NATIONAL
SCIENCE
ADVISORY
BOARD FOR
BIOSECURITY

ADDRESSING BIOSECURITY CONCERNS RELATED TO THE SYNTHESIS OF SELECT AGENTS

~ DRAFT RECOMMENDATIONS ~

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PREPARED BY THE

WORKING GROUP ON SYNTHETIC GENOMICS

FOR THE

NATIONAL SCIENCE ADVISORY BOARD FOR BIOSECURITY

Introduction:

Background

DNA synthesis technology, in combination with other emerging capabilities in the life sciences, has galvanized segments of the scientific community, captured the attention of the general public and policymakers, and prompted far-reaching questions about the potential uses of this technology—including the synthesis of novel forms of life. On one hand, this platform holds the promise of revolutionizing scientific inquiry as this array of technologies, commonly referred to as synthetic genomics, can be used to create virtually any specified DNA sequence by synthesizing and then combining fragments of DNA (oligonucleotides). On the other hand, this technology could be misused to generate dangerous pathogens *de novo* without proper authorization, thus circumventing the extant regulatory framework for controlling the possession and use of such organisms. This dichotomy illustrates the dual-use nature of synthetic genomics and underscores the need to develop strategies to address the possibility that knowledge and technologies emanating from vitally important biological research will be misused to threaten public health or national security.

In this regard, rapid advances in DNA synthesis technology and the open availability of Select Agent DNA sequence data have raised concerns in the scientific community and general public regarding the possible use of this technology and information to generate Select Agents to threaten public health, the environment, agriculture or national security. While traditional recombinant DNA technology has raised similar or related concerns, approaches based on *de novo* synthesis avoid any need for access to the naturally-occurring agents or naturally-occurring nucleic acids from these agents. The National Science Advisory Board for Biosecurity (NSABB) has been charged with identifying the potential biosecurity concerns raised by the ability to synthesize Select Agents and providing advice on whether current United States Government (USG) policies and regulations adequately cover the *de novo* synthesis of Select Agents or whether additional biosecurity measures are necessary.

This report describes the biosecurity concerns identified by the NSABB Working Group on Synthetic Genomics that are raised by the ability to reconstruct Select Agents *de novo*, the Working Group's assessment of the adequacy of the current regulatory framework to safeguard against the misuse of this science and its recommendations for addressing these concerns.

Issue

Viral genomes can be reconstructed using time-intensive recombinant DNA methods and reverse engineering techniques. Such methods typically require access to a natural source of the virus of interest. Recent advances in DNA synthesis technologies enable the *de novo* construction of viral genomes and have dramatically increased both the ease and accuracy with which large fragments of genomic sequences can be constructed. This has greatly enhanced the ability of researchers to acquire, with a short turnaround time, accurate and specific gene-length sequences from an increasing number of commercial suppliers, both nationally and internationally. These technological developments are significantly advancing life sciences research. However, DNA synthesis technologies can and have been used to generate the viral genomes of dangerous pathogens. Furthermore, the scientific community anticipates that synthetic approaches will

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change this capability to include larger, bacterial and fungal pathogen genomes. This has raised questions about the adequacy of extant regulations to safeguard against the use of these technologies to threaten public health, the environment, agriculture or national security.

Working Group Charge

The NSABB was charged with examining the potential biosecurity concerns raised by the synthesis of Select Agents and by synthetic biology[1] in general and with recommending strategies for addressing these concerns.

As a first step in addressing this charge, the NSABB Working Group on Synthetic Genomics was tasked with assessing whether synthetically-derived Select Agents are adequately covered by the current regulatory framework for Select Agents. In other words, do Select Agents synthesized *de novo* escape the purview of the extant oversight system?

As follow-on to that phase of the charge, the Working Group (WG) will identify, assess and recommend strategies to address potential dual-use concerns that may arise from work being performed in the nascent field of synthetic biology. This will be the subject of a later report.

