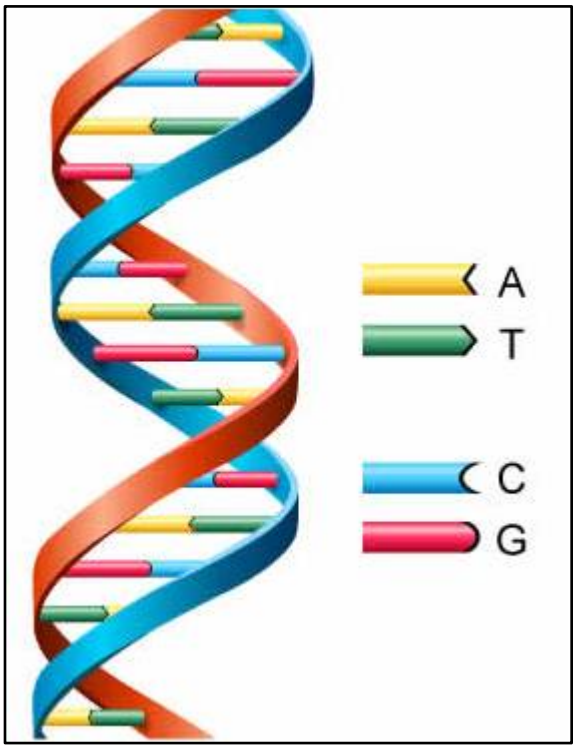

Figure 1: DNA Double Helix structure, (Nature Biotechnology, 2004)

A six-membered-ring base always pairs with a double-ring base, so the spacing between the two strands of DNA is maintained throughout the length of the molecule, and the overall shape of the molecule is the same regardless of the sequence or the length (Berg et al., 2006). In addition, the "frame" of the structure remains consistent. This repeated pattern of sugar-phosphate groups (the red boxes in Figure 2) creates a uniformity that makes it possible to automate the synthesis of DNA. Because of this constant frame, the chemical reaction required to combine the bases does not change. The DNA sequencing command then reduces to using the right nucleotide building blocks in the right order (Berg et al., 2006).

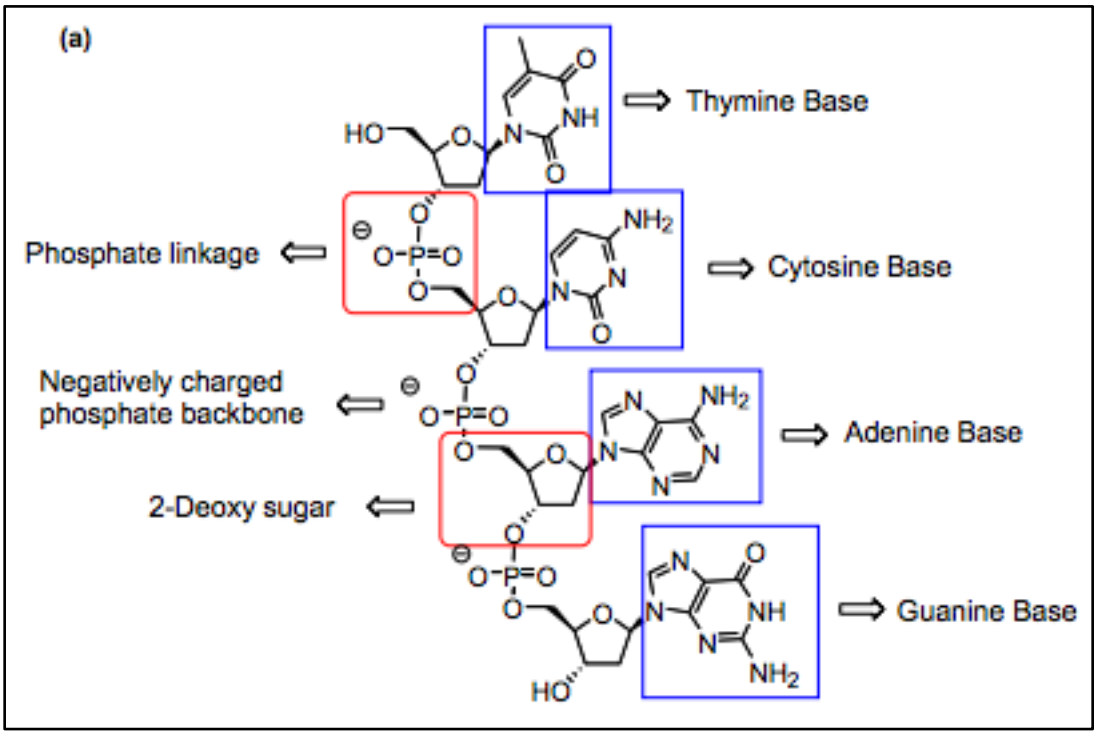

Figure 2: DNA structure is an example of the four bases forming a short single-stranded segment of DNA (Sanghvi, 2007)

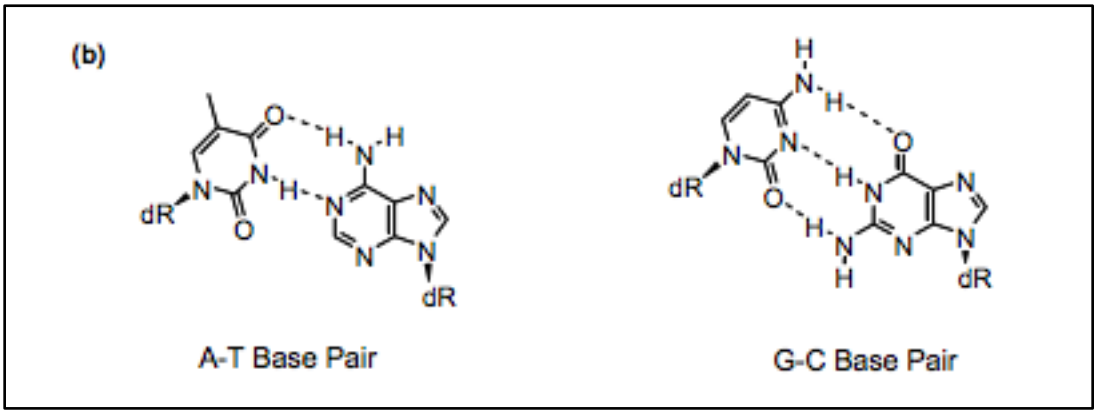

Figure 3: Base pairs create a double helix when chained (Sanghvi, 2007)

2.2 History of DNA Synthesis

The ideas underpinning DNA synthesis were formulated more than 150 years ago in Germany. In 1869, Friedrich Miescher isolated nuclein from pus cells recovered from hospitals. In 1889, Richard Altman purified nuclein by removing the proteins from the structure: he called this product nucleic acid. In 1900, Albrecht Kossel studied the chemical composition of nucleic acids and found that

they contained only four bases: adenine, cytosine, guanine, and thymine (Mohr, 2013).

In 1955, the first chemical synthesis of a DNA molecule was completed. By 1976, the longest reported synthesis of a DNA segment was only 126 base pairs long. This project took 8 years to complete. Today, the same DNA segment can be made in minutes using an automated DNA synthesizer (Sanghvi, 2007).

The first commercial DNA synthesizers were built and sold in the early 1980s by Applied Biosystems (Applied Biosystems, 2006). They were simple devices that could construct one DNA sequence at a time on a very small scale.

2.3 Creating a Desired DNA Sequence

Today, the assembly of a desired sequence of DNA starts with the creation of what is termed an oligonucleotide or a "short oligo." An oligonucleotide is an assembly of several nucleotides into a medium length strand of DNA, generally less than twenty base pairs. This process is done using automated solid-phase synthesis. In this process, the chain of nucleotides is built on a bead, one by one, and washed in between each new nucleotide addition (Sanghvi, 2007).

There are a number of instruments on the market that have the capability to produce hundreds or thousands of DNA sequences in parallel.[4] The Applied Biosystems model 3900 DNA synthesizers can use 384-well plates, constructing a different sequence in each well (Springer, 2006). Some companies have specialized further. Illumina has adapted a well plate technique to create large synthesizers with many platforms, each carrying 384-well plates (Sanghvi, 2007). In addition to becoming faster and more powerful, modern synthesizers have become increasingly cheaper and more ubiquitous. The advancement of DNA synthesizers is shown in Figure 4 where the Automated sequencers from 1985,

[4] This means many different strands of DNA can be constructed at the same time.

1997, 2005, and 2011 are shown side by side for comparison. The number of DNA synthesizers available for purchase on eBay and other low cost websites shows the diffusion of technology due to this trend in increasing capabilities and falling costs (Madrigal, 2007).

Figure 4: Applied Biosystems DNA synthesizers in 1985, 1997, 2005, and 2011 from left to right (Applied Biosystems, 2013)

In addition to these available technologies, many companies are in the process of developing, patenting, and licensing new DNA synthesis technologies that are faster. Gen9, based in Cambridge, MA, claims to be developing a DNA synthesis facility that will eventually have the same sequencing capacity as one-third of the world's current DNA synthesis capacity (Goldberg, 2013). However, without seeing evidence of this sequence capacity, it is difficult to determine if this claim is an exaggeration.

2.3.1 Rising Capabilities and Falling Costs

Research by Rob Carlson, a biotechnology professor and biotechnology consultant, has shown that DNA sequencing technologies have been advancing at a rate that outperforms Moore's Law. Moore's law states that processing power for computers will double roughly every two years at the same cost. The parallel would be the ability of DNA synthesis to double every two years at the same cost. The rapid advancement of DNA synthesis ability is shown in Figure 5. This is coupled with Figure 6, which shows the rapidly falling costs of synthesis.

Figure 5 is a graph of DNA sequencing ability (Exponential scale on the Y-axis) over time (X-axis). Sequencing ability is shown in yellow. Starting in 1990, it shows that the global DNA synthesis community's ability to create synthetic DNA has grown exponentially since 1990. The increase continues with the introduction of the Capillary sequencer in 1998 and the second-generation sequencers developed in 2005. Rob Carlson stops the DNA synthesis estimate in 2008, citing that no new synthesizer technologies have been commercialized since then (Carlson, 2013). The scale of the Y-axis in Figure 5 shows the number of base pairs that can be synthesized per worker per day.

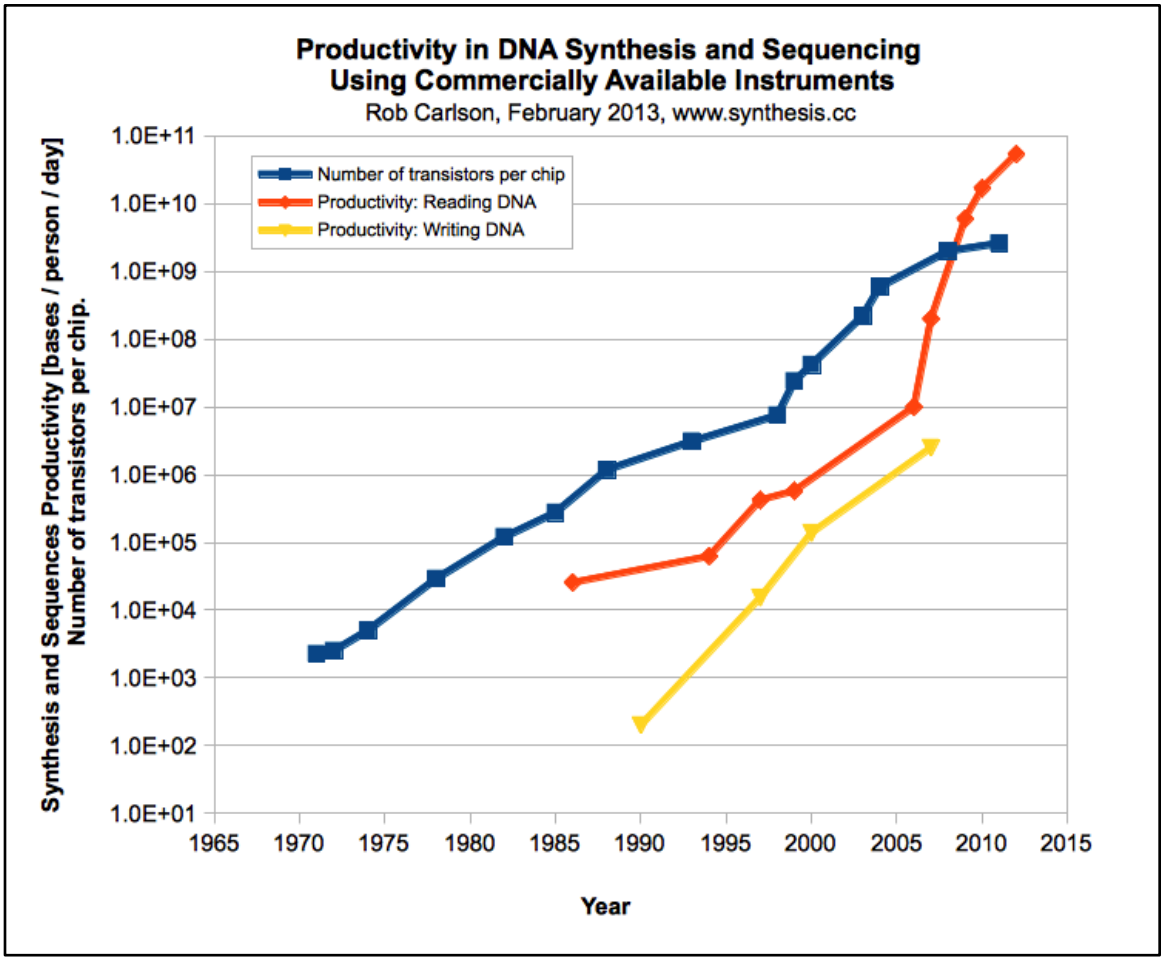

Figure 5: DNA synthesis capability over time (note the exponential scale on the Y-axis) (Carlson, 2013)

Figure 6 shows the decrease in the cost of DNA synthesis, both in terms of short oligos (shown in red) and full-length genes (shown in yellow). From this figure the costs of synthesizing DNA has dropped by more than two orders of magnitude in less than a decade. Carlson predicts that DNA synthesis will change very soon, based on his personal conversations with industry players and based on the fact that the industry is using chemistry techniques that are several decades old (Carlson, 2013).

