# SUMMARY

## A Practical Perspective on DNA Synthesis and Biological Security

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Few developments have leapfrogged over predecessor technology as quickly and extensively as synthetic biology. Based on cutting-edge DNA synthesis technology, synthetic biology has already fueled an expansion of opportunities in biological engineering, with advanced capabilities that surpass those provided by traditional recombinant DNA technology. Improvements in synthesis technology are accelerating the pace of innovation in everything from the development of renewable energy to the production of bulk and fine chemicals, from information processing to environmental monitoring, and from agricultural productivity to breakthroughs in human health and medicine. Synthetic biology promises vast improvements to our well-being and our understanding of the living world.

Like any powerful technology, DNA synthesis has the potential to be misused. In the wrong hands, the new capabilities enabled by synthetic biology could give rise to both known and unforeseeable threats to our biological safety and security. Current government oversight of the DNA synthesis industry falls short of addressing this unfortunate reality.

Here, we introduce and outline a practical plan for developing an effective governance framework for the DNA synthesis industry. A thoughtfully crafted and effectively implemented framework would protect our continued well-being in at least two ways. First, the framework would promote our biological safety and security. Second, the framework would encourage the further responsible development of synthetic biology technologies and their continued, overwhelmingly constructive application. The proposed plan represents the collective views of the International Consortium for Polynucleotide Synthesis, the U.S. Federal Bureau of Investigation, the Chief Executive Officers or Presidents of several of the principal synthetic biology companies, and representatives from academia.

Our framework calls for the immediate and systematic implementation of a tiered DNA synthesis screening process. In order to establish accountability at the user level, individuals who place orders for DNA synthesis would be required to identify themselves, their home organization, and all relevant biosafety level information. Next, individual companies would use software tools to check synthesis orders against a set of select agents or sequences to help ensure regulatory compliance and flag synthesis orders for further review. Finally, DNA synthesis and synthetic biology companies would work together, and interface with appropriate government agencies, to rapidly and continually improve the underlying technologies used to screen orders and identify potentially dangerous sequences, as well as develop a clearly defined process to report behavior that falls outside of agreed-upon guidelines.

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### *Introduction*

Improving the human condition and our security depends on an ever-increasing understanding of health and medicine and a more thoughtful relationship with the natural world. The process of basic and applied biological research through which these goals are realized requires that scientists and engineers decipher and manipulate genetic material (DNA and RNA) in order to discover how living organisms work and advance our ability to interact with the natural world in a determined fashion. At present, all organisms – from bacteria to humans – appear complex and are imperfectly understood. During the 21st century, our ability to resolve biological complexity and usefully manipulate genetic material will become as important to our economy and security as is our current prowess at understanding and manipulating digital information using computers [Brent, 2004].

Today, most DNA is manipulated by individual researchers using powerful but labor-intensive methods that were developed in the 1970s and 1980s. For example, recombinant DNA (rDNA) technology is used to cut and splice pre-existing DNA fragments [Cohen et al., 1973]. As a second example, the polymerase chain reaction (PCR) is used to amplify targeted DNA fragments and to make a limited number of changes to pre-existing genetic material [Gefter et al., 1972; Mullis et al., 1986]. Experimental biologists spend a significant fraction of their research effort manipulating DNA in order to produce the genetic material that is needed to perform their desired experiments. For example, the estimated cost to the US National Institutes of Health (NIH) for supporting such preparatory work is up to $1.5 billion per year, or ~5% of the NIH annual budget [Mulligan, 2006].

An alternative approach for preparing genetic material de novo is DNA synthesis [Baker et al., 2006]. DNA itself is a polymer composed of nucleotides. Nucleotides are distinguished by the type of subunit, called a base, they contain: adenine (A), cytosine (C), guanine (G) or thymine (T). DNA synthesis is a technology that allows genetic material to be assembled de novo starting from relatively simple and readily accessible reagents. The synthesis of DNA is automated by use of machines, DNA synthesizers, which combine the individual reagents in the order required to produce the desired genetic material (i.e., the sequence of the desired DNA). Rather than manually manipulating pre-existing DNA using classical methods (above), a user of DNA synthesis specifies the information that defines the desired DNA fragment, sends this information to a DNA synthesizer, and receives the requested physical genetic material in return.