Summary of WG Findings:

Approach

Assessing the adequacy of the current regulatory framework requires the identification and assessment of pertinent laws, regulations and policies in addition to gauging the current state of the science. Therefore, in carrying out the first phase of its charge, the WG examined the state of the science and technology[2] that can be used to synthesize a Select Agent *de novo* and the pertinent oversight framework. Specifically, the WG received presentations from and held discussions with:

- industry experts about the current technological capabilities for synthesizing nucleic acids and the resources needed to do so;
- eminent researchers on the state of the science, in a few key application areas, for deriving infectious agents from synthetic nucleic acids;
- USG officials from the Department of Health and Human Services (HHS) Centers for Disease Control and Prevention (CDC), Department of Commerce (DOC), and Department of Agriculture (USDA) on the extant legal/regulatory framework for controlling Select Agents; and
- key stakeholders regarding their perspectives about biosecurity concerns related to the ability to synthesize Select Agents.

[1] The goal of synthetic biology is to extend or modify the behavior of organisms and engineer them to perform new tasks. Andrianantoandro et al. "Synthetic biology: new engineering rules for an emerging discipline" *Molecular Systems Biology* 2: 1 – 14, 2006.

[2] Such technologies are referred to as synthetic genomics in the remainder of this report since the term generally refers to an array of technologies that can be used to create virtually any specified DNA sequence by synthesizing and then combining fragments of DNA (oligonucleotides).

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State of the Science

The presentations from industry experts focused on the capabilities of current synthesis technologies and what oversight procedures are being employed by commercial entities to ensure compliance with the Select Agent Rules (SAR) and other pertinent regulations. Much of the industry is composed of suppliers of small oligonucleotides used in routine experiments, whereas providers of gene-length sequences are a smaller fraction of the sector, and the generation of genome-length sequences is left to a handful of companies servicing a boutique market. Participants differed in their interpretation of what is required of them under the current regulatory system; they also noted that not all providers felt legally obligated to know what sequences they were making and providing to clients. Furthermore, complying with U.S. requirements is further complicated due to the global distribution and multi-national nature of DNA synthesis providers, their clients and suppliers of key ingredients and equipment.

The briefings by eminent researchers described methodologies used to recover infectious virus from DNA of Select Agent viruses. Through these presentations it became apparent that it is possible to construct infectious agents from synthetic or recombinant DNA. Although each scientist's research focused on different viruses, it was evident from their presentations that the science of reconstructing viruses in the laboratory is technically complex and remains somewhat of an art. In contrast, the technology for synthesizing nucleotides is both readily accessible and simple to apply.

Based upon these briefings and the review of key scientific literature, the WG finds that:

- reagents and equipment for synthesizing DNA are readily available around the globe;
- synthesizing oligonucleotides accurately up to 120 base pairs (bp) in length is routine and common; beyond 180 bp remains somewhat of an art;
- complete genomes of some viruses can be synthesized at the present time, but not all DNA synthesis companies have this capability;
- it is possible to recover/reconstruct infectious virus from DNA for certain Select Agents (and routine in some laboratories); however, successful use of such reverse genetic systems currently requires that one be "skilled in the art"; and
- researchers have successfully created infectious chimeric viruses using combinations of genomic material from various select agents; these novel organisms do not fit into traditional classification schemes.

Pertinent Legal Authorities

Understanding the scientific landscape allowed the WG to determine possible biosecurity concerns for which oversight might be necessary. Before recommending any strategies to address such concerns, the WG assessed the current oversight framework to determine if it adequately covers recent advances in synthetic genomics that allow for the creation of Select Agents *de novo*.

Using information provided via briefings from federal agencies responsible for the implementation and enforcement of controls for Select Agents, the WG identified those components of the oversight system for Select Agents that are most relevant to synthetic genomics. These are the SAR (42 CFR 73, 7 CFR 331, and 9 CFR 121), 18 U.S.C. 175(c),

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Export Administration Regulations (15 CFR 7), and biosafety guidelines for working with DNA (National Institutes of Health - NIH Guidelines for Research Involving Recombinant DNA Molecules (NIH Guidelines) and Centers for Disease Control and Prevention and National Institutes of Health - Biosafety in Microbiological and Biomedical Laboratories Manual (BMBL Manual 4th ed.)