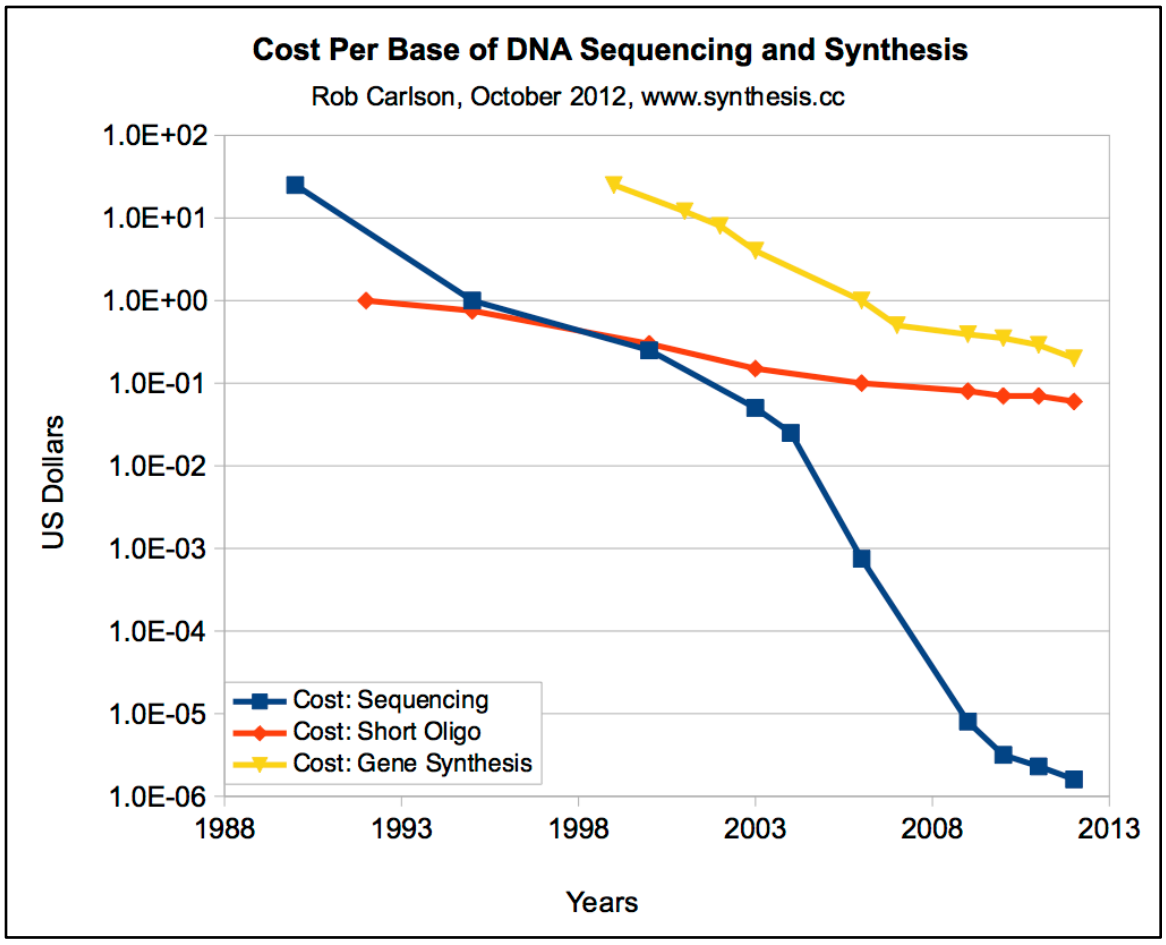

Figure 6: Cost per base of DNA sequenced over time (note the exponential scale on the Y-axis) (Carlson, 2013)

Carlson also predicts that breakthroughs in sequencing technology will not necessarily be followed by an increase in demand. This is because there is currently little need for more synthetic DNA than maximum production. Currently, synthetic circuits are simple and consist of a relatively small amount of DNA.

However, he states, “the market dynamics of biological technologies will remain difficult to predict precisely because of the diversity of technology and the difficulty of the tasks at hand. We can plan on prices going down; how much, I wouldn't want to predict” (Carlson, 2013).

2.4 The Current DNA Synthesis Industry

“As the market for DNA on demand continues to grow, increases in the scale and efficiency of new genome engineering approaches promise to accelerate product discovery and even open up new commercial opportunities.”

Mike May, writer for Nature Biotechnology

The cost of DNA synthesis has dropped and the ability of large sequencers has increased over time. However, due to reliability issues and general economies of scale, most DNA synthesis is carried out in large facilities that provide one or more services to the biological and biotechnology communities (Bugl et al., 2007).

The core of the DNA synthesis industry is generally separated into two groups that perform slightly different functions. The first group consists of generally smaller companies that provide short fragments of DNA material using non-proprietary techniques and tools. These fragments are generally fewer than 200 nucleotides in length. These smaller sequences are used in research and are often combined further in laboratory settings. The second group contains companies that provide longer fragments of DNA. These DNA fragments are usually greater than 200 nucleotides in length and can code for whole genes and even the majority of DNA material coding for single celled organisms (many thousands of genes in length).

As interconnected as these two groups are, they differ in terms of their maturity (Bugl et al., 2007). The first group that specializes in short oligo production is considered a mature industry. The process is fast and supplies a commodity

service to various (usually, local) markets. The industry does this with low costs and delivers often in fewer than 48 hours (Bugl et al., 2007). This industry is facing competition from small capacity desktop synthesizers that are now commonly found in academic labs and can be purchased online (Madrigal, 2007). However, many researchers will still order through these providers, as they are better able to exercise economies of scale. The second group is a less mature industry. Designing and constructing gene length sequences of DNA is still in its infancy when compared to short oligo construction. The technological demands of gene length sequence construction increase the price of these sequences. However, there is still a large demand for a number of gene length and greater constructs by large industrial consumers. Many of these customers are large pharmaceutical companies (Bugl et al., 2007).

An example of the development and spread of DNA synthesis technologies and capabilities is in China. BGI (formerly Beijing Genomics Institute) runs more than 100 of the most powerful DNA synthesizers available today (Callaway, 2011). In addition, BGI runs 150 next generation sequencers. Combining these technologies with other advanced tools (such as cloud computing) BGI is creating a “one stop shop” for DNA synthesis. David Dooling, a bioinformatician at the Genome Institute at Washington University in St. Louis, thinks that BGI’s eventual creations of a tool to cover all stages of DNA synthesis makes sense as those who are working on gene research become less experienced as the technologies diffuse. In addition to the creation of a “one stop shop” he thinks that vertical integration, or companies combining with each other at different stages of the production chain, will be one way that DNA synthesis firms continue to evolve (Callaway, 2011).

2.5 Future Advances and their Security Implications

This chapter provided general background knowledge about DNA, DNA synthesis, and its commercial industry. In addition, it described the accelerating progress of DNA synthesis capabilities and how some researchers predict that

this trend will continue to accelerate. This will greatly increase our ability to use automated DNA synthesis to create longer and more complex DNA sequences more rapidly. At the same time, it is clear that the cost of producing these synthetic DNA sequences is quickly falling.

The pace of advancement of DNA synthesis technologies makes it difficult for a static form of regulation to enhance security for any length of time. At this point, how DNA synthesis technology will advance and who will be at the forefront are continually changing. With this in mind, it would be more advantageous to have minimal government interference in the security regulation of DNA synthesis. This would allow industry and practitioners to have a stronger voice in how the security regime evolves and would enable speed, flexibility and rapid change. In the long run, such a system will be more effective than rigid security mandates passed through government agencies.

3. Industrial Structure of the DNA Synthesis Industry

Early DNA synthesis companies were located near Boston, MA and San Francisco, CA (Penhoet, 2013). By the end of 2013, gene synthesis will be an estimated $2.4 billion global industry (May, 2009). There are now dozens of gene synthesis companies that exist all over the world. The world's largest producer of custom synthetic DNA is currently Integrated DNA Technologies (Cevanaux, 2013). In addition to the international diffusion of gene synthesis technology and companies producing synthetic DNA, there has been a separation in the industry itself.

In 2010, the J. Craig Venter Institute (JCVI) constructed a 1.08-mega base pair synthetic genome that contained more than one million bases. It is the largest synthetic DNA construct created to date. This synthetic genome was placed into a host cell that had its genetic material removed and created a viable cell.[5] They constructed this synthetic genome[6] with help from Blue Heron Biotechnologies (Gibson et al., 2010). The construction took several years, and companies like JCVI and Blue Heron Biotechnologies developed new techniques to create the large genome.

However, many labs do not need very large DNA constructs. Instead, they need smaller constructs in a faster time frame than that offered by a large DNA synthesis company. Labs often test the efficacy of smaller constructs to be sure they are functioning as designed, and then test these larger constructs for further research.

[5] A viable cell is a cell that functions as a life form. It is capable of sustaining itself and replicating.

[6] All of the organism's hereditary information, in this case the *Mycoplasma mycoides* genome, was inserted into the nucleus of a *Mycoplasma capricolum* cell (Gibson et al., 2010).

Small companies collect DNA orders for small oligonucleotides and can often deliver the orders overnight (McMurry, 2013). This is much faster than the time it would take for a larger company, where it could be weeks.

Figure 7 shows the globalization of the gene synthesis industry in 2007. Western countries, India, China, Iran, South Africa, and others are expanding their gene synthesis ability. The figure today looks similar, with additional consolidation of larger companies and a rise in smaller companies (Carlson, 2010).

Figure 7: Commercial gene-synthesis providers, circa 2007 (Carlson, 2010)

3.1 The Large Firms

Larger players in the DNA synthesis industry compete with one another. Even though the DNA synthesis technology and techniques have improved over the past few years, the assembly of large DNA circuits is still a technological challenge (Carlson, 2013). This challenge suggests that companies will gain advantage over one another by having newer, faster, and more accurate DNA synthesizers with larger capacity. Larger players work with licensed and patent protected technologies.

A recent example of newer technology is the DNA synthesis technology under development by Gen9, based in Cambridge, MA. The technology, know as BioFab, allows for very rapid and accurate construction of DNA material (Weintraub, 2012). The company aims for a four-week turnaround time for large constructs (Goldberg, 2013). This type of rapid technological advance leaves large firms at risk of being left behind by their competitors.

3.2 The Small Firms

Smaller players are able to survive due to the need for rapid turnaround times for smaller synthetic DNA constructs. Companies and laboratories doing research on many different DNA constructs need multiple copies of a smaller construct (Gibson et al., 2010). These buyers often prioritize rapid turnaround time over strict quality control, in order to test as many DNA sequences as possible (McMurry, 2013). These companies coexist with the larger firms because many of the technologies and techniques that are used to construct smaller oligonucleotides are no longer under patent protection. These technologies include techniques and technologies like PCR. These smaller companies are able to work in local markets to provide rapid turnaround of shorter DNA sequences.

3.3 New Firms and Sources of Synthetic DNA

DNA synthesis technologies are rapidly advancing in capability, market placement, and geographic location. This means that today's industrial structure may not be the same in ten years or even in five years.[7] DNA synthesis companies are being created in U.S., Europe, and developing countries. Many of them are being designed as national champions (where national resources are devoted to creating one large firm in the country to compete overseas) or using

[7] One theory is that the gene synthesis industry is transitory; the technology will become so cost effective and widespread that large companies will no longer be needed for their expertise (Carlson, 2009).

newly developed proprietary technologies that threaten to make older technologies obsolete in the industry.[8]

An example of this phenomenon is Singapore focusing a large amount of resources toward establishing a high value biotechnology hub in South East Asia (Arnold, 2003). The payoff of this government investment is currently unknown, and it may take years before Singapore gains a return on its investment. Currently, Singapore is struggling to fill many of the labs and offices it has constructed for biotechnology firms.

3.3.1 BGI as an Example of a Country's Champion

Developing nations are devoting resources to build their own biotechnology sectors including funds for DNA synthesis technology development.

China's BGI (formerly the Beijing Genomics Institute) is currently one of the world's largest DNA synthesis and sequencing firms. BGI has already developed a name for itself internationally, and has been employed for several high profile sequencing and screening operations in China, including sequencing the Severe Acute Respiratory Syndrome (SARS) genome (BGI, 2013). Some U.S. officials are concerned that as BGI acquires other companies and collects more information, the knowledge might not be used properly (Abraham & Wheeler, 2012). The U.S. government first became concerned when BGI bought 128 synthesizers from Illumina, based in San Diego. At the time, these synthesizers were the most powerful in the world. In 2012, BGI purchased the company, Complete Genomics of California. This gave them access to over 30,000 whole human genomes (Flinn & Vance, 2012). This is 10 times more than any other company. This move by BGI also prevents the market for DNA synthesizers (where Illumina is a major player) from becoming even more concentrated.

[8] These include firms such as BGI in China or Gen9 in Cambridge, MA.

BGI is one of many DNA synthesis firms in emerging economies. There are DNA synthesis companies scattered all over the world from Bioserve Biotechnologies in India to The Zilinski Institute in Russia (Carlson, 2011). There are other entities in countries that the U.S. has limited official contact with, including Iran. In 2010, undergraduate students at the Tarbiat Modares University in Tehran requested to join the iGEM competition. Due to U.S. export controls and possible scrutiny from the U.S. government, iGEM decided not to allow this team into the iGEM competition (Rettberg, 2012).

3.3.2 Gen9's Advances as an Example of Rapidly Changing Technology

Gen9 is a company started and partially owned by three pioneers in genetic technologies and research: George Church, Joe Jacobson, and Drew Endy. Gen9 is already a member of the IGSC, and already screens their customers and their customer's orders for dangerous sequences. The company has not publicly released its technologies, but several patents have been granted and several more are on the way. The company claims to have developed a chip-based technology that will increase the speed and accuracy of DNA synthesis. They claim that the company's new facility in Cambridge, MA will increase global DNA synthesis capacity by one third (Goldberg, 2013).

3.4 University Laboratories

In addition to companies, there are several hundred laboratories across the world that can construct synthetic DNA. These facilities rarely construct genes for outside use, but we cannot rule out that such laboratories would not do so in the future (Maurer, et al., 2009).

3.5 The Industry's Reasons for Voluntarily Screening

The DNA synthesis industry has become stratified by the size of the industry players. Large firms compete with one another using proprietary tools and technology. They are often able to operate with larger margins because they have the technology and expertise to create large DNA constructs (Carlson,

2009). This contrasts with the smaller, localized firms who cater to a local clientele who know and trust them. For smaller firms, their tools and techniques are not proprietary and their margins for each delivery are smaller than those of the larger firms. Falling prices due to large firms' economies of scale may drive small firms out of the market, but many small synthesis companies continue to survive in localized markets where turnaround time is key (Maurer et al., 2009).

3.5.1 Customer Pressures

Customers of synthetic DNA are concerned about price, which is evident in the competition between synthetic DNA providers to provide the highest quality DNA at lower prices than their competitors. Even if screening only adds a small cost to each order, smaller firms may find it difficult to retain their customer base. Their customers can easily switch to another firm (with less rigorous screening procedures) or might even bring the work in-house. This is less of a problem for larger firms, because it is easier for them to transfer the screening costs to their customers due to less competition stemming from proprietary technologies and techniques. In addition, some substantial customers of the larger DNA synthesis firms expect good corporate governance from their suppliers. AstraZeneca, a British pharmaceutical company, does not order synthetic DNA from suppliers that do not follow the ISAB or IGSC codes (AstraZeneca, 2008). Such actions from the largest customers of DNA synthesis firms further encourages them to apply the voluntary standards.

For customers in Asia, purchasing certain types of synthetic DNA from U.S. suppliers, can be difficult. If a reputable company or researcher outside of the U.S. wishes to purchase a "dual-use gene," a gene from an organism that is on an export control list, then the DNA synthesis company must license the order. This process itself can take up to eight weeks and can add a large cost to the order. This system is likely to encourage buyers outside of the U.S. and EU to purchase their synthetic DNA in their own countries even if the price is higher,

quality is lower, or the screening methods are not as rigorous (Maurer et al., 2009).

3.5.2 Legal Liability

Currently, large firms are using the voluntary screening consortia, and their use is encouraging newer and smaller companies to join as well. Some of these firms are motivated by the fear of legal liability. If a company's product is used in a weapon, attempted attack, or even an accident by an untrained scientist, the company may be found legally liable. Firms are likely to join a voluntary best practices regime if they receive legal protection.

Customer confidentiality is another issue. Customers who have a strong interest in the intellectual property of their DNA sequences will likely be concerned about having a third party screen and synthesize their work. In addition to the screening and synthesis, many companies might be concerned that their DNA sequence orders are also being stored for eight years (see IGSC Harmonized Screening Protocol in Appendix B).

3.6 Drawbacks of the Voluntary System

The structure of the DNA synthesis industry makes traditional regulation difficult. In addition to stifling an emerging industry, regulation would likely be marginally effective. Hard rules would put firms that operate on thin margins out of business, and expensive export controls encourage overseas customers to use overseas providers, who might not use proper screening. Even if only a small handful of firms provide synthetic DNA without screening, the whole system is at risk. Nefarious actors could simply use a supplier who does not screen orders.