In the 1970s chemical DNA synthesis was developed as a method for producing relatively short fragments of DNA called oligonucleotides (< 200 nucleotides) [e.g., Agarwal et al., 1970]. From the 1970s through the 1990s additional methods were developed for assembling oligonucleotides into recombinant, biologically active genes [e.g., Stemmer et al., 1995]. Over the last 30 years, significant investments in the process of DNA synthesis and assembly have made it practical to construct longer fragments of DNA of up to 50,000 nucleotides [e.g., Kodumal et al., 2004]. Today, the direct synthesis and assembly of the DNA encoding genes and some viral genomes is routine, and DNA synthesizers are available internationally [Carlson, 2005].

As automated DNA synthesis technology improves, biologists and biological engineers are able to better focus their efforts on the research needed to advance our understanding of biology and ability to interact with the living world. For example, modern DNA synthesis technology is vastly accelerating advances in:

1. Biological production of energy,
2. Bulk and fine chemicals biosynthesis,
3. Bio-based manufacturing of materials,
4. Biological information processing,
5. Environmental sensing and remediation,
6. Agriculture, and

7. Human health and medicine [Endy, 2005; Arkin & Fletcher, 2006].

However, DNA synthesis technology presents issues for serious consideration. On the one hand, synthesis technology offers a boon for helping to resolve some of our most pressing issues such as hunger, health, energy, and environmental quality. On the other hand, the same technology poses a potential threat to personal, national, and international biological safety and security if it were misapplied to produce or modify human pathogens or other disruptive biological agents for nefarious purposes [Fraser & Dando, 2001; Chyba, 2006].

We cannot prohibit or restrict the use of DNA synthesis technology without great risk of compromising our short- and long-term economic competitiveness and security. Because DNA synthesis accelerates the pace by which human pathogens can be studied and therapeutics developed [e.g., Baric et al., 2006], the continued responsible development of synthesis technology will play an essential role in the execution of a successful strategy for promoting biological safety and security worldwide. Thus, a process is needed that allows the development and use of DNA synthesis technology to be integrated into a governance framework that oversees and promotes the constructive development and application of biological research and technology.

***Concern & Governance of the Manipulation of Genetic Material***

Recombinant DNA technology allows individuals to construct novel DNA molecules by joining selected fragments from pre-existing material (above). While it is not yet possible to predict the encoded properties of all novel combinations of genetic material, it is possible to imagine dangerous combinations of genetic material. The researchers who invented recombinant DNA technology wanted to directly address issues of biological safety and thus developed an oversight framework for regulating the use of recombinant DNA technology in the U.S. [Office of Biotechnology Activities, 2006]. In practice, the resulting framework requires that researchers who are working at organizations that receive funding from the National Institutes of Health (NIH), or at organizations or within jurisdictions that choose to adhere to the NIH guidelines, submit a description of their proposed research to an Institutional Biosafety Committee (IBC). Such committees are responsible for ensuring, among other things, that the research, if approved, takes place at the appropriate biological safety level and within appropriate guidelines. To date the IBC-based oversight framework has been successful due in part to the fact that rDNA- and PCR-based manipulation of genetic material is labor intensive, and such work tends to take place in laboratories and organizations that endorse and support an IBC or IBC-like oversight process. The National Science Advisory Board on Biosecurity (NSABB) is currently evaluating the potential for IBCs to be used as a resource to evaluate broader dual-use research of concern, including research using synthetic biology approaches [NSABB, 2006].

DNA synthesis, when combined with other advances since the 1970s, such as development of the internet and overnight shipping, challenges the existing rDNA-era governance framework for both biological safety and security on two fronts. First, synthesis allows for the physical decoupling of the design and use of engineered genetic material from the actual construction of the material; DNA can be readily designed in one location, constructed in a second location, and delivered to a third. Second, synthesis might provide an effective alternate route for obtaining specific pathogens. Today, this group includes: (i) pathogens for which the natural reservoirs remain unknown or that are otherwise difficult or dangerous to obtain from nature (e.g., Ebola virus), (ii) pathogens that are physically under lock and key in a very small number of facilities (e.g., variola major, the causative agent of smallpox), and (iii) pathogens that no longer exist (e.g., 1918 influenza virus). Our current approach to biological security relies on limiting physical access to pathogens. However, since the sequence information that defines the full genomes encoding these pathogens is freely available online; DNA synthesis could be used to obtain the genetic material encoding these pathogens. While additional expertise would be needed to produce infectious agents from the resulting genetic material, such work would not necessarily be subject to any review or oversight via the conventional rDNA governance framework.