The SAR, the central component of this framework, aim to monitor and track the possession and use of certain dangerous pathogens (deemed Select Agents) and provide a legal basis for the prosecution of individuals who violate the SAR by possessing, using or transferring these pathogens without proper authorization. Further, the SAR cover both genetic material that encodes for Select Agent toxins and Select Agent genomic material that is inherently capable of producing a Select Agent virus. Such genomes include RNA viruses that are in message sense, DNA viruses that do not require a special viral enzyme to replicate and nucleic acids that, if inserted in the appropriate host system, can create a fully functional toxin (Attachment 2). Accordingly, synthesized genomes and toxin expression systems of these Select Agents are also regulated.

Specifically, the SAR describe regulated nucleic acids and genetically modified entities as:

> ***Genetic Elements, Recombinant Nucleic Acids, and Recombinant Organisms:***
> (1) Nucleic acids that can produce infectious forms of any of the select agent viruses
> (2) Recombinant nucleic acids that encode for the functional form(s) of any of the select toxins 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) Select agents and toxins that have been genetically modified

Title 18 of the U.S. Code includes federal criminal statutes applicable to biological agents and toxins. Section 175(c) specifically applies to the synthesis of the variola virus. This statute deems it unlawful to knowingly produce, synthesize or engineer variola virus, which is defined in the Code to include "any derivative of the variola major virus that contains more than 85% of the gene sequence of the variola major virus or the variola minor virus."

The Export Controls implemented and enforced by the DOC are another key regulation for the genetic material of Select Agents in that they control export of such material from the U.S. The DOC Bureau of Industry and Security classifies items or types of items through the use of a specific Export Control Classification Number (ECCN). All ECCNs are listed in the Commerce Control List (CCL), which includes genetic elements (defined to include, among other matter, chromosomes, genomes, plasmids, transposons and vectors, whether genetically modified or unmodified) and genetically modified organisms.

The definition of recombinant DNA molecules covered by the NIH Guidelines includes synthetic DNA segments. The NIH Guidelines detail safety practices and containment procedures for basic and clinical research involving recombinant DNA, including the creation and use of organisms and viruses containing recombinant DNA. An institution must follow the NIH Guidelines if it is conducting or sponsoring any recombinant DNA research that is funded by the NIH. Also, adherence to the NIH Guidelines may be a condition of support from other federal agencies or privately funded research. Regardless of NIH funding, institutions may be subject to local

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ordinances, federal or state regulations, or agency guidelines that require compliance with the NIH Guidelines.

The BMBL Manual describes combinations of standard and special microbiological practices, safety equipment, and facilities that constitute Biosafety Levels 1-4, which are recommended for working with a variety of infectious agents in various laboratory settings. The recommendations are advisory. They are intended to provide a voluntary guide or code of practice as well as goals for upgrading operations. They also are offered as a guide and reference in the construction of new laboratory facilities and in the renovation of existing facilities. This is a commonly used reference within the scientific community.

Although the WG noted that synthetically-derived DNA is addressed in the legal framework, there are points where clarification is needed to ensure compliance with these U.S. requirements. Furthermore, the speed of advances in this technology will require governance options that are capable of keeping pace with rapidly evolving science.

Biosecurity Concerns

The biosecurity concerns identified by the WG stem from the finding that synthetic genomics enables the synthesis and production of a Select Agent by nontraditional means, perhaps bypassing HHS/USDA review. Additionally, it is possible to develop and produce agents that resemble and have the attributes of specific Select Agent(s) without being clearly identifiable as a Select Agent(s) based on their sequence and are therefore not covered by extant regulatory framework for Select Agents. These concerns arise from scientific advances and current industry practices, and highlight several associated issues (Figures 1 and 2), which include:

- ease of acquisition of synthetic Select Agent nucleic acids;
- need for additional regulatory clarity in specific areas; and
- difficulty in developing a suitable regulatory framework due to the lack of consensus among scientists regarding preferred approach and methods for identifying/defining Select Agents and for screening sequences, and due to current capabilities for constructing new pathogens.

Ease of Acquisition: The SAR regulate the use, possession and transfer of certain Select Agent nucleic acids; however, even when requests to genome providers are screened for sequences covered under the SAR, interpreting the results of such screens is complex and difficult. Currently there are no highly effective standardized procedure(s) for accomplishing this objective. Moreover, synthetic genomics technology is globally distributed and used by scientists worldwide.