4. Construction of the Current DNA Synthesis Regime

This chapter seeks to describe the current DNA synthesis security regime and how it was established. It begins by describing the first conference on recombinant DNA ethics and safety, the Asilomar conference in 1975. It then describes a series of experiments and public mishaps that motivated the largest DNA synthesis companies to establish the International Association of Synthetic Biology (IASB), a voluntary consortium. However, not all companies joined this consortium, and several large companies established their own consortium with similar standards, the International Gene Synthesis Consortium (IGSC).

4.1 The Asilomar Conference on Recombinant DNA

The framework that guides the new DNA synthesis industry consists of many of the concepts and ideas from the influential 1975 Asilomar Conference on Recombinant DNA (Bugl et al., 2007). This conference was designed to ensure safety and public participation in DNA research. However, the conference and resulting framework were not designed to deal with the intentional misapplication of DNA. Also, this conference was held several years before the advent of PCR and the growth of the DNA synthesis industry. The conference also suggested that, “work on construction of recombinant DNA molecules should proceed provided that appropriate safeguards, principally biological and physical barriers adequate to contain the newly created organisms, are employed. Moreover, the standards of protection should be greater at the beginning and modified as improvements in the methodology occur and assessments of the risks change.” (Berg et al., 1975). However, it should be noted that the Asilomar Conference did not focus on security in recombinant DNA research, but on the general risks and implications of recombinant DNA technology.

4.2 Examples of Security Gaps

Industries will often voluntarily respond to problems (or what the public perceives as problems) to avoid strong regulation by the government (Oye, 2012). The DNA synthesis industry has behaved in a similar way. The voluntary consortia

formed in the aftermath of several unforeseen and potentially dangerous events and the negative reaction of the public.

4.2.1 Mouse Pox and 100% Lethality

In 2001, researchers in Australia attempted to create a virus that would sterilize mice (You, 2011). The experiment had legitimate scientific use: during large grain harvests in Australia, there is often an accompanying "mouse plague" of mice feeding on the grain. The goal of the experiment was to create a virus that could be rapidly and easily transmitted among the mice, and would cause sterility leading to a crash in the mouse population. This would quickly and effectively end the mouse plague. The experiment was supposed to be quite simple and was meant to work by slightly modifying an existing virus, mousepox. This virus is similar to a version that can be lethal in humans, smallpox. The World Health Organization (WHO) declared that smallpox was eradicated in 1980 (Henderson, 1998). The research team modified the mousepox genome with a simple receptor, used quite often in genetic research, called interleukin-4 (Jackson et al., 2001).

The results obtained by the study surprised the researchers. Not only did this slight modification to the mousepox genome make the virus very deadly to non-inoculated[9] mice, but it also resulted in a 100% mortality rate for mice that had been inoculated against mousepox (Jackson et al., 2001). The research team published the results, including the methods for the modification of the mousepox genome. This type of method reporting is done in almost all scientific studies, so that other research teams can confirm the findings. However, many experts in security policy were concerned that such an experiment could be repeated on smallpox or another dangerous pathogen (You, 2011).

While the creation of the mousepox virus does not deal directly with DNA synthesis or its associated technologies, the episode did show the biological

[9] Mice that had not been given an immunization to the mousepox virus.

security community that dangerous pathogens could potentially be created, even by accident.

4.2.2 Reconstruction of Polio

In 2002, researchers at the State University of New York at Stony Brook published how to reconstruct the poliovirus, which had been eliminated in the U.S. for several decades (Samuel et al., 2009). Much of the work done in 2002 was based on an earlier study by Sarnow, Berstein, and Baltimore in 1986. In that study a pathogenic portion of the poliovirus was inserted into a genome and replicated (Sarnow et al., 1986). The most important issue raised during the research was that "the results show that it is possible to synthesize an infectious agent by in vitro chemical-biochemical means solely by following instructions from a written sequence" (Cello et al., 2002). This study was considered an advancement in the current global campaign to eliminate polio. As with the mousepox study, security policy experts also saw the ability to resurrect or construct dangerous human pathogens. Unlike the mousepox study, poliovirus DNA was sequenced and synthesized on purpose.

4.2.3 Reconstruction of the Spanish Flu

In 2005, researchers reconstructed the influenza virus that was responsible for over 50 million deaths worldwide and almost 700,000 in the U.S. alone in the early 1900s (Samuel et al., 2009). This influenza strain was unique in its lethality to young adults, aged 15-34 year olds (Tumpey et al., 2005). The researchers recovered lung tissues from a victim of the virus that had been frozen for nearly a century in the Alaskan permafrost (Tumpey et al., 2005). This study was undertaken in order to ascertain the virulence of this influenza strain and to make a direct comparison to the modern H1N1 and H3N2 influenza viruses.

4.2.4 *The Guardian* Smallpox Story

In 2006, a reporter for UK's publication, *The Guardian*, managed to order part of the Smallpox genome from a synthetic DNA provider. He ordered the sequence

online for about $40.00 and it was successfully delivered to his home (Randerson, 2006). His article described how easy it was to order synthetic DNA of any sequence and that there was no effort made to screen the order or customer.

This was a clear indication of how easy it is for someone with a basic understanding of DNA synthesis to acquire potentially dangerous synthetic DNA. The DNA ordered by *The Guardian* was not dangerous by itself, but with the right set of tools and knowledge, it could have created an organism similar to smallpox.

4.3 Creation of the Voluntary Screening Consortia

The following sections are heavily reliant on the extensive work of the late Jonathan B. Tucker.

From the beginning, some synthetic DNA suppliers realized the dangers associated with their work and its dual use nature. Blue Heron Biotechnology, founded in 2001, was one of the original companies working in this area (Blue Heron Biotechnology, 2013). At first, the company screened customers just to verify that they were actual researchers or industry users. After September 11, 2001 and the anthrax letter attacks, Blue Heron began to develop and deploy a "second line of defense" by screening the DNA orders as well (Tucker, 2010).

As part of this effort, Blue Heron used a software package called Blackwatch, developed by Craic Computing in Seattle, WA (Tucker, 2010). It used a set of algorithms to compare incoming synthesis orders against a database of DNA sequences of known pathogens.[10] If an order had a very close match to a genetic sequence in the database, the program flagged the order as a "hit." If a hit is recorded, then a human expert employed by the company assessed the risk associated with the sequence. Additionally, the human expert checked the

[10] Viruses and bacteria that cause infectious disease.

customer's identity, verified a legitimate end use, and confirmed responses to biosafety and biosecurity questions (Tucker, 2010).

To this date, many pathogenic sequences were detected, but malicious intent was never found. The orders that go through additional screening are almost always ordered for testing and development of new vaccines or basic research (Tucker, 2010). Craic Computing is now developing an improved version of Blackwatch, called Safeguard, that is designed to more accurately spot pathogenic sequences, but less likely to raise a false positive hit cause by "housekeeping genes" that exist in both pathogenic and nonpathogenic sequences (Hayden, 2009).

False positives are a concerning issue with the current DNA consortia. These false positives add to the cost of screening because a human screener needs to ensure that each "hit" is not just part of a nonpathogenic gene that has a similar sequence to a pathogenic one. A false negative is even more dangerous and involves the screening software allowing a potentially dangerous genetic sequence to move forward without additional safety assessment.

By 2005, many companies were voluntarily screening their customers and orders, but the methodology varied from company to company and a few firms resisted entirely. In 2006, seven of the leading gene-synthesis companies, listed in Table 1, formed the International Consortium for Polynucleotide Synthesis to promote safety and security (Tucker, 2010).

Table 1: Locations of seven DNA synthesis companies associated with the International Consortium for Polynucleotide Synthesis (Tucker, 2010)

Company	Location
Blue Heron Biotechnology	United States
GENEART	Germany
Codon Devices (closed in 2009)	United States
Coda Genomics	United States
BaseClear	The Netherlands
Bioneer	Republic of Korea
Integrated DNA Technologies	United States

The seven firms worked with the U.S. Federal Bureau of Investigation (FBI) on a small pilot project called the Synthetic Biology Tripwire Initiative (Tucker, 2010). The project resulted in a mechanism for participating companies to contact the FBI if they saw suspicious orders. One of the major drawbacks with the tripwire system was its reliance on volunteer labor that was supplied by the participating companies. Over several years, the Tripwire Initiative slowly became inactive.

During this time, a group of five German companies, listed in Table 2, formed another consortium called the International Association of Synthetic Biology (IASB). In 2008, the IASB held a workshop in Munich that gathered DNA synthesis experts from Europe and the U.S. to discuss creating a uniform "code of conduct" for screening customers and orders (Tucker, 2010). This code of conduct would be based on the best practices currently used by several leading DNA synthesis companies.

Table 2: Five original companies in the IASB (Tucker, 2010)

Company
ATG:biosynthetics
Biomax Informatics
Entelechon
Febit Holding
Sloning BioTechnology

Major ideas emerged from the conference, including that biosecurity in DNA synthesis should not be an area of competition between firms and that all firms would benefit from a secure DNA synthesis industry. The companies pledged to

share resources in developing a mutually beneficial screening system that would also create a level playing field for screening. A draft called the "Code of Conduct for Best Practices in Gene Synthesis" was submitted for comment in late 2008 (Tucker, 2010).

However, by 2009 a split emerged within the industry over the role of human experts in the screening process (Fischer & Maurer, 2010). The two largest suppliers of synthetic genes (DNA2.0 and GENEART) wanted to eventually replace human experts with a completely automated system that would screen orders against a regularly updated list of virulence-related sequences (Hayden, 2009). The rationale was that the automated system would be faster and cheaper to implement. This proposal was met with resistance from other participants because it was less capable than existing screening methods. Both DNA2.0 and GENEART continued to pursue a separate code of conduct and held closed door meetings with other large gene-synthesis providers (Hayden, 2009).

A second IASB workshop was held in late 2009. Companies at the workshop reached a consensus on a basic set of guidelines, but the details were delegated to a Technical Expert Group on Biosecurity. All five members of the IASB endorsed the code and the first non-IASB company (Generay Biotech in Shanghai) adopted it soon after. However, several leading firms declined to sign onto the IASB code because they did not feel secure with giving so much power to a group of experts that did not report to the firms (Tucker, 2010).

The IASB system allows firms to adopt and comply with the IASB Code of Conduct and receive a "seal of approval" that can be publicly displayed, as shown in Figure 8. This seal is designed to give companies a competitive advantage because it identifies them as reputable suppliers who screen their orders. In order to prove its effectiveness, the IASB plans to certify members on an annual basis. Through "red team" strategies that involve sending fake orders

containing dangerous sequences to test their screening procedures (Maurer et al., 2009). This strategy has had some payoff for the IASB as some large customers have concluded that DNA synthesis screening is in their best business interest.

Figure 8: IASB seal of approval (IASB, 2013)

Several weeks after the IASB code of conduct was finalized, five of the leading gene synthesis companies, listed in Table 3, announced the formation of another separate industry group, the International Gene Synthesis Consortium (IGSC). The IGSC also launched their own code of conduct called the "Harmonized Screening Protocol for Gene Sequence and Customer Screening to Promote Biosecurity" (Tucker, 2010). See Appendix 2 for the IGSC Harmonized Screening Protocol.

Table 3: Original members of the International Gene Synthesis Consortium (IGSC) (Tucker, 2010)

Company
GENEART
DNA2.0
Blue Heron Biotechnology
Integrated DNA Technologies (IDT)
GenScript

The IGSC screening protocol says that companies should "screen the complete DNA sequence of every synthetic gene order…against all entities found in one or more of the internationally coordinated sequence reference databanks" (Tucker, 2010). Whenever a sequence is associated with pathogenicity is identified, it will

receive further screening from a human expert, including stronger customer screening. The IGSC members developed a Regulated Pathogen Database that includes all gene sequences identified as potentially hazardous in several existing national lists, including the U.S. Select Agent List listed in Appendix 4 and the Core Control List from the Australia Group listed in Appendix 3. If an ordered sequence raises suspicion and the customer cannot confirm their legitimacy in working with the dangerous sequence, members of the IGCS will notify the FBI or another law enforcement agency. The members of the IGSC will keep all customer, order, and screening records for at least eight years (IGSC Harmonized Screening Protocol, Appendix 2).

Even though the reason for the schism between the IASB and the IGSC is the use of human screeners in the process (The IASB wanted them, the IGSC did not), both consortia were developed when no system existed that could have removed human screeners from the process. To this day, both the IASB and the IGSC use human screeners to check orders that are flagged as potentially dangerous. It is possible that the issue of using humans in the screening process was not the main concern of the companies that went on to form the IGSC.

The IASB Code of Conduct and the IGSC Harmonized Screening Protocol are functionally similar. The main difference between the two standards is their development process. The IASB Code of Conduct was developed in an open atmosphere with all of the firms that wished to participate. In contrast, the IGSC Harmonized Screening Protocol was developed behind closed doors and developed by a self-selected group limited to suppliers with the largest market share at the time (Tucker, 2010). Although the IGSC wants all gene-synthesis providers to use its standards, only member companies will influence how the screening system will evolve in the future. Figure 9 shows an example flow chart for an order for synthetic DNA for Life Technology, an IGSC member.

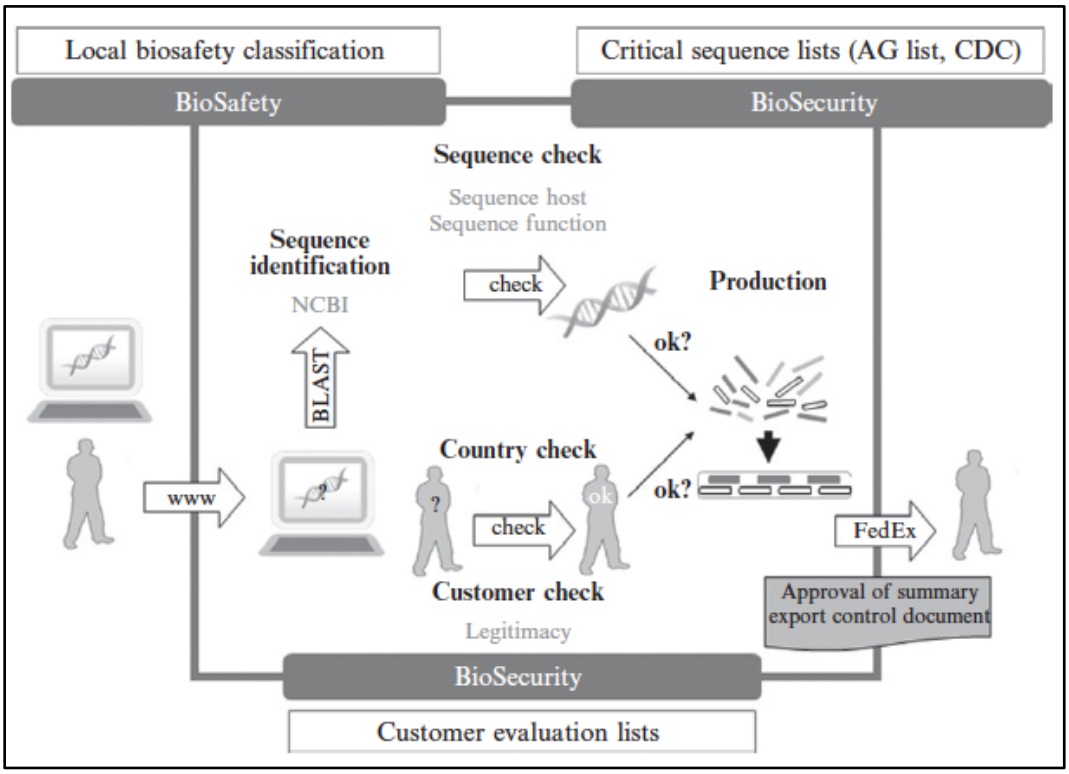

Figure 9: Life Technologies' biosafety and biosecurity screening practice for its gene synthesis orders (Notka et al., 2011)

4.4 Future Development of the Voluntary Screening Consortia

The two DNA Screening Consortia did not evolve in a vacuum. They developed in response to unique external stimuli mentioned in section 4.2, along with other pressures. However, even with a majority of the industry participants in agreement that a system must be established to ensure security, a single system did not develop. The IGSC and the IASB have different long-term goals for using human screeners in their processes. Currently, the screening technologies are not advanced enough that humans can safely be removed, but as quickly as automated screening technology is advancing, it may come to pass in the future.