Thus, practical steps should be taken now to ensure that the existing and future use of DNA synthesis

technology does not undermine our current biological safety framework or compromise the development and implementation of an effective strategy for future biological security.

### *DNA Synthesis in Practice*

Because of operational reliability issues and economies of scale, most DNA synthesis is carried out at commercial organizations or institutional facilities that provide one or more services to the biological and biotechnology research communities. The core of the DNA synthesis industry is loosely segregated into two sectors: companies and institutional facilities that provide short fragments of DNA (oligonucleotides, < 200 nucleotides), and companies that provide longer fragments of DNA (such as genes, > 200 nucleotides).

From a business and supply perspective, oligonucleotide synthesis is a technically facile and relatively mature industry in which providers compete to supply a commodity service to various markets. For example, oligonucleotide costs have fallen over the last decade (at least by a factor of 10 to ~$0.20 per nucleotide) and expected delivery times are currently ~48 hours (end-to-end) [Note 1]. While small capacity DNA synthesizers can be found in academic laboratories and are available for purchase via online auction, most researchers choose to obtain oligonucleotides via large-volume providers.

By comparison, gene- and longer-length DNA synthesis is still a technically demanding and relatively immature industry. The industry started in response to high-demand for a very small number of gene-length constructs from well-financed industrial customers (e.g., pharmaceutical companies). For example, in 2000 the market price for gene-length DNA synthesis was ~$10 per nucleotide [Carlson, 2003]. Early gene-length synthesis companies sought to profit from (and reduce) the cost differential between oligonucleotide- and gene-length DNA synthesis. By late 2005 there were at least 39 gene synthesis companies located around the world, including localities such as Boston, Hong Kong, Moscow, San Francisco, Seattle, Shanghai, and Tehran [Carlson, 2005].

Three factors are promoting the maturation and consolidation of the gene-length DNA synthesis sector. First, the market price of gene-length DNA has dropped by a factor of two roughly every 18 months, with current prices averaging just over ~$1 per nucleotide [Note 2]. Second, gene synthesis companies that have invested in foundational research have realized substantial process improvements and technology developments. Third, given increased process reliability, increasing customer volume, and expected economic opportunities, the gene-length synthesis sector has begun to attract modest amounts of investment capital [Herper, 2005]. Still, delivery times for gene-length fragments are measured in weeks not days and there remain many opportunities for technical innovation, process improvement, and business development. It is reasonable to expect that this combination of competitive and economic pressures may drive market consolidation to fewer, larger companies in the coming years.

### *Needs of Industry*

Continued improvements in DNA synthesis technology are critical for reducing the costs and increasing the pace of basic and applied biological research, and enabling the engineering of needed biological technologies. As part of the process of improving DNA synthesis technology, it is imperative that DNA synthesis companies develop and implement effective biological safety and security procedures, while retaining the ability to deliver high-quality products, at low cost, with very rapid delivery times. The full constructive potential of DNA synthesis technology will only be realized if a governance framework is developed that is compatible with the needs of industry and customers, and that supports best practice in biological safety and security, including the effective deterrence and investigation of any criminal uses of synthetic DNA.

For any governance framework to be effective, it must be compatible with the growth and success of industry. A governance framework that stymies the open commercial development of synthesis technology will retard research and make the challenge of responsibly developing the technology more difficult. Likewise, a regulatory framework that hampers a single country or group of countries'

commercial market without international consensus will drive users to the cheapest available country and have a limited impact in enhancing global security. Conversely, a governance framework that works in practice and that can be integrated into the practice of synthesis at modest cost and with little or no impact on delivery times would directly promote the responsible development of the technology and its constructive application. Because DNA synthesis technology and its commercialization are undergoing rapid development and improvement, now is the time to develop a governance framework process that will result in the effective oversight of DNA synthesis technology.

***Needs of Law Enforcement***

Traditional and novel biological security risks arise when considering synthetic biology and DNA synthesis technology in particular (above). While we all have responsibilities to prevent or at least limit any threats that may occur via the misuse of this promising technology, it is the specific responsibility of law enforcement to protect individuals and communities against such threats. Effective law enforcement requires a suite of approaches for deterring, interdicting, responding to, and investigating criminal acts. Prevention requires a framework of deterrents including methods that enable awareness and detection of threats and investigation and attribution of criminal acts. In developing effective methods for detecting threats and preventing and resolving crimes, it is essential to recognize that no single approach will be 100% effective. The strongest and most effective framework will require the thoughtful integration of responsibilities and capabilities across individuals, commercial organizations, private and non-governmental organizations, and government.

In the United States, federal law enforcement agencies, such as the Federal Bureau of Investigation (FBI), have defined responsibilities regarding biological agents that could be used to produce biological weapons. These responsibilities include deterrence, prevention, interdiction, criminal investigation, and providing forensic evidence for convictions. The FBI is also charged with lead agency responsibility for investigating violations that may be terrorist in nature as defined in Weapons of Mass Destruction (WMD)-related statutes [Note 3]. For example, any threatened use of a disease-causing organism directed at humans, animals, or plants is a crime, regardless of whether the perpetrator actually possesses a disease-causing agent. As a second example, the Biological Weapons Anti-Terrorism (BWAT) Act revisions contained within the USA PATRIOT Act establishes that knowingly possessing a biological agent, toxin, or delivery system that cannot be justified by a prophylactic, protective, bona fide research, or other peaceful purpose can result in arrest, prosecution, and fines or imprisonment of up to ten years [Note 4]; a result of this provision is that individuals and organizations in possession of potentially harmful biological agents document that they have such material for legitimate purposes. In the United States, the current Select Agent Rule (SAR) is central to prevention and investigation of misuse of potentially harmful biological agents [Center for Disease Control, 2006]. The SAR enables the monitoring and tracking of specified pathogens and toxins (i.e., “select agents”). In considering DNA synthesis technology it is important to note that the SAR applies primarily to the physical biological agent (e.g., an intact virus particle) and only to genetic material for a subset of select agents. This subset is determined on the basis of whether or not the genetic material can be readily used to produce the intact and infectious agent itself or functional form of the toxin (e.g., the intact genomes of positive-sense, single-stranded RNA viruses, the DNA encoding certain toxins, et cetera). The SAR enables the arrest and prosecution of individuals who illegally possess or distribute such agents.

Deterrence and prevention of the use of potentially harmful biological agents requires the effective coupling of intelligence and investigative activities so that it becomes possible to detect and disrupt the malicious acquisition or use of such agents. To be worthwhile, these activities must be integrated across the private sector and Federal, State, local, and international agencies. Effective prevention will also require heightened awareness throughout academia, industry, and the public as to the potential misuse of the technologies, reagents, and know how needed to produce such agents. Communication networks, both formal and ad hoc, must be developed so that the information that would allow investigators to prevent or disrupt any harmful acts becomes available in time to act. Developing such networks will require that government agencies foster widespread awareness of their needs by, for example, reaching out to scientific and technical communities via presentations at conferences and society meetings.

Additional relationships with specific sectors are also needed in order to promulgate awareness of defined threats and to establish two-way communication channels that allow for notification of events and identification of vulnerabilities.