In addition to the two screening consortia, the company Synthetic Genomics has constructed a proprietary tool called Archetype that brings together design, construction, and sequence security for clients seeking synthetic DNA. This tool could have a large impact on the current screening consortia and the industrial structure of the DNA synthesis industry. Archetype is designed to allow a one

stop shop for customers and would let them bypass a separate design stage for their DNA constructs. The customers would then outsource this to Synthetic Genomics where the customer could have Synthetic Genomics construct the DNA as well.

The current DNA synthesis industry has put effort into mitigating the security risks posed by DNA synthesis technologies. However, the current security regime is unstable (Fischer & Maurer, 2010; Goldberg, 2013). It is unlikely that the industry will continue to exist with two separate and distinct consortia (the IASB and the IGSC). In addition, each company in either consortium agrees to use the guidelines laid down in the agreement, but each company can enforce these guidelines in its own way. This means that each company may be using different techniques to screen its sequences and customers. Along with the two consortia, there are the voluntary guidelines published by the U.S. government in the *Screening Framework Guidance for Providers of Synthetic Double-Stranded DNA*, (2010) and described in greater detail in Chapter 5.

As the consortia now exist, the only substantive difference between the IASB and the IGSC is openness (Fischer & Maurer, 2010). The IGSC limits its membership by market share; it seems unwise and unfair to not allow smaller DNA synthesis firms to have influence in the standard setting process. In addition, the rapid advancement of DNA synthesis technology means that these smaller firms might be tomorrow's powerhouses.

In addition, firms will need to think logically and creatively about how to screen customers for those very rare orders that do contain a pathogenic sequence. What happens if it is a legitimate researcher associated with a smaller start-up company? What about the use of public databases of researchers and their credentials that is subject to fraud? (Fischer & Maurer, 2010). How will companies handle orders such as these? In addition, firms might cooperate and set up an open exchange system for certain repeat sequences and customers to

ensure that the same enhanced screening is not conducted several times. However, firms with proprietary information might not want their data to be stored on a more open database.

5. Current U.S. and International Biological Security Measures

The international community has several agreements in place that broadly deal with biological security. Synthetic DNA and DNA synthesis are not explicitly mentioned in many of these agreements, but they are generally covered due to their dual use nature. In addition, the U.S. has its own laws and regulations dealing with dangerous or potentially dangerous biological technology, including recent guidance for producers of double stranded synthetic DNA.

5.1 International Treaties and Agreements

Several international treaties and agreements have been created since the early 1970s to increase the difficulty of acquiring and using biological weapons. These agreements include the United Nations Biological Weapons Convention (UNBWC) established in 1975, the Australia Group established in 1985, and the United Nations Security Council Resolution 1540 adopted in 2004.

5.1.1 United Nations Biological Weapons Convention

The Convention of the Prohibition of the Development, Production and Stockpiling of Bacteriological (Biological) and Toxic Weapons and Their Destruction entered into force on March 26, 1975. By mid-2005, over 173 nations had signed the convention, while 23 nations did not sign (Lennane, 2011). The convention was designed to supplement the Geneva Protocol of 1925 that had prohibited only the use of chemical and biological weapons during the First World War (Findlay & Woodward, 2004).

Article I states that signatories shall not “develop, produce, stockpile or otherwise acquire or retain…Microbial or other biological agents or toxins whatever the origin or method of production, of types and in quantities that have no justification for prophylactic, protective or other peaceful purposes…Weapons, equipment or means of delivery designed to use such agents or toxins for hostile purposes or

in armed conflict" (Leannane, 2011. p. 45). In addition, the convention requires signatories to destroy existing biological agents and toxins, and prohibits transfer to others, which could transfer or develop dangerous substances. Figure 10 shows nations that are members of the BWC in blue, and nonmembers in grey.

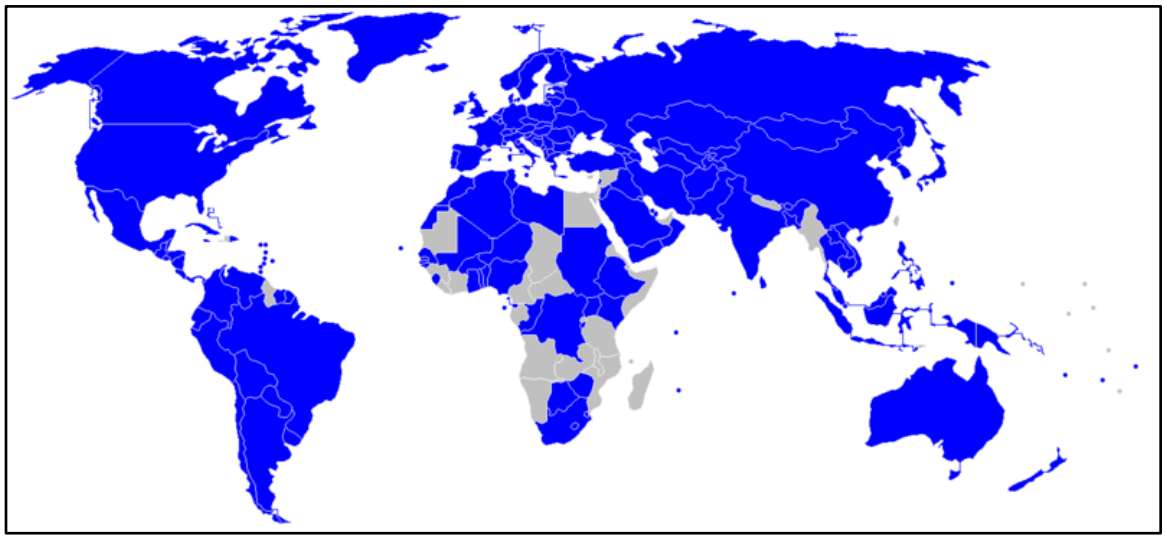

Figure 10: Countries that have signed and ratified the Biological Weapons Convention, in blue (Biological and Toxin Weapons Convention, 2013)

5.1.2 The Australia Group

In response to the use of chemical weapons in the Iraq-Iran war, fifteen countries created the Australia Group in 1985. Its goal was to prevent countries from acquiring materials to produce chemical weapons through what seemed like legitimate trade channels. The Australia group proposed to harmonize export controls among its participating members. The Australia Group is an informal group that has no legally binding obligations to each other. All members of the Australia Group are also members of the UN Biological Weapons Convention (see section 5.1.1 above).

The Australia Group has grown to over 40 members and developed "common control lists" of materials and technologies that could slow the spread of chemical and biological weapons. These restrictions are enforced through the licensing of chemical and biological agents and, most importantly for DNA synthesis, dual-

use chemical and biological manufacturing equipment (The Australia Group, 2007). The biological agents (listed on the Core Control List in Appendix 3) include a range of bacteria, fungi, and viruses that are harmful to human health. In addition, the Core Control List states that pathogenic parts derived from any of the listed organisms are also under regulation (Pei, 2007).

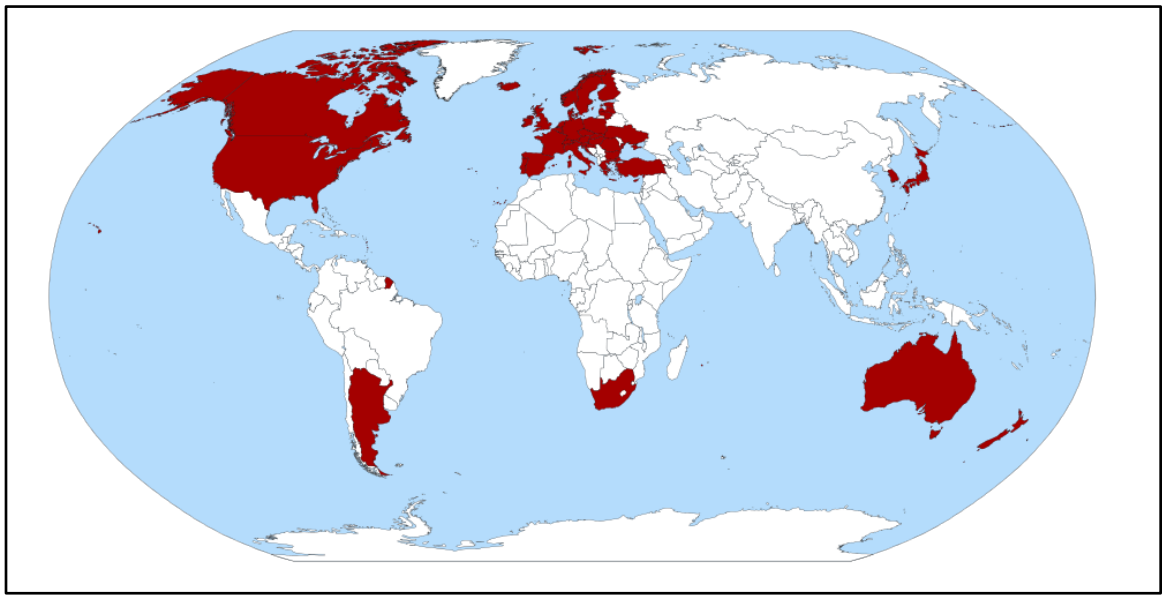

Figure 11: Country map of Australia Group members (Australia Group, 2013)

5.1.3 United Nations Security Council Resolution 1540

The UN Security Council unanimously adopted Resolution 1540 on April 28, 2004 (1540 Committee, 2004). Their goal was to create an effective global response to the threat posed by nuclear, chemical, and biological weapons by strengthening global non-proliferation activities. The resolution forbids states from helping non-state actors that seek to develop chemical, biological, or nuclear technologies. The resolution also establishes that mandatory domestic control measures be implemented in all nations in order to prevent weapons proliferation. States are required to develop and maintain effective physical measures, border control, export control laws, and enforcement mechanisms (1540 Committee, 2004).

5.2 U.S. Rules and Regulations

In addition to being a part of the international agreements listed in section 5.1, the U.S. has its own set of rules and guidelines to combat possible biological threats. These rules have been strengthened since the September 11, 2001 terrorist attacks and the 2001 Anthrax attacks.

5.2.1 National Strategy for Countering Biological Threats

The National Security Council published the National Strategy for Countering Biological Threats in November 2009. It argues that rapid advances in the life sciences hold incredible potential for beneficial civilian progress, but could also be used by nefarious actors for harmful purposes. It cites the decreasing barriers of cost and technological knowledge as a central problem, especially with the proliferation of severe threats from small terrorist groups or individuals (National Security Council, 2009).

It calls for broad government action to address novel threats and suggests new norms for conduct, including insight on current and emerging risks, and reasonable steps to increase international dialogue on potential biological threats. The report does not assign direct responsibilities, but it does describe specific actions that federal agencies should take (National Security Council, 2009).

5.2.2 Export Administration Regulations

The Export Administration Regulations (EAR) was created in order to implement the Export Administration Act passed in 1979. This Act gave the President of the United States the legal authority to control U.S. exports to protect national security and enforce foreign policy, especially if the material was in short domestic supply. The EAR is implemented by the U.S. Department of Commerce (Title 15, chapter VII, subchapter C of the U.S. Code). The Commerce Control List contains the specific items that are subject to export controls. Category 1 of this list contains “Materials, Chemicals, Microorganisms

and Toxins" and this is where dual-use biological items and equipment are specified.

The Commerce Control List includes a number of viruses, bacteria, toxins and fungi that could cause disease in humans, animals, and plants. It also includes genetic elements that contain nucleic acid sequences known to be associated with pathogenicity of any organism on the control list. This is much like the Australia Group's Guidelines. The most restricted destinations include embargoed countries and those supporting terrorist activities (US Department of Commerce, 2010).

Table 4: List of countries under U.S. embargo (Department of Commerce, 2010)

Country
Cuba
Iran
North Korea
Northern Sudan
Syria
Sudan

5.2.3 Select Agent Regulations

In 2005, The Select Agent Regulations were endorsed to implement the Public Health Security and Bioterrorism Preparedness and Response Act of 2002. Congress passed this act in response to the September 11 and 2001 Anthrax attacks to "improve the ability of the United States to prevent, prepare for and respond to bioterrorism and other public health emergencies." The Act requires the Department of Health and Human Services (HHS) to establish and regulate a list of biological agents and toxins that pose a severe threat to public health (Public Health Security and Bioterrorism Preparedness and Response Act, 2002).

HHS controls the Select Agents Regulations through the Center for Disease Control and Prevention (CDC) under regulation 42 §73 *Select Agents and Toxins*

(Gonder, 2005). This gives the CDC authority to monitor and control the use and transfer of these select agents and toxins. Examples of these organisms include the Ebola virus, *Yersinia pestis* (causative agent of plague), and *Bacillus Anthracis* (the causative agent of anthrax). The regulation controls:

- all work that involves genetically modified versions of any organism on the select agents list
- nucleic acids that can produce the infectious forms of any of the select agents' viruses
- nucleic acids that encode for the functional forms of the toxins *in vivo* or *vitro*.

For the Select Agents and Toxins list see Appendix 4.

5.3 The National Science Advisory Board for Biosecurity

The National Science Advisory Board for Biosecurity (NSABB) was created to advise the federal government regarding technologies in the life sciences with dual use potential. In addition, "the NSABB advises on and recommends specific strategies for the efficient and effective oversight of federally conducted or supported dual use biological research, taking into consideration national security concerns and the needs of the research community." (National Institutes of Health, 2013).

In 2006, the NSABB developed its own set of guidelines for commercial gene synthesis. The recommendation attempted to "develop and promote standards and preferred practices for screening gene-synthesis orders and require that orders be screened by providers" (Shea, 2006). The White House responded in 2007 by convening an interagency working group to develop biosecurity guidelines for the U.S. gene synthesis industry. The NSABB called for legally binding regulations, but the interagency working group created voluntary guidelines and tested them for several years to view their effectiveness (Wadman, 2009). The government supported this approach because it did not impede legitimate scientific research and did not put U.S. companies at a

disadvantage relative to international competitors (Tucker, 2010). Another reason for the lack of binding regulations was that regulations are best suited for static situations, while gene synthesis is a new and rapidly evolving field.

There was no formal coordination between industry and government; however, enough discussion occurred to ensure that the efforts were not drastically different. In 2009, the government published a draft of guidelines named *Screening Framework Guidance for Synthetic Double-Stranded DNA Providers*. The guidelines called for the screening of new customers and orders for double-stranded DNA longer than 200 nucleotides (Eisenstein, 2010). The screening involved confirmation of the purchaser's identity and institutional affiliation. Suppliers must also look for "red flags" that suggest illicit activity, such as the use of a post office box instead of a street address (Screening Framework Guidance for Synthetic Double-Stranded DNA Providers, 2009). One issue that remains unresolved is whether gene-synthesis companies should supply synthetic DNA to researchers who lack an institutional affiliation, such as hobbyists working in home laboratories or small start-up companies (Tucker, 2010).

The main difference between the U.S. government guidelines and the two existing industry standards is the method for screening the gene orders. In the U.S. guidelines, companies must use a "best match" algorithm that flags an order if it is more closely associated with a pathogenic gene than a non-pathogenic one. This contrasts with the current industry standard that has a human inspect every order resembling a pathogen or toxin found in the U.S. government's GenBank (Fischer & Maurer, 2010). Fischer has suggested that these lesser guidelines could lead to a "race to the bottom," where companies would fight for market share by lowering prices through less screening (Hayden, 2009). In 2013, this prediction has yet to pass, even though no stricter non-voluntary standards have come into force.