Finally, an effective biological security framework requires that government agencies be prepared to respond to the threatened or actual use of a harmful biological agent. The response to an alleged incident begins with rapid and comprehensive assessment of the threat. For example, again in the United States, federal policy mandates that the FBI conduct a formal Threat Credibility Assessment. This process draws upon a number of interagency experts, including those within the Department of Health and Human Services (HHS), Centers for Disease Control and Prevention (CDC), and the U.S. Department of Agriculture (USDA). The Threat Assessment process includes an analysis of technical feasibility, operation practicability, and behavioral resolve. The results of this assessment are incorporated in the decisions involving the deployment of FBI response assets, the request, coordination and deployment of other U.S. government assets, and the notification of state and local authorities. Comprehensive technical information concerning DNA synthesis technology will be critical to law enforcement to accurately assess the technical feasibility and operation practicability of the threat. In addition, given an actual event, law enforcement often relies on scientific and technical analysis of evidence to assist in the capture and conviction of the individual(s) responsible for the event. Evidence can be any material, physical or electronic, that can associate or exclude individuals, victims, or suspects with a crime. To be useful, evidence must be collected in a manner that allows for proper documentation and it must be maintained and preserved in such a way that subsequent analysis yields information of investigative value. Analysis of collected evidence must consist of robust and reliable technical methods to ensure reliability of results. Forensic laboratories historically have well-established procedures for the collection of traditional evidence such as fingerprints, bullets and body fluids. Whether or not similar methods can be developed for DNA synthesis technology should be explored. For example, methods that enable recognition of the presence or use of synthetic DNA components in a harmful biological agent could facilitate investigation if the source of the synthetic DNA could also be identified. As a second example, DNA sequence information might be useful in linking a unique synthetic DNA element to a possible crime scene or suspect.

Developing an improved framework for deterring, preventing, detecting, disrupting, and responding to the intentional use of biological agents for the purpose of causing harm is required for our biological security. Given the numerous and paramount constructive uses of DNA synthesis technology, it remains essential that the resulting framework not have a chilling effect on the ongoing development and use the technology. Success will require the cooperative efforts of individuals throughout academia, corporations, private and non-government organizations, and governments worldwide.

### *Goals of a Governance Framework*

An ideal governance framework for DNA synthesis would (1) allow continued improvements to the process and commercialization of DNA synthesis technology, (2) reinforce and expand the existing community of responsible users of DNA synthesis technology, (3) deter any individuals or groups who might otherwise attempt to actively misapply DNA synthesis technology, (4) identify any individuals or groups who succeed in misapplying DNA synthesis technology, and (5) enable law enforcement to carry out effective and efficient investigations. To be effective, these goals must be balanced against a spectrum of costs and practical issues [Church, 2004; SB2.0 Declaration, 2006].

We believe that it is possible to realize an effective governance framework today, but that some aspects will take time to resolve. Nevertheless, it is paramount that a process for developing a governance framework begins immediately so that safety and security concerns are addressed as the technology develops. To be successful, any process will need to be amenable to industry structure and capabilities, acceptable to governments and users of DNA synthesis technology, and be recognized as fair and useful by the public and other stakeholders. All participants in the process should strive to understand the issues and improve their ability to foster the responsible development, application, and oversight of this foundational technology.

***Impractical Governance Options***

(1) Limited Access to Material, Equipment, and Know-how: The process of DNA synthesis starts with raw materials that are processed to produce the reagents used directly in the synthesis process; the resulting reagents are used to synthesize oligonucleotides that are subsequently assembled into longer DNA fragments. The chemicals used in synthesis are derived from common materials (e.g., sugarcane) and are widely used beyond DNA synthesis itself. Methods and equipment for synthesizing small numbers of oligonucleotides are available worldwide; recently developed equipment that allows for the production of millions of oligonucleotides simultaneously is less widely distributed although the knowledge for constructing such machines is widely disseminated. Methods for assembling oligonucleotides into long fragments of DNA (currently < 50,000 bp) have been published in the recent research literature. No specialized reagents or materials are required for synthesis. Taken together, these observations suggest that it is not practical, and likely impossible, to limit access to the materials, equipment or know how enabling DNA synthesis. However, as stated above, it is worth noting that economical, high-quality, high-throughput synthesis operations depend on investments in process and technology improvements; in the future, a modest number of organizations will likely operate most of the world's DNA synthesis capacity.

(2) Restricted Access to Select DNA Sequence Information: Would it be practical to limit access to the DNA sequence information of those biological agents whose genetic material is only publicly accessible via direct chemical synthesis? For example, could the genetic sequences of smallpox, Ebola, and 1918 influenza be stricken from the public databases, purged from the Internet, and any novel sequence information specifying these or other "restricted-access" pathogens remain secret? In practice, this strategy would be difficult to implement. While a government could restrict access to sequence information, such restrictions would be unlikely to be effective on an international level. Furthermore, sequencing technology is readily available and used extensively worldwide; thus, the sequence could be acquired and/or published independently. Moreover, the broader biological research community and government advisory boards (e.g., the National Science Advisory Board for Biosecurity, NSABB, National Academy of Sciences) have presented compelling arguments that justify making such information publicly available [Sharp, 2005]. Particularly, without such information, vaccines and other therapeutics could not possibly be developed, leaving us more vulnerable to emerging and re-emerging diseases and to attack by future biological terrorists.

(3) A Centralized Government Clearinghouse for Screening DNA Sequences:
DNA sequences can be checked prior to synthesis and assembly in order to reduce the chance of unknowingly constructing a prohibited or harmful DNA fragment. Sequence screening software has been developed and is used at many but not all gene synthesis companies [Note 5]. In theory, a centralized government facility could also screen DNA synthesis orders, only approving the fulfillment of orders that satisfy all regulatory and use requirements. While this approach may have immediate intuitive appeal, more thoughtful analysis leads to the conclusion that centralized screening would yield a less secure end-state due to (1) greatly hampered commercial development and user adoption of DNA synthesis technology, and (2) lack of effectiveness as a security measure.

First, a centralized clearinghouse approach would greatly hamper commercial development and user adoption of DNA synthesis technology and would fail in practice for a multitude of reasons, including a lack of transparency, increased product delivery times, and data confidentiality issues. Communicating the results of a centralized screening clearinghouse back to a potential customer would be cumbersome and would lack the transparency needed to allow customers to fully understand why a potential order might not have been approved. Also, the successful adoption of DNA synthesis technology and the tremendous positive impact of the technology depend on continued reductions in product delivery times. Any increase in process turn-around time associated with centralized screening would move the use of this technology outside typical and accepted research planning schedules and substantially retard widespread adoption. The biotechnology industries in any countries adopting a centralized screening clearinghouse approach would be disadvantaged relative to those in countries that used a more

commercially acceptable approach. Finally, many DNA synthesis customers consider their DNA sequence information to be proprietary and confidential. When these companies place orders with DNA synthesis companies, they typically insist upon tight data security and confidentiality procedures. Any requirements that orders placed at commercial DNA synthesis companies be subject to centralized screening would result in another layer of third-party disclosure into an environment with unknown, untested data security, and disclosure to a third party who has no legal or contractual obligations of confidentiality. The aggregate effect of all the above factors would be significantly chilling on the commercial adoption and economic feasibility of DNA synthesis technology in any country choosing a centralized clearinghouse approach.

Second, a centralized clearinghouse would be ineffective as a security measure. For example, reference has been made to the potential for centralized screening to detect a would-be biological terrorist who distributes their DNA synthesis order across a multitude of firms. Any such person would instead be likely to place a partial order, combining the resulting synthetic DNA with existing material derived from nature (e.g., non-synthetic sources), thereby preventing any efforts to aggregate the information needed to detect such behavior. Therefore, in addition to significant implementation costs, a centralized approach would provide no preventive security benefit.

Meanwhile, improvements in DNA synthesis technology are critical for enabling our ability to rapidly respond to naturally emerging biological pathogens and to any intentional bio-terrorist event (above). A centralized screening approach that chills the development or adoption of synthesis technology without providing a substantial benefit would result in a net less secure end state.

### *A Practical Beginning*

An effective initial governance framework should meet four goals. First, the framework should promote and later compel responsible behavior on the part of users of DNA synthesis technology. Second, the framework should be adoptable as best practice throughout industry. Third, the framework should enable common improvement of needed technologies and promote sharing of operational wisdom throughout industry and government. Finally, the framework should build on the existing practices that have enabled the safe development and application of recombinant DNA technology over the past three decades.

In mid-2006, four leading synthetic biology companies formed the International Consortium for Polynucleotide Synthesis (ICPS) to promote the development and adoption of corporate best practice with regard to safety and security in synthetic biology. Additionally, the ICPS was envisioned to serve as a platform for industry-government relations. By joining together, ICPS member companies can best serve their common purposes of promoting responsible use of DNA synthesis technology and providing a common point of interaction with government officials, agencies, and others.