In early 2010, the Center for Science, Technology, and Security Policy at the American Association for the Advancement of Science (AAAS) held a workshop to discuss several of the guidelines suggested by the government in its screening framework guidance. First, the 200-nucleotide cutoff for screening was arbitrary and hard to justify. It was suggested instead that screening should be done on any DNA, regardless of the length (Tucker, 2010). Second, critics argued that the "best match" algorithm may be simple and easy to implement, but it is weaker than the current industry standards because it cannot detect pathogens that are not on the U.S. Select Agent List.[11] The consensus of the AAAS workshop was that there is a need to capture a larger group of sequences of concern. Static defenses such as the Select Agent List are easily beaten, and the marginal cost of screening pathogens outside the list is low (Tucker, 2010).

At the workshop, one participant warned that "if the U.S. government endorses the Best Match algorithm, companies that have argued in the past for fast and cheap screening methods will almost certainly embrace this approach. In that case, other firms will follow suit to remain competitive, moving the industry toward a screening standard that is less capable than what is already practiced by most companies today" (Hayden, 2009). In addition, some participants argued that the screening software should be open source so that it would be quickly updated and validated as our understanding grows. This is in comparison to proprietary software that tends to be more static (Tucker, 2010).

5.4 Screening Framework Guidance for Providers of Synthetic Double-Stranded DNA

The U.S. Department of Health and Human Services published *Screening Framework Guidance for Providers of Synthetic Double-Stranded DNA* in October of 2010. An important point is that this guidance is voluntary. However, it shows how the federal government might aim to limit security risks associated with synthetic DNA production.

[11] Examples include SARS or other recently emerged viruses.

Providers of synthetic, double-stranded DNA have two responsibilities under this guidance. First, they must establish whom they are distributing their product to. Second, they should know when their product contains a "sequence of concern."[12]

In the Guidance, DNA providers are asked to conduct customer and sequence screening processes for their orders. The purpose of the customer screening is to establish the legitimacy of customers ordering synthetic double-stranded DNA sequences by verifying the identity and affiliation of customers and identifying any "red flags" that would arise when there is suspicion that the order could be used inappropriately. The Guidance also recommends that providers check the customer against several lists of proscribed entities, such as the Department of the Treasury's Office of Foreign Asset Control List of Specifically Designated Nationals and Blocked Persons, and the Department of Commerce Denied Persons List for domestic orders. Lastly, the providers are required to follow the laws and regulations of U.S. trade sanctions and export controls for international orders.

Sequence screening identifies whether sequences of concern are ordered. If the complete sequence or unique parts of the sequences are identified, providers must make sure that customers have a Certificate of Registration from CDC for using select agents or toxins. For international orders, providers also screen for items on the Commerce Control List to ensure that they are in compliance with the Export Administration Regulations (EAR).

If either the customer or sequence screening causes concern, a follow-up screening must take place to verify the legitimacy of the customer and end-use of the double-stranded DNA order. This follow-up screening has less guidance and

[12] Defined as sequences that code for the select agents and toxins identified by CDC in the Select Agent Regulations

is less specific than for the initial screenings. The customer's identity, affiliation, legitimacy, and intended use are obtained. If the follow-up screening does not solve the concerns raised, the provider contacts the FBI, the Select Agent Programs of CDC, or the Department of Commerce, for assistance and guidance on further action.

One issue that was raised between industry and the NSABB was that the mandatory process could deter innovation in a new field. However, the *Screening Framework Guidance for Providers of Synthetic Double-Stranded DNA* was created in consultation with industry. Jessica Tucker, one of the main authors of the framework, does not think these standards will impede scientific advancement, because they were developed with the input of industry (Wadman, 2009).

5.5 Moving Forward

The analysis in sections 5.2 thru 5.3 demonstrate that the U.S. government and the international community have both taken the threat of biological weapons and possible biological terrorism seriously. Only recently has the government suggested methods to reduce possible dangers stemming specifically from synthetic DNA technologies. These are still only voluntary guidelines and it is up to each individual synthesis company to decide what screening regulations to follow. However, if a DNA synthesis company ships the genetic material coding a whole or partial pathogenic organism, the company could be charged under the EAR. Therefore, there is a strong incentive to ensure that dangerous pathogenic parts are not shipped, customers' identities are known, and their credentials are verified. In addition, all companies know that if any synthetic DNA sequence is used to damage human health or the environment, the entire industry will be scrutinized. Such an event might lead to hasty and overzealous responses by politicians and regulators that could seriously weaken the industry.

Fischer & Maurer (2009) have published that without hard and fast guidelines to which companies must adhere, there would be a “race to the bottom” between DNA synthesis companies as they competed with one another in price and brought prices down through less screening (Hayden, 2009). However, both the IASB and the IGSC continue to exist and continue to hold their companies to standards when screening orders. In addition, Michael Imperiale, a professor of microbiology and immunology at the University of Michigan Medical School, states that the U.S. government guidelines are not necessarily less than what the IASB and the IGSC have come up with on their own (Wadman, 2009).

6. A Comparison with Other Technologies and Industries

A dual use technology is a technology that is used for a legitimate and useful civilian purpose (i.e., biotechnologies) but can easily be converted for nefarious purposes (i.e., a biological weapon). DNA synthesis is considered a dual use technology. There are several other notable examples of dual use technologies that will be discussed in this chapter. In addition, this chapter compares DNA synthesis with other dual use technologies.

6.1 Dual Use Technology: Nuclear

Enriched or reprocessed fissile materials (most commonly Uranium or Plutonium) can be used to power a nuclear power plant or a nuclear bomb. Natural Uranium ore consists of several isotopes of Uranium.[13] U-235 is the radioactive isotope, and its nuclear decay can power nuclear reactions. Natural Uranium contains only about 0.72% Uranium 235 (Tobey, 2012). When enriched to only 3%-5%, U-235 can be used as fuel in a nuclear reactor. If that same Uranium is enriched to more than 90%, U-235 can be used in a nuclear bomb. Uranium enrichment technologies are internationally available, but they are controlled by international agreements. These agreements were designed to prevent the proliferation of nuclear weapons, while encouraging the growth of a peaceful nuclear industry for power generation.

6*.1.1* The Nuclear Non-Proliferation Treaty

The Nuclear Non-Proliferation Treaty (NPT) was established in 1968 and came into force in 1970 (NPT, 2013). It divides all members into two separate and distinct groups. First, there are nuclear weapon states, which are the countries that detonated a nuclear explosion prior to January 1, 1967. Second are all other members, the non-nuclear-weapon states (Cirincione et al*.,* 2005).

[13] An isotope is the same element with very similar physical and chemical properties, but the differing number of neutrons leads to a different atomic mass.

Under the NPT, non-nuclear weapons states pledge not to manufacture or receive nuclear explosives, of any type. These states also agree upon safeguards on all nuclear activities and facilities under the International Atomic Energy Agency (IAEA), an affiliate of the United Nations. It attempts to "seek to accelerate and enlarge the contribution of atomic energy to peace, health and prosperity throughout the world. It shall ensure, so far as it is able, that assistance provided by it or at its request or under its supervision or control is not used in such a way as to further any military purpose" (IAEA, 2013). All countries agreed not to ship nuclear equipment or material except under IAEA safeguards and to ensure the spread of peaceful nuclear technologies (Cirincione et al., 2005). Lastly, all nuclear weapons states agreed to work in good faith to achieve nuclear disarmament under international control.

The IAEA is the verification system for the NPT. Under the NPT, all states must accept the IAEA safeguards, with very few exemptions. These exemptions can include nuclear materials for narrow military purposes like nuclear naval vessels (Cirincione et al., 2005). However, the IAEA does not have the legal power to search for nuclear weapons or the production of nuclear weapons.

6.1.2 The Nuclear Suppliers Group

In addition to the NPT, there is a coalition of nations called the Nuclear Suppliers Group (NSG) that voluntarily restricts the movement of nuclear equipment and materials that could be used to develop nuclear weapons (Tobey, 2012). This group pledged to provide physical security for nuclear materials and in 2004 they added a mechanism permitting member states to prevent the export of materials they suspect might be used for a nuclear weapons program.

6.1.3 International Regulation of Nuclear Technologies

The NPT and the NSG, along with the IAEA as an inspection mechanism, allows for a robust regulation of nuclear materials and equipment. However, without an

enforcement mechanism, the NPT is unable to prevent countries from acquiring nuclear technologies on the black market or developing their own homegrown technologies that can evolve from legitimate civilian programs.

6.2 Chemical Technologies

With the advent of the modern chemical industry, chemical technologies moved from a limited dual use technology to a very important part of many nations' economies. After the use of deadly chemical weapons in the First World War, the 1925 Geneva Convention banned their use in war, but not their creation or stockpiling. During the Cold War, the U.S. and Soviet Union started negotiations on the Chemical Weapons Convention, in an attempt to eliminate chemical weapons from their arsenals. The Australia group is a group of countries that voluntarily control their export of technologies and materials that are capable of being used for the manufacture of chemical weapons, see section 5.1.1.

6.2.1 Chemical Weapons Convention

In 1997, The Convention on the Prohibition of the Development, Production, Stockpiling and Use of Chemical Weapons and on their Destruction (or the Chemical Weapons Convention, known as the CWC). As its title suggests, the CWC prohibits members from developing, producing, acquiring, stockpiling, or retaining chemical weapons (CWC, 2013). In order to build confidence among member states, the CWC includes a verification regime that allows for systematic inspections of all declared production facilities. This includes both civilian and military facilities. The CWC also includes several provisions to encourage chemical equipment trade between its member states for peaceful purposes. Lastly, the CWC created the Organization for the Prohibition of Chemical Weapons to oversee the inspections and verification proceedings (Cirincione et al., 2005).

6.2.3 International Regulation of Chemical Technologies

Together, the CWC and the Australia Group control the flow of technologies and materials that will be used to develop chemical weapons. The CWC contains a stronger enforcement mechanism than the NPT's IAEA inspection system, but is not able to inspect non-member states, such as Syria and Israel.

6.3 Rocket and Missile Technologies

Rocket and missile technologies are dual use because a rocket that is used for a legitimate space exploration or satellite program can be converted into a tool that delivers a weapon over a great distance.

6.3.1 Missile Technology Control Regime

In 1987, The Missile Technology Control Regime (MTCR) came into force. It is designed to slow the spread of unmanned delivery systems for weapons (MTCR, 2013). The MTCR is an informal group that uses export controls on technology that could be used for ballistic and cruise missiles capable of traveling more than 300 kilometers with a 500-kilogram payload (Mistry, 2003).

In 2002 the Hague Code of Conduct (also known as the ICOC) was developed to strengthen the MTCR. This included attempting to ensure that any space launch vehicle (SLV) technology or aid is not manipulated to further a missile program, voluntarily allowing international observers to SLV launch sites, and providing prelaunch notification for both missiles and SLV launches (Cirincione et al., 2005).

6.3.2 U.S. Unilateral Measures

In addition to the MTCR and the ICOC, the U.S. has imposed unilateral sanctions on certain foreign companies suspected of helping to develop missile programs in locations such as Iran and North Korea. These measures are often used under laws passed to prevent weapons technologies from moving to certain

countries and such actions are allowed under the international agreements listed in sections 6.3.1 (Tobey, 2012).

6.4 Lessons Learned from Dual Use Technologies: Nuclear, Chemical, and Missile

The examples in sections 6.1, 6.2, and 6.3 are often cited as the quintessential dual use issues. All of these technologies began their careers without much, if any, formal government oversight. These different dual use technologies and their international enforcement mechanisms may be models for the emerging DNA synthesis technologies. However, these technologies and their regulatory regimes are not perfectly analogous to DNA synthesis.

6.5 Key Differences in DNA Synthesis

DNA synthesis technologies are cheaper and more ubiquitous than nuclear, chemical, or missile technologies. The recent trend of rising DNA synthesis ability, coupled with falling costs for synthesis, has led to a global proliferation of DNA synthesis technologies and companies. DNA synthesis technologies are already diffused and their development is cheaper than nuclear or missile technologies, which often require substantial government support. High quality second-generation DNA synthesizers can already be purchased on eBay for less than $50,000 (eBay, 2013).

In addition to becoming cheaper and more dispersed than nuclear, missile, and most chemical technologies, DNA synthesis technology also has a globalized system of reagents, the precursors needed to construct synthetic DNA (Maurer et al., 2009). Unlike chemical technologies or nuclear materials, controlling the reagents would be difficult through international regulation, as many providers already exist.

Lastly, DNA synthesis technology is still a maturing industry. Unlike nuclear, chemical, and missile technologies, DNA synthesis is advancing rapidly and

predicting its future course is very difficult (Carlson, 2009). This means that using written rules and lists, such as those used by the existing international frameworks, will be ineffective in the long run. In one possible scenario, the technology will simply work around these “road blocks” and use other means and materials for advancement and diffusion. In another possible scenario, the advancement of the technology could be halted by strong international measures controlling its creation and diffusion.

7. DNA Synthesis Tools and Industry: Possible Future Paths

Over the lifetime of the DNA synthesis industry, there have been a series of important breakthroughs that have created a virtuous cycle. This cycle was created by lowering the cost of synthetic DNA, which stimulated demand for more synthetic DNA. In turn this encouraged more development in DNA synthesis. However, this cycle has begun to encounter diminishing returns (Maurer et al., 2009). New technologies will be developed that promise to further improve DNA synthesis, as long as a healthy market for synthetic DNA continues to grow. In the end, the size and structure of the DNA synthesis industry and the development of the technology will be determined by emerging economic, technical, and regulatory factors (Carlson, 2009).

7.1 Advancing Technologies

DNA synthesis technology can still be improved and advanced upon. Academic labs and research labs at companies like the Cetus Corporation and Gen9 are constantly working to improve existing technology and to develop new technology to construct synthetic DNA. In the future, it will be impossible to predict where the next large technological breakthroughs will emerge. However, if they drive down the price of synthetic DNA while maintaining speed and quality, research efforts and societal benefits will accelerate.

7.1.1 Advanced Synthesizers

As stated above, the Cambridge, MA based company Gen9 claims to be in the process of developing tools and techniques that will increase the global DNA synthesis ability by one third (Goldberg, 2013). If their claims are accurate, this technology could have the potential to change the DNA synthesis industry. If there are currently a handful of large DNA synthesis companies that use economies of scale to produce synthetic DNA at a lower cost, then having the most advanced technology is vital. Assuming Gen9's technology is as accurate

as the current industry's best technologies and that it can create similar length DNA sequences, the users of this technology would have an advantage over other firms. The CEO of Gen9 claims that the cost will drop by "orders of magnitude." (Carlson, 2013). However, without hard data on the technology and costs of Gen9's synthesis tools, it is difficult to determine if their claims of a game changing technology are accurate.

7.2 Changing Market Structure

As DNA synthesis technology continues to advance, the benefits are not limited to the large firms using the most advanced technology. Less advanced or wealthy users will have more access to DNA synthesis because more DNA synthesizers will be available on the market as firms upgrade their existing hardware. A simple search of eBay.com for "DNA synthesizer" yields over a dozen high quality (used) machines (eBay.com, 2013). In addition to driving down the costs of DNA synthesis technologies, the newest machines are able to automate what used to be done by highly trained technicians (Maurer et al., 2009). This means that industries that consume synthetic DNA, but were not able to economically produce it for themselves, may now be able to. This represents a lateral diffusion of the DNA synthesis technologies, but security will become a more important issue as the technology and industry decentralize.