Operationally, we support the development and validation of a tiered screening process that clearly identifies the contributions to safety and security due to (1) user responsibilities, (2) corporate practice, and (3) corporate technologies. User responsibilities would include the requirement that individuals who place orders for DNA synthesis identify themselves, their home organization, and any relevant biosafety level information. As a result, individual researchers and any local review committees would take some accountability for safety and security issues at the very beginning of the process, before a DNA synthesis order was placed. Next, individual companies would use ICPS-approved screening software tools to check synthesis orders against a set of select agents (or select sequences) to help ensure compliance with the SAR and, as needed, flag synthesis orders for further review. Finally, synthetic biology companies would work together, and interface with appropriate government agencies, to rapidly and continually improve the underlying technologies used to screen orders and identify potentially dangerous sequences, as well as develop a clearly defined process to report behavior that falls outside of agreed-upon security guidelines.

### *Unresolved Issues & Possible Opportunities*

The key strengths of the process that we endorse here are that it (1) directly extends the existing framework governing classical recombinant DNA work to account for recent and ongoing advances in DNA synthesis technology, (2) provides a focal point for developing and disseminating improvements in user and corporate best practice, (3) allows for the continued commercial improvement and application of DNA synthesis technology, and (4) provides a platform for industry-government interactions to work through remaining issues in an open and cooperative fashion. It is critical to state clearly that we are endorsing a process for developing effective governance of DNA synthesis technology and that several unresolved issues must be addressed over time in order to improve our future biological safety and security. The most pressing issues and opportunities for process improvement are:

(1) The best available screening software that is used to check DNA sequences against databases of select agents [Note 5] has a high false positive rate – non-harmful sequences are frequently flagged for manual review**.** As a result, experts must "hand check" many orders prior to synthesis, a process that is slow, expensive, and fallible. Funding and work should be organized immediately so that improved software can be produced and widely adopted early on. Government funding should play an important role in helping to organize and carry out such work.

(2) The current computational costs and false-positive rates of sequence screening preclude effective in-line screening of high-volume oligonucleotide synthesis orders. Unless addressed by improvements in screening software or approach (above), the combination of increasing order volume and a demand for reduced delivery times will eventually cause this issue to impact gene synthesis companies as well. Instead, sufficiently high-quality software should be developed so that it can be deployed at both oligonucleotide and gene synthesis companies.

(3) There are no defined minimal standards or guidelines for DNA sequence screening tools by either industry or government.

(4) With Germany as the only exception to our current knowledge, there are no clear or official points of contact within any national government for developing or following any to-be-defined standards and where unusual or problematic requests are forwarded.

(5) Select agent lists that name individual biological agents are not well matched to the requirements of sequence screening software, which would benefit from the definition of sets of select DNA sequences.

(6) The DNA synthesis industry operates worldwide. Within the United States there is incomplete agreement regarding best corporate practice; points of disagreement may be exacerbated worldwide. As a governance process is demonstrated to be effective, government and community endorsement (e.g., via extension of existing NIH rDNA guidelines) may be needed to drive (by model or negotiation) effective worldwide adoption.

(7) Comprehensive implementation of best practices by companies and their customers will not prevent individuals or groups from misapplying DNA synthesis technology. Best industrial practice may need to include an expansion of record keeping, including identification of equipment, for the purposes of accounting and guaranteeing that commercial DNA synthesis facilities are demonstrably responsible and to facilitate forensic investigation if such law enforcement needs arise.

**Conclusion**

Synthetic biology is accelerating the pace of scientific advancement in biotech applications and beyond, but minimizing specific associated biological security risks has remained unaddressed. DNA synthesis

is a powerful technology that exceeds the scope of the governmental oversight framework that was developed 30 years ago to foster the safe development and application of recombinant DNA technology. We have proposed a practical approach for developing a governance framework in the DNA synthesis industry, and to promote the constructive development and application of biological research and technology more generally. Only through a thoughtfully crafted and effectively implemented framework will we actually promote biological safety and security while realizing the tremendous potential of synthetic biology to address pressing human needs.

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Note 1. Google “oligonucleotide synthesis” and study the resulting sponsored links section.

Note 2. Google “gene synthesis” and study the resulting sponsored links section.

Note 3. US Code 18.1.113B.2332a

Note 4. US Code 18.1.10.175b

Note 5. Craic Computing, http://biotech.craic.com/blackwatch/ (2006).

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