7.2.1 Large Consumers Bring DNA Synthesis In House

As DNA synthesis capacity grows all around the world, another trend is emerging. This trend is not from the DNA synthesis industry, but from their largest customers. As drugs and therapies based on genetic information and living systems begin to play a larger role at pharmaceutical companies, these companies may begin to limit their use of outside DNA synthesis companies. Many large pharmaceutical companies claim this is for quality control and rapid turnaround time. However, there are also associated Intellectual Property issues. Many large firms have already been the victims of industrial espionage. As the industry is currently organized, these firms must send out orders for

synthetic DNA to another company. While nearly all DNA synthesis companies have non-disclosure agreements, there is still substantial financial risk (Maurer et al., 2009).

In addition to having another company see proprietary data, that company is also going to screen the order as a member of the IASB or the IGSC. This screening will attempt to determine what each part of the order does individually and as a whole. Some regulators have suggested a centralized screening system that makes it difficult to order various parts from different suppliers to assemble into a dangerous sequence later. Also, if such a centralized system was established, many firms would be reluctant to send their intellectual property to be screened and then sequenced.

7.3 The Necessity of the DNA Synthesis Industry

It is possible that the entire DNA synthesis industry will only exist for a short amount of time. As the technology advances and diffuses, the value that these companies are able to provide with their highly trained workforce and economies of scale is likely to diminish. Assembling large DNA constructs is currently a technological challenge, but newer DNA synthesizers are beginning to automate the construction of larger and larger DNA sequences. As the technology advances, the capability to create such large constructs will diffuse and the value currently added by DNA synthesis companies may diminish (Carlson, 2009).

7.4 Government Regulation

It seems counterintuitive that companies would want the government to enter their market, set up, and enforce strict rules or guidelines on safety or security. However, many industries encourage just that. This is called regulatory capture, a theory associated with Nobel Laureate Economist, George Stigler. This theory describes how regulatory agencies will eventually become dominated by the very industries they are designed to regulate. The firms encourage this to protect their market share from new entrants and to create a type of market imperfection

where new entrants into the industry must pass very costly standards in order to compete (Oye, 2012).

7.5 The Changes in the DNA Synthesis Industry

The DNA synthesis industry, including the synthesizing companies and their customers, is advancing and growing rapidly. In the future, newer technologies will change both the DNA synthesis technologies and also the industry's structure.

As the technology improves and costs decline, there will likely be both vertical and horizontal diffusions of DNA synthesis technology. From a security standpoint, this will make it difficult to ensure that nefarious actors are not able to acquire synthetic DNA. As the technology becomes more diffused, users will no longer have to rely on commercial synthesizers. Another method must be developed to ensure that synthetic DNA is not created for nefarious purposes.

8. iGEM as a Case Study in Security Methods

The International Genetically Engineered Machine competition (iGEM) began in 2003 at the Massachusetts Institute of Technology (MIT). Originally, the competition challenged student groups to design and construct a unique biological system that could make a network of cells “blink,” or change fluorescence in the presence of different stimuli. In the 2012 competition, there were more than 190 teams from 35 countries with more than 3,000 undergraduate students in participation. Each year, iGEM sends a kit with different genes to student groups at different universities. The parts are the physical DNA that are placed into a ring of DNA material known as a plasmid, which allows for easy insertion into a host cell. The students then spend the summer designing and building biological systems. The ideas and goals are only limited by the teams’ imagination and their technical ability (iGEM, 2013).

The competition’s expansion from an MIT winter term class to a truly international competition puts the iGEM leadership at the forefront of many issues relating to safety and security of biological technologies, and synthetic DNA in particular.

8.1 Registry of Standard Biological Parts

The iGEM Registry of Standard Biological Parts describes itself as a "continuously growing collection of genetic parts that can be mixed and matched to build synthetic biology devices and systems. Founded in 2003 at MIT, the Registry is part of the Synthetic Biology community's efforts to make biology easier to engineer. It provides a resource of available genetic parts to iGEM teams and academic labs" (Registry of Standard Biological Parts Website, 2013). The Registry is based on an open source philosophy similar to the Linux operating software. Everyone is allowed to use the information provided in it, as long as what he or she creates with the information is given back to the Registry in order to improve it. However, issues have arisen with this open source platform. Everyone is allowed to contribute to the Registry, and some of these contributions could lead to dangerous uses. Because of its free and open source

nature, the Registry had never screened its parts. It relied entirely on the skill and dedication of those submitting parts to provide the part (a DNA sample sent to iGEM headquarters) and an accurate and complete description of the part, including where it came from and how it was separated from its original host.

8.2 iGEM Safety Committee

The iGEM Safety Committee is a small group that ensures that iGEM is conducted safely and securely, and that there are no violations of U.S. or international law. In 2012, the members of the iGEM safety committee included Peter Carr, Kenneth Oye, Piers Millett, Todd Kuiken, King Chow, Allen Lin, Ralph Turlington, Shlomiya Bar-Yam, Julie McNamara, Rocco Casagrande, Michael Imperiale, Jef Boeke, George Church, Toby Richardson, and Ed You. In order to ensure safety, members of the Committee spend hours looking over project ideas and their safety submissions and monitor the teams' efforts in relation to their safety submissions. Over time, the screening has grown in both size and complexity. The ad hoc nature of the screenings allowed several incidents (described in sections 8.2.1 and 8.2.2) that prompted changes in iGEM, the Registry, and how safety information is exchanged between participants and the Safety Committee.

In addition to the online materials that the teams need to complete, there are safety courses and videos for teams whose universities do not have biological safety committees and protocols. At the annual world championship at MIT, U.S. FBI Special Agent, Ed You, gives a presentation on security in the biological sciences. This is one of the best-attended talks during the championship and always generates a lot of discussion. Many attendees are international students who are curious about biosecurity and best practices in the U.S. Such outreach can have positive effects, as ideas spread about best practices and both U.S. and international students realize the importance of safety and security in their research.

8.3 iGEM's Responses to Safety and Security Gaps

In the 2011 and 2012 iGEM competitions there were two separate incidents that prompted changes in iGEM's screening process of projects and safety information. First was the decision to screen the Registry of Standard Biological Parts to ensure the safety and efficacy of the parts. Second was the effort to screen projects earlier to be sure that potentially dangerous parts were not shipped across the world (possibly in violation of U.S. and international laws).

8.3.1 Team Attempts to use *Vibrio cholerae* and iGEM's Response

In the 2011 iGEM competition, the Safety Committee screeners noticed that a team had indicated that they were using a part from the organism *Vibrio cholerae* on their safety page. Some strains of this type of bacteria can cause the disease, Cholera. *Vibrio cholerae* is a biosafety level 3 organism. This means special precautions must be taken when handling the organism or its parts. In addition, these organisms are defined as infectious agents that may cause serious or potentially lethal diseases as a result of exposure by inhalation (Onderdonk, 2013). This means that special precautions should be taken when working with *Vibrio cholerae*. Some of these precautions include a specialized (and secure) laboratory to work with the organism, specialized equipment to dispose of biological residues associated with the organism, and highly specialized equipment worn by laboratory workers.

The Safety Committee also noted that the student team had not marked off that *Vibrio cholerae* was a dangerous organism. In addition, the team also stated that their university had no local biosafety committee that oversaw biological work at the university. After a small amount of research, members of the Safety Committee discovered that the university did in fact have a local biosafety committee. This prompted the committee to contact the team and its supervisor. The supervisor was not quick to respond; it took several weeks and a visit from an international member of the Safety Committee to figure out what the team was

doing. In the meantime the Safety Committee had disqualified the team from the iGEM competition until they could prove that they were working safely and were in compliance with their local biosafety committee.

Learning from this experience, iGEM and the Safety Committee rewrote the competition rules. In addition, iGEM worked towards improving communication with team advisors to ensure that they had adequate knowledge about biosafety and biosecurity practices.

8.3.2 Team Attempts to use *Yersinia pestis* and iGEM's Response

In the 2012 iGEM competition, a team attempted to use *Yersinia pestis*, the causative agent of plague. Much like *Vibrio cholerae*, *Yersinia pestis* is a biosafety level 3 organism. In addition, the team attempted to use a pathogenic gene from *Yersinia pestis* to insert genetic material into a mammalian cell. The team neglected to present the use of *Yersinia pestis* on their safety page, and the Safety Committee did not know that the team was attempting to work with *Yersina pestis* until the world championships.

When asked where their DNA sequence came from, the team said that they had requested and received DNA from an academic laboratory in the U.S. In addition, they noted that the original piece they had originally tried to use was in the Registry of Standard Biological Parts and had been shipped out from iGEM headquarters.

With a quick examination of the Registry, the Safety Committee learned that the part that was shipped out was only 14 base pairs long. This is too short to be a useful gene and could not have been a part of the pathogenic system of *Yersinia pestis*. However, had this been a functional part, would iGEM have been in violation of not only U.S. export control laws, but also the Australia Group?

8.4 Screening the Registry of Standard Biological Parts

In addition to researching norms and regulations that are now affecting iGEM in the international arena, the Safety Committee developed a new screening checklist that must be completed by each team in their initial phases. This checklist includes all parts that have been or will be used and where they came from. In addition, if the team's project changes, they will need to update the list and get approval from their adviser. All changes must then be sent to the safety committee.

In addition to these changes, the iGEM Safety Committee, led by Kenneth Oye, has enlisted the help of Synthetic Genomics and the IGSC to screen the Registry of Standard Biological parts. The IGSC screening will be representative of current industry's best practices. Synthetic Genomics will be using their new Archetype tool to screen the Registry. It is expected that the two screenings will produce useful insight on the safety and efficacy of the Registry's parts. Both of these screenings will be done along with a computer-based text screening to address mislabeled parts.

8.5 iGEM as an Example of Successful Adaptation to Safety and Security Gaps

iGEM is an example of an open and international organization facing numerous challenges. Through an open engagement process with the community and within itself, it has weathered many challenges listed in section 8.3, but now has stronger safety and security positions going forward.

iGEM has worked closely with the FBI and regulators such as Public Health Canada to improve its best practices. iGEM strives to teach student groups that while synthetic biology research has enormous potential for good, it could also be harmful if improperly used.

9. Policy Recommendations and Implications

The DNA synthesis industry is a globalized and rapidly changing industry. Large gene synthesis orders already move all over the world; a company's physical location is becoming less important. In addition, the opportunity for researchers to acquire synthetic DNA from all over the world is growing. In the 2013 iGEM competition, a team from Asia asked for a part from an MIT lab. The part was shipped across the world for an undergraduate competition in fewer than two weeks. In an already globalized world, with all trends pointing to further integration of technologies and industries, what can be done to best promote and enhance security in the DNA synthesis industry?

9.1 Other Dual Use Technologies are Different than Synthetic DNA

Heavy government intervention is likely to be minimally effective if applied to DNA synthesis. This is because DNA synthesis technology is fundamentally different than technologies that are heavily regulated by governments, such as nuclear, chemical, or missile technologies. Nuclear and missile technologies are very expensive and require large capital expenditures to acquire specially designed and constructed components. This makes it difficult for anyone but national governments to purchase and promote these types of technologies. Because of these costs, it is also easier for intelligence agencies and the international community to monitor and track these technologies. Chemical technologies do not require the intensive capital that nuclear and missile technologies require. However, in order to construct effective chemical weapons, specialized precursors are needed in large quantities.

Synthetic DNA is also different from these other technologies because the necessary precursors to constructing synthetic DNA are only needed in small quantities to construct a dangerous organism. This stems from the self-replicating nature of life forms: one dangerous pathogen can replicate itself and spread across the globe.

9.2 U.S. Government Involvement: A Light Touch

Heavy government involvement is unlikely to be effective in promoting security in the DNA synthesis industry; the government should try a different approach. The U.S. government should promote existing best practices and devote resources to studying and improving these practices. There are a number of ways to do this:

Setting and publicizing a minimum allowable standard that follows the current IGSC and IASB protocols. The current U.S. government standard is voluntary and has been criticized for being less stringent than the existing industry's best practices under the IGSC Harmonized Screening Protocols or the IASB Code of Conduct. The government could follow industry's best practices and publicize them to encourage DNA synthesis firms. This would also encourage consumers of synthetic DNA to pressure their suppliers to follow these best practices as well. In addition, the government could provide companies that are following best practices legal immunity if a nefarious actor attempted to use their synthetic DNA.

Using "Red Teams" to test and enforce the current screening consortia. The use of red teaming to try and breech the screening defenses of companies would ensure that all companies take the screening seriously and that no company feels that another company is slacking in their screening.

Creating and maintaining a list of overseas companies, institutions, and researchers that can order synthetic DNA without being further investigated. Creating a database of certified researchers and labs overseas would allow these researchers to purchase synthetic DNA from U.S. based suppliers and would reduce their incentive to use less reputable suppliers.

Maintain up to date registries for dangerous sequences and persons. The government already maintains such databases, but they are scattered and often redundant. The government could aid the screening consortia and the scientific

community in general by maintaining an up-to-date and easy to access database of dangerous pathogens, and persons or companies of concern. Having a one stop shop for this information would reduce the screening costs for companies and would also encourage better screening.

9.2 Future Policy Recommendations

Even today, DNA synthesizers can be acquired quickly and at relatively low cost. There are numerous examples of DNA synthesis tools available for online purchase (eBay, 2013). Because DNA synthesis is not yet a fully automated technology, training and experience are still required to create gene length synthetic DNA. However, as the technology advances, DNA synthesis tools will move from the industrial and laboratory setting into the realm of Do-It-Yourself Biologists and amateur scientists. The current screening consortia and government guidelines may lose effectiveness as DNA synthesis technologies become more diffused, in geographic location and across levels of expertise. However, there exist strategies that government, academia, law enforcement, and the synthesis industry can follow to mitigate these possible future security issues.

Encourage reporting of suspicious behavior and reduce negative repercussions for incorrect leads. The FBI is currently conducting an outreach program to academic labs and members of the Do-It-Yourself Biology Community (You, 2011). Special Agent Ed You, who is spearheading the effort, is encouraging this outreach and formation of community alliances. The FBI knows that if a nefarious actor wanted to construct a dangerous pathogen, they are likely to let someone know either intentionally or by accident. By reaching out now, the FBI hopes that community members would report suspicious behavior before the nefarious actor can do harm.

Encourage safety and security best practices through outreach and educational programs like iGEM. The iGEM competition is an excellent test

bed to encourage and study issues in safety, security, and best practices. In addition to iGEM's educational ability, it is also heavily international. This gives iGEM a captive audience of members who are likely to be leaders in biotechnologies, biological engineering, and synthetic biology. Using educational outreach programs like iGEM to promote best practices in synthetic biology could be applied to other areas of biotechnology, including DNA synthesis.

9.3 Closing Thoughts

DNA synthesis is fundamentally different than other dual use technologies. However, general lessons drawn from other dual use technologies can still be applied. International cooperation will be vital to promoting best standards for DNA synthesis around the globe. Having experts and leaders in the DNA synthesis field meet to discuss best practices and security issues will improve the security of DNA synthesis. In addition, countries that are often shut out of discussions led by the U.S. or Europe should still be invited to participate in such discussions. In the end, it is in their best interest to promote security in their DNA synthesis industries. It is surely in the U.S.'s best interest to have everyone understand and promote high levels of safety and security.

10. Conclusions and Areas of Further Study

The global biotechnology industry may be a game changing technology for the 21st century. The growing biotechnology industry feeds the growing demand for synthetic DNA. However, there are associated security issues with the ability to synthesize longer and more complex DNA sequences. These include the potential that a nefarious actor or group would purchase the genetic code for a dangerous human pathogen to develop a weapon. The global DNA synthesis industry has instituted two voluntary consortia (the IGSC and the IASB) where members screen DNA orders and their customers placing the orders. The industry hopes that these screening processes will deter those who would acquire synthetic DNA in order to do harm, and would alert authorities to suspicious orders and persons.

Looking forward, there will be more discussion of what changes should be made to the current screening regime. Currently, the U.S. government does not have legally binding regulations and the released guidelines are currently less capable than what is mandated by the current screening consortia. Many of these future policy actions need to be based on how the DNA synthesis industry changes over the coming years if it continues to exist as a service.

However, even without promulgating mandatory regulations for the DNA synthesis industry, there are several governmental policies that would improve DNA synthesis security in the near and long term. These include encouraging suspicious behavior reports by everyone who works in biotechnology, including DNA synthesis providers, Do-It-Yourself Biologists, and researchers at universities. Additionally the government should encourage the use of industry's best practices and publicize the benefits of the voluntary screening consortia. In addition, the government can aid the consortia by creating a master list of dangerous pathogens and their sequences, as well as a list of individuals or groups who are forbidden from ordering synthetic DNA. Also, the government can act as a red team by initiating suspect orders to synthetic DNA providers to

test their screening protocols. Lastly, the government, industry, academia, and regulators can seek international cooperation in the iGEM competition to move forward on issues of safety and security through the use of adaptive regulation.

DNA synthesis technology has the potential to positively transform our world. This technology will have the greatest chance of achieving its potential if it is not held back by stiff regulations. However, like all dual use technologies, it also has the potential to do great harm if it is misused intentionally or accidentally. It is clear that there are policy options that would encourage development of DNA synthesis technologies and improve the current security regime. The analysis presented in this thesis offers a perspective into the DNA synthesis industry and its security regime, and how the government can take proactive policy measures that would improve future security.

Looking forward, this thesis compared DNA synthesis to other dual use technologies and how the U.S. and the international community regulate these technologies. Additional research could examine other industries that are not considered dual use industries but have parallels to DNA synthesis in their ubiquity, growing importance, and ease of access.

11. Appendices

11.1 IASB Code of Conduct

Created in Cambridge, MA. Nov. 3, 2009

1 Preamble

The field of Synthetic Biology is gaining momentum in the academic and commercial world and evolving rapidly. In parallel, a market for Synthetic Biology products and services has developed and grown rapidly over the past ten years.

The International Association Synthetic Biology represents a number of companies and organizations with a stake in Synthetic Biology, for instance as providers of double-stranded recombinant DNA synthesis (hereinafter “gene synthesis”) or bioinformatics products. IASB has created this Code of
Conduct in order to secure the foundations of this fledgling field against abuse and to bring Synthetic Biology to its full potential. It is aimed at all providers of gene synthesis services.

The most fundamental tools for the design of Synthetic Biology applications are synthetic genes and their intrinsic features of freedom of design and artificial biological function. This Code of Conduct helps companies that provide DNA synthesis services and products and academic and public institutions that practice DNA synthesis to conduct their business in a sensible and responsible way.

Declaration:

The Undersigned herewith declare that they are in full agreement with the need for a safe and responsible use of synthetic DNA. They strictly follow all regulations and international standards designed to safeguard against intentional or unintentional abuse of synthetic DNA.

2 General Considerations

Synthetic Biology provides the means to accelerate the assembly of complex biological networks and to rapidly create biological entities with new properties. These powers will undoubtedly lead to a number of beneficial developments such as sustainable biofuels, new therapeutics, and biodegradable plastics. However, the efficiency and potential power of Synthetic Biology can also create the risk of abuse. Through rapid DNA synthesis, biorisk-associated genes such as toxin genes or virulence factors become accessible to a large number of users.

In order to contain the risks of Synthetic Biology and to protect the field against misuse, the Undersigned have adopted this Code of Conduct, which provides guidelines for safe, secure, and responsible commercial or non-commercial DNA synthesis. One important consideration of any regulation for biosafety and biosecurity is the freedom of research: A lot of beneficial developments would be impossible without the freedom to explore organisms and genes that bear a certain environmental or health risk. It is our conviction that such a risk can be managed and contained in a secure manner, while at the same time ensuring the level of freedom that is necessary for desired scientific advancements.

It is our declared intention to raise barriers for malign attackers through a number of measures that will combine to protect Synthetic Biology from abuse. We aim at encouraging continued improvements and harmonization in this field, as well as adoption and further evolution of this Code of Conduct and the Best Practice Guidelines in the future.

The Undersigned will participate or otherwise reasonably contribute for regular scientific dialogue on the further evolution of screening, best practices and the topic of virulence factors and positive or negative lists of elements against which synthetic genes should be screened.

The Undersigned promise to develop a compliance plan for adherence to this Code of conduct. This Code has been expressly designed to guide companies

and other entities engaged in the synthesis of double stranded DNA of minimum 200 base pairs in length and multi-gene constructs.

The Undersigned express no opinion about the extent to which the standards described herein may be applicable to the much shorter sequences known as “oligos.”

3 Risk assessment and risk management

Abuse of synthetic genes in hazardous applications is possible in two ways only: Intentionally, and by failures in risk assessment and management.

The technology of handling synthetic genes uses complex procedures, which by their nature are self contained and tightly controlled under existing standards of good practice.

For biosecurity, risk assessment entails the screening of DNA sequences for genes which can be intentionally abused, for example, in terrorist activities, whereas risk management entails the restriction of access to synthetic DNA to legitimate users.

4 Record keeping

• Records of suspicious inquiries and positive screening hits will be kept for at least 8 years.

• Statistics on biosecurity and biosafety related inquiries and orders will be kept for at least 8 years. Information to be retained shall include the total number of inquiries and orders for synthetic genes, the number of inquiries and orders with positive screening hits, and the number of orders with positive screening hits which have been respectively filled or rejected.

5 Cooperation with Authorities

Gene synthesis providers shall take reasonable steps to maintain communications with the government in the nation where they are

headquartered. Gene synthesis providers shall promptly inform these authorities each time they encounter evidence which clearly suggests possible illegal activities. Such evidence will include, by way of example, inquiries and orders that strongly suggest illegal activities, such as attempts to conceal a nonbusiness delivery address."

6 Sequence Screening

• Gene synthesis companies should always take reasonable steps to determine the relationship of the requested sequences to risk-associated sequences before sending them to customers. The following procedure reflects IASB members' best collective judgment of how to achieve this goal within the framework of existing technology:

1) DNA sequences submitted as inquiries or orders for DNA synthesis by customers will be screened against GENBANK for reasonable sequence similarity to pathogens. Members may take further reasonable steps to determine the function and evaluate the associated biorisk associated with homologous genes following procedures to be defined by the Technical Experts Group on Biosecurity (hereinafter "TEGB"). Pending such procedures, providers shall determine and follow their own best practices.
2) In addition to determining biorisk, entities shall also comply with all national laws. This will include reviewing and comparing top homology hits against (a) all Australia Group biological dual-use organisms, (b) The U.S. Select Agent and Toxins list, and (c) against national organism lists for export control or biological safety/security.

• The foregoing procedure establishes a benchmark capability for detecting threat sequences. However we expect researchers to develop new sequence screening technologies over time. Members shall be free to adopt such alternative technologies provided that the new methods have first been empirically shown to detect threat sequences at reliability levels that meet or

exceed the benchmark methods described above, as elaborated by TEGB over time. IASB members pledge to promptly update this Code of Conduct to reflect such new (and potentially higher) standards as they appear.

• IASB members pledge to take ongoing, collective efforts to refine and improve today's screening technologies over time. These shall include:

1) Establishing a standing Committee to review and if necessary update and extend this Code of Conduct in light of changing threats and/or technology advances over time.

2) Regularly exchanging literature searches, virulence judgments, and other data needed to determine the function and/or threat potential of Genbank genes through a secure on-line collaboration to be hosted by the University of California's Goldman School of Public Policy (VIREP).

3) Regularly exchanging, discussing, and collaborating on best practices and ideas through person-to-person contacts and through a secure on-line collaboration.

• Providers that find that a requested gene may code for functions that pose a biosecurity risk shall not fill such orders unless and until they have conducted intensive customer screening at the highest levels provided for in Section 8 of this Code.

7 Response to Identified Threats

• Whenever any of the procedures described in Section 6 produce a "hit" as defined by the then-applicable TEGB guidance, the hit will be assessed by a molecular biologist or similar subject matter expert.

• When the hit is deemed authentic,

1) the customer will be notified and made aware of the perceived risk,

2) the order will be accepted only if the customer is a legitimate user (see section 8) and all national regulations that apply to the exporting/producing company have been met.

3) National authorities shall be contacted as to the extent provided for in Section 5.

8 Customer Screening

Gene synthesis providers should always take reasonable steps to confirm that their customers are who they say they are. Where customers seek risk-associated sequences, providers should take further reasonable efforts to confirm that the customer seeks the requested sequence for legitimate purposes, and has carefully considered any safety or security risks potentially associated with their use of the sequence. The following procedure reflects IASB members' best collective judgment of how to achieve these goals within the framework of existing technology:

• In a first step, which is to be performed for all orders independent of whether they are considered to be risk-associated:

1) A minimum set of identification data for the customer will be retrieved, including postal address, institution, country, telephone number, and email address

2) These data will be kept on record according to section 4.

• When an ordered synthetic gene is identified as a risk-associated sequence, the following steps are to be performed:

1) The legitimacy of the customer will be determined by a commercially-reasonable inquiry by the gene synthesis provider and the decision of legitimacy will be documented.

2) It will be ensured that the stated postal address is not a residential address nor a PO box or similar address with limited traceability.

3) The foregoing determination shall include, inter alia, verifying the addresses of businesses and institutions which placed the order, and ensuring that the address owner is a legitimate organization (such as a registered business or an internationally recognized academic institution).

The foregoing procedure establishes a benchmark capability for screening customers. However we expect researchers to develop new screening methods over time. Members shall be free to adopt such alternative methods provided that they meet or exceed the benchmark methods described above. IASB members pledge to promptly update this Code of Conduct to reflect such new (and potentially higher) standards as they appear.

IASB members pledge to take ongoing, collective efforts to refine and improve today's screening technologies over time. These shall include (a) establishing a standing Committee to review and if necessary update and extend this Code of Conduct in light of changing threats and/or technology advances over time, and (b) regularly exchanging, discussing, and collaborating on best practices and ideas through person-to-person contacts and through a secure on-line collaboration.

Where the provider's investigation reveals that its immediate customer of a risk-associated gene is not the intended end-user but will instead re-ship the risk-associated gene to a third party end user, gene synthesis companies shall either (a) identify and investigate the end-user as provided for in this Code, or (b) take

reasonable steps to confirm that its immediate customer has adopted and routinely follows procedures comparable to those provided for in this Code.

9 Cooperation on Biosafety and Biosecurity

• The Undersigned will participate in the formation of a Technical Expert Group on Biosecurity (TEGB). This group will review current design and implementations of biosafety and biosecurity measures, and will propose and initiate improvements.

• The TEGB shall develop an IASB operated seal of approval program to certify compliance with this Code. Providers will be encouraged to apply for seals whether or not they are currently IASB members.

11.2 IGSC Harmonized Screening Protocol

Preamble

This document outlines the standards and practices that IGSC gene synthesis companies apply to prevent the misuse of synthetic genes. By screening the sequences of ordered genes and vetting customers, IGSC companies help to ensure that science and industry realize the many benefits of gene synthesis technology while minimizing risk.

The ICGS companies together represent approximately 80% of commercial gene synthesis capacity world-wide.

1. Gene Sequence Screening

IGSC companies screen synthetic gene orders to identify regulated pathogen sequences and other potentially dangerous sequences.

1. IGSC companies screen the complete DNA sequence of every synthetic gene order against the DNA sequences in a Regulated Pathogen Database, and against all entries found in one or more of the internationally coordinated

sequence reference databanks (i.e., NCBI/GenBank, EBI/EMBL, or DDBJ). The IGSC is currently assembling a Regulated Pathogen Database that will include data from all organisms on the Select Agent list, the Australia Group List, and any other national list of regulated pathogens. Until this is deployed, each company is using its own database of pathogen sequences. At a minimum, IGSC companies screen for all pathogen and toxin genes from the U.S. Select Agents and Toxins List and/or from the list specified in paragraphs 1C351-1C354 of European Union Council Regulation 428/2009.

2. IGSC companies translate all six reading frames of each synthetic gene into an amino acid sequence. This sequence is screened against the protein sequences derived from the databases described above.

3. IGSC companies use automated screening as a filter to identify pathogen and toxin DNA sequences. When automated screening identifies a potential pathogen or toxin sequence, the order is reviewed by a human expert and is either accepted, accepted with a requirement for additional customer review, or rejected.

2. Gene Customer Screening

1. IGSC companies require identification data from all potential customers for synthetic genes, including at a minimum a shipping address, institution name, country, telephone number, and email address. We do not ship to PO Boxes.

2. Potential customers are screened against OFAC's SDN List, the Department of State's Debarred List, and BIS's Denied Persons, Entity, and Unverified lists, or the HADDEX list, and/or any other list required by applicable national regulations.

3. IGSC companies require additional customer screening before accepting orders for DNA sequences from regulated pathogens. Although the U.S. Select Agent Regulations and the European Commission regulations do not restrict access to all Select Agent genes, IGSC companies supply genes from regulated pathogens only to researchers in government laboratories, universities, non-profit research institutions, or industrial laboratories demonstrably engaged in legitimate research. Customers ordering Select Agent or Australia Group DNA fragments must provide a written description of the intended use of the synthetic product; we verify independently a) the identity of the potential customer and purchasing organization, and b) that the described use is consistent with the activities of the purchasing organization.

IGSC companies use the current recommendations from the U.S. CDC and/or the Department of Agriculture and/or the European Commission (CR42) to determine which DNA sequences are Select Agents as recombinant DNA fragments. We supply genes with such sequences only if the supplier and the customer are able to comply with all Select Agent regulations applicable to that gene.

In general, IGSC companies only sell DNA or fragments of regulated pathogens to bone fide end-users. We do not sell or ship such material to distributers or other resellers, unless those companies identify the end-user receiving the products and demonstrate their compliance with every requirement otherwise applicable to that end-user.

3. Record keeping

1. Sequence Screen Results: IGSC companies retain records of every gene sequence screening result for at least 8 years.

2. Customer Screen Results: IGSC companies retain records of every customer screening result for at least 8 years.

3. Product & Delivery Information: IGSC companies retain records of every gene synthesized and delivered for a minimum of 8 years after shipping, including at least the following: (a) the synthetic DNA sequence; (b) the vector; and (c) the recipient's identity and shipping address.

4. Order Refusal & Reporting

1. IGSC companies reserve the right to refuse to fill any order and to notify authorities upon identifying potentially problematic orders.

2. IGSC companies have established relationships with local and national law enforcement and intelligence authorities with whom we can share information to report and to prevent the potential misuse of synthetic genes.

3. IGSC companies will report any request for a gene associated with the pathogenicity of an organism received from a suspicious potential customer and/or potential customer failing to establish its bone fides in application of the practices set forth in section 2.

5. Regulatory Compliance

1. IGSC companies comply with all applicable laws and regulations governing the synthesis, possession, transport, export, and import of gene synthesis and other products.

2. We comply with World Health Organization recommendations concerning the distribution, handling, and synthesis of Variola virus DNA.

Consortium Collaborative Activities

IGSC companies intend to work together in order to:

1. Develop and update a Regulated Pathogen Database to include all gene sequences identified as potentially hazardous by authoritative groups such as the CDC, the Australia Group, and the U.S. and European governments.

2. Ensure that we use the best and most effective algorithms to screen gene sequences against the Regulated Pathogen Database.

3. Collaborate with our respective national governments in support of effective oversight of gene synthesis technology, and to encourage international coordination.

4. Incorporate recommendations from the regulatory, scientific, and public interest communities into our screening and other biosecurity processes.

Revisions to the Harmonized Screening Protocol

This document represents an initial effort by a group of companies committed to the responsible use of gene synthesis technology. IGSC companies welcome comments and suggestions to improve the Harmonized Screening Protocol from scientists, regulators, and other interested parties. This document will be revised periodically in response to these suggestions and to changes in the scientific, technical, or regulatory environment.

Terminology

Gene Synthesis: This document uses the phrase “gene synthesis” to refer to the production of double-stranded, recombinant DNA fragments from oligonucleotides. Synthetic genes are typically provided in plasmid vectors.

Oligonucleotides: Chemically-synthesized, single-stranded DNA fragments, typically supplied as a solution in a tube or a multi-well plate.

Synthetic Gene: A gene or other DNA fragment produced by gene synthesis, typically between 50 and 50,000 base pairs in length.

Related Links

Select Agents and Toxins List:
http://www.selectagents.gov/Select%20Agents%20and%20Toxins%20List.html

EU Council Resolution 428:
http://www.consilium.europa.eu/showPage.aspx?id=408&lang=en

HADDEX:
http://www.ausfuhrkontrolle.info/ausfuhrkontrolle/de/arbeitshilfen/haddex/index.html

OFAC's SDN List:
http://www.treas.gov/offices/enforcement/ofac/sdn/

Department of State's Debarred List:
http://www.pmddtc.state.gov/compliance/debar.html

BIS's Denied Persons, Entity, and Unverified lists:
http://www.bis.doc.gov/complianceandenforcement/liststocheck.htm

Current Recommendations from the U.S. CDC:
http://www.selectagents.gov/SyntheticGenomics.html

Australia Group Listed Source Organisms:

http://www.australiagroup.net/en/biological_agents.html

World Health Organization Recommendations Concerning the Distribution, Handling, and Synthesis of Variola Virus DNA:
http://www.who.int/csr/disease/smallpox/SummaryrecommendationsMay08.pdf

11.3 Australia Group Core Group

List of Biological Agents for Export Control

Viruses:

Andes virus
Chapare virus
Chikungunya virus
Choclo virus
Congo-Crimean haemorrhagic fever virus
Dengue fever virus
Dobrava-Belgrade virus
Eastern equine encephalitis virus
Ebola virus
Guanarito virus
Hantaan virus
Hendra virus (Equine morbillivirus)
Japanese encephalitis virus
Junin virus
Kyasanur Forest virus
Laguna Negra virus
Lassa fever virus
Louping ill virus
Lujo virus
Lymphocytic choriomeningitis virus
Machupo virus
Marburg virus

Monkey pox virus
Murray Valley encephalitis virus
Nipah virus
Omsk haemorrhagic fever virus
Oropouche virus
Powassan virus
Rift Valley fever virus
Rocio virus
Sabia virus
Seoul virus
Sin nombre virus
St Louis encephalitis virus
Tick-borne encephalitis virus (Russian Spring-Summer encephalitis virus)
Variola virus
Venezuelan equine encephalitis virus
Western equine encephalitis virus
Yellow fever virus

Bacteria:

Bacillus anthracis
Brucella abortus
Brucella melitensis
Brucella suis
Chlamydophila psittaci (formerly known as Chlamydia psittaci)
Clostridium botulinum
Clostridium argentinense (formerly known as Clostridium botulinum Type G), botulinum neurotoxin producing strains
Clostridium baratii, botulinum neurotoxin producing strains
Clostridium butyricum, botulinum neurotoxin producing strains
Francisella tularensis
Burkholderia mallei (Pseudomonas mallei)

Burkholderia pseudomallei (Pseudomonas pseudomallei)

Salmonella typhi

Shigella dysenteriae

Vibrio cholerae

Yersinia pestis

Clostridium perfringens, epsilon toxin producing types[2]

Shiga toxin producing Escherichia coli (STEC) of serogroups O26, O45, O103, O104, O111, O121, O145, O157, and other shiga toxin producing serogroups[3]

Coxiella burnetii

Rickettsia prowazekii

Toxins as follow and subunits thereof (4):

Botulinum toxins[5]

Clostridium perfringens alpha, beta 1, beta 2, epsilon and iota toxins

Conotoxin[5]

Ricin

Saxitoxin

Shiga toxin

Staphylococcus aureus enterotoxins, hemolysin alpha toxin, and toxic shock syndrome toxin (formerly known as Staphylococcus enterotoxin F)

Tetrodotoxin

Verotoxin and shiga-like ribosome inactivating proteins

Microcystin (Cyanginosin)

Aflatoxins

Abrin

Cholera toxin

Diacetoxyscirpenol toxin

T-2 toxin

HT-2 toxin

Modeccin toxin

Volkensin toxin

Viscum Album Lectin 1 (Viscumin)

Fungi:
Coccidioides immitis
Coccidioides posadasii

(1) Biological agents are controlled when they are an isolated live culture of a pathogen agent, or a preparation of a toxin agent which has been isolated or extracted from any source, or material including living material which has been deliberately inoculated or contaminated with the agent. Isolated live cultures of a pathogen agent include live cultures in dormant form or in dried preparations, whether the agent is natural, enhanced or modified.

An agent is covered by this list except when it is in the form of a vaccine. A vaccine is a medicinal product in a pharmaceutical formulation licensed by, or having marketing or clinical trial authorization from, the regulatory authorities of either the country of manufacture or of use, which is intended to stimulate a protective immunological response in humans or animals in order to prevent disease in those to whom or to which it is administered.

(2) It is understood that limiting this control to epsilon toxin-producing strains of Clostridium perfringens therefore exempts from control the transfer of other Clostridium perfringens strains to be used as positive control cultures for food testing and quality control.

(3) Shiga toxin producing Escherichia coli (STEC) is also known as enterohaemorrhagic E. coli (EHEC) or verocytotoxin producing E. coli (VTEC).

(4) Excluding immunotoxins.

(5) Excluding botulinum toxins and conotoxins in product form meeting all of the following criteria:

are pharmaceutical formulations designed for testing and human administration in the treatment of medical conditions;
are pre-packaged for distribution as clinical or medical products; and are authorized by a state authority to be marketed as clinical or medical products.

Genetic Elements and Genetically-modified Organisms:
Genetic elements that contain nucleic acid sequences associated with the pathogenicity of any of the microorganisms in the list.

Genetic elements that contain nucleic acid sequences coding for any of the toxins in the list, or for their sub-units.

Genetically-modified organisms that contain nucleic acid sequences associated with the pathogenicity of any of the microorganisms in the list.

Genetically-modified organisms that contain nucleic acid sequences coding for any of the toxins in the list or for their sub-units.

Technical note:
Genetically-modified organisms includes organisms in which the genetic material (nucleic acid sequences) has been altered in a way that does not occur naturally by mating and/or natural recombination, and encompasses those produced artificially in whole or in part.

Genetic elements include inter alia chromosomes, genomes, plasmids, transposons, and vectors whether genetically modified or unmodified, or chemically synthesized in whole or in part.

Nucleic acid sequences associated with the pathogenicity of any of the micro-organisms in the list means any sequence specific to the relevant listed micro-organism:

that in itself or through its transcribed or translated products represents a significant hazard to human, animal or plant health; or
that is known to enhance the ability of a listed micro-organism, or any other organism into which it may be inserted or otherwise integrated, to cause serious harm to human, animal or plant health.

These controls do not apply to nucleic acid sequences associated with the pathogenicity of enterohaemorrhagic Escherichia coli, serotype O157 and other verotoxin producing strains, other than those coding for the verotoxin, or for its sub-units.

Warning List (1)

Bacteria:
Clostridium tetani (2)
Legionella pneumophila
Yersinia pseudotuberculosis
Other strains of Clostridium species that produce botulinum neurotoxin (3)

Fungi:
Fusarium sporotrichioides
Fusarium langsethiae

(1) Biological agents are controlled when they are an isolated live culture of a pathogen agent, or a preparation of a toxin agent which has been isolated or extracted from any source, or material including living material which has been deliberately inoculated or contaminated with the agent. Isolated live cultures of a

pathogen agent include live cultures in dormant form or in dried preparations, whether the agent is natural, enhanced or modified.

An agent is covered by this list except when it is in the form of a vaccine. A vaccine is a medicinal product in a pharmaceutical formulation licensed by, or having marketing or clinical trial authorization from, the regulatory authorities of either the country of manufacture or of use, which is intended to stimulate a protective immunological response in humans or animals in order to prevent disease in those to whom or to which it is administered.

(2) The Australia Group recognizes that this organism is ubiquitous, but, as it has been acquired in the past as part of biological warfare programs, it is worthy of special caution.

(3) It is the intent of Australia Group members to add to the control list strains of species of Clostridium identified as producing botulinum neurotoxin.

Genetic Elements and Genetically-modified Organisms:

Genetic elements that contain nucleic acid sequences associated with the pathogenicity of any of the microorganisms in the list.

Genetic elements that contain nucleic acid sequences coding for any of the toxins in the list, or for their sub-units.

Genetically-modified organisms that contain nucleic acid sequences associated with the pathogenicity of any of the microorganisms in the list.

Genetically-modified organisms that contain nucleic acid sequences coding for any of the toxins in the list or for their sub-units.

Technical note:

Genetically-modified organisms includes organisms in which the genetic material (nucleic acid sequences) has been altered in a way that does not occur naturally by mating and/or natural recombination, and encompasses those produced artificially in whole or in part.

Genetic elements include inter alia chromosomes, genomes, plasmids, transposons, and vectors whether genetically modified or unmodified, or chemically synthesized in whole or in part.

Nucleic acid sequences associated with the pathogenicity of any of the micro-organisms in the list means any sequence specific to the relevant listed micro-organism:

that in itself or through its transcribed or translated products represents a significant hazard to human, animal or plant health; or
that is known to enhance the ability of a listed micro-organism, or any other organism into which it may be inserted or otherwise integrated, to cause serious harm to human, animal or plant health.

11.4 Select Agents and Toxins List

§ 73.3 HHS select agents and toxins.

(a) Except for exclusions under paragraphs (d) and (e) of this section, the HHS Secretary has determined that the biological agents and toxins listed in this section have the potential to pose a severe threat to public health and safety.
(b) HHS select agents and toxins:

- Abrin
- Botulinum neurotoxins
- Botulinum neurotoxin producing species of
- Clostridium
- Cercopithecine herpesvirus 1 (Herpes B virus)
- Clostridium perfringens epsilon toxin

• Coccidioides posadasii/Coccidioides immitis
• Conotoxins
• Coxiella burnetii
• Crimean-Congo haemorrhagic fever virus
• Diacetoxyscirpenol
• Eastern Equine Encephalitis virus
• Ebola viruses
• Francisella tularensis
• Lassa fever virus
• Marburg virus
• Monkeypox virus
• Reconstructed replication competent forms of the 1918 pandemic influenza virus containing any portion of the coding regions of all eight gene segments (Reconstructed 1918 Influenza virus)
• Ricin
• Rickettsia prowazekii
• Rickettsia rickettsii
• Saxitoxin
• Shiga-like ribosome inactivating proteins
• Shigatoxin
• South American Haemorrhagic Fever viruses (Junin, Machupo, Sabia, Flexal, Guanarito)
• Staphylococcal enterotoxins
• T–2 toxin
• Tetrodotoxin
• Tick-borne encephalitis complex (flavi) viruses (Central European Tick-borne encephalitis, Far Eastern Tick-borne encephalitis [Russian Spring and Summer encephalitis, Kyasanur Forest disease, Omsk Hemorrhagic Fever])
• Variola major virus (Smallpox virus) and
• Variola minor virus (Alastrim)

• Yersinia pestis

(c) Genetic Elements, Recombinant Nucleic Acids, and Recombinant Organisms:

(1) Nucleic acids that can produce infectious forms of any of the select agent viruses listed in paragraph (b) of this section.

(2) Recombinant nucleic acids that encode for the functional form(s) of any of the toxins listed in paragraph (b) of this section if the nucleic acids:

(i) Can be expressed in vivo or in vitro,

or

(ii) Are in a vector or recombinant host genome and can be expressed in vivo or in vitro.

(3) HHS select agents and toxins listed in paragraph (b) of this section that have been genetically modified.

(d) HHS select agents or toxins that meet any of the following criteria are excluded from the requirements of this part:

(1) Any HHS select agent or toxin that is in its naturally occurring environment provided the select agent or toxin has not been intentionally introduced, cultivated, collected, or otherwise extracted from its natural source.

(2) Non-viable HHS select agents or nonfunctional HHS toxins.

(3) HHS toxins under the control of a principal investigator, treating physician or veterinarian, or commercial manufacturer or distributor, if the aggregate amount does not, at any time, exceed the following amounts: 100 mg of Abrin; 0.5 mg of Botulinum neurotoxins; 100 mg of Clostridium perfringens epsilon toxin; 100 mg of Conotoxins; 1,000 mg of Diacetoxyscirpenol; 100 mg of Ricin; 100 mg of Saxitoxin; 100 mg of Shiga-like ribosome inactivating proteins; 100 mg of Shigatoxin; 5 mg of Staphylococcal enterotoxins; 1,000 mg of T–2 toxin; or 100 mg of Tetrodotoxin.

(e) An attenuated strain of a HHS select agent or toxin may be excluded from the requirements of this part based upon a determination that the attenuated strain does not pose a severe threat to public health and safety.

(1) To apply for an exclusion, an individual or entity must submit a written request and supporting scientific information. A written decision granting or denying the

request will be issued. An exclusion will be effective upon notification to the applicant. Exclusions will be published periodically in the notice section of the FEDERAL REGISTER and will be listed on the CDC Web site at http://www.cdc.gov/.

(2) If an excluded attenuated strain is subjected to any manipulation that restores or enhances its virulence, the resulting select agent or toxin will be subject to the requirements of this part.

(3) An individual or entity may make a written request to the HHS Secretary for reconsideration of a decision denying an exclusion application. The written request for reconsideration must state the facts and reasoning upon which the individual or entity relies to show the decision was incorrect. The HHS Secretary will grant or deny the request for reconsideration as promptly as circumstances allow and will state, in writing, the reasons for the decision.

(f) Any HHS select agent or toxin seized by a Federal law enforcement agency will be excluded from the requirements of this part during the period between seizure of the select agent or toxin and the transfer or destruction of such agent or toxin provided that:

(1) As soon as practicable, the Federal law enforcement agency transfers the seized select agent or toxin to an entity eligible to receive such agent or toxin or destroys the agent or toxin by a recognized sterilization or inactivation process,

(2) The Federal law enforcement agency safeguards and secures the seized select agent or toxin against theft, loss, or release, and reports any theft, loss, or release of such agent or toxin, and

(3) The Federal law enforcement agency reports the seizure of the select agent or toxin to CDC or APHIS. (i) The seizure of Botulinum eurotoxins, Ebola viruses, Francisella tularensis, Lassa fever virus, Marburg virus, South American Haemorrhagic Fever virus (Junin, Machupo, Sabia, Flexal, Guanarito), Variola major virus (Smallpox virus), Variola minor (Alastrim), or Yersinia pestis must be reported within 24 hours by telephone, facsimile, or e-mail. This report must be followed by submission of APHIS/CDC Form 4 within seven calendar days after seizure of the select agent or toxin.

(ii) For all other HHS select agents or toxins, APHIS/CDC Form 4 must be submitted within seven calendar days after seizure of the agent or toxin.
(iii) A copy of APHIS/CDC Form 4 must be maintained for three years.
(4) The Federal law enforcement agency reports the final disposition of the select agent or toxin by submission of APHIS/CDC Form 4. A copy of the completed form must be maintained for three years.

[70 FR 13316, Mar. 18, 2005, as amended at 70 FR 61049, Oct. 20, 2005; 73 FR 61365, Oct. 16, 2008; 73 FR 64554, Oct

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