Need for Additional Regulatory Clarity: Responsible agencies, affected scientists and commercial providers differ in their interpretation of key laws, regulations and policies. The WG identified specific concerns pertaining to the SAR, the CCL and 18 U.S.C. 175(c).

Under the SAR, regulated viral nucleic acids are defined as "[n]ucleic acids that can produce infectious forms of any of the select agent viruses." Proper interpretation of this definition necessitates that one understand what is meant by *"can produce"* and what constitutes a *"select*

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agent virus." Despite the description in the SAR of what is regulated, gene synthesis providers remain uncertain about what they are allowed to manufacture and ship without prior authorization from the CDC or the USDA Animal and Plant Health Inspection Service (APHIS).

The CCL and the SAR differ in their description of genetic material subject to these regulations such that it might be interpreted that the transfer of certain genetic material is allowed under one regulation while restricted by the other. Yet, the effectiveness of an oversight system relies upon the coordination of activities across agencies sharing the oversight responsibility.

Also of concern is the statutory language pertaining to the synthesis of variola virus, 18 U.S.C. 175(c). It allows for multiple interpretations of what is actually covered, and the sequence homology stipulation is arbitrary. Other regulations already provide protection against unauthorized conduct with respect to this agent.

Difficulty Developing Suitable Regulatory Framework: It is now feasible to produce synthetic genomes that encode novel and taxonomically unclassified agents with properties equivalent to, or potentially "worse" than, current Select Agents. The rapid rate of scientific and technological advancements outpaces the development of the current list-based regulations. Furthermore, not all countries recognize the dissemination of synthetic genomics research and technology as an issue of global biosecurity concern. The development of a complementary or alternative oversight framework will require broad scientific consensus and may require an ongoing process for its effective maintenance.

Policy Options Considered

The WG recognized that various groups outside the NSABB have been grappling with issues pertaining to the potential misapplication of synthetic genomics. Therefore, the WG sought outside input regarding the biosecurity concerns and possible solutions. This was accomplished via consultations with stakeholders and by considering strategies proposed by scientists and policy analysts in workshops and conferences not associated with the NSABB.

The stakeholders consulted included practicing synthetic biologists, representatives from the intelligence community, organizations that have conducted or are conducting policy studies relevant to the charge of the WG, and federal agencies responsible for implementing and enforcing the SAR. These deliberations provided the WG with points to consider in developing their recommendations.

A general sentiment was that biosecurity concerns stem from advances in synthesis technology that make the manipulation and creation of DNA sequences more simple, faster and more accessible. The WG was also advised to recognize that synthetic genomics is an international technology. Because major primary sources of key material are located outside of the United States, it is not feasible to control or monitor access to this material. Also, the WG learned that the primary investment in synthesis technology is from private sources and was reminded that the strongest argument for investing in synthetic genomics is to increase research efficiency, which could be undermined by ill-conceived regulations.

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An additional issue raised was that current biosafety guidelines are implemented in institutional settings, so as to present problems with respect to synthetic genomics: Not only is this technology being embraced by communities that are not always closely associated with academic institutions with Institutional Biosafety Committees (IBCs), such as high school and undergraduate students, but also many practitioners of synthetic genomics are generally educated in disciplines that do not routinely include formal training in biosafety, such as engineering.

Although each of the stakeholders recognized the value of screening requested sequences for homology with the known sequences of pathogens, they also emphasized the need for guidance in identifying the specific sequences for which current regulations require prior authorization for use, possession or transfer. Nevertheless, these stakeholders provided suggestions as to how screening could be employed to guard against misuse of synthesis technologies. It was noted that the USG could provide incentives to encourage providers to screen by 1) requiring grantees to acquire synthetic DNA only from entities that screen, and 2) investing in improved screening software and in an enhanced understanding of sequences associated with virulence.

The WG was also advised to consider the spirit of the regulations in assessing their adequacy. In the case of the SAR, they intentionally do not apply until the point at which a functional infectious agent or toxin is generated. Thus, the language pertaining to nucleic acids and genetically modified entities aims to regulate the penultimate step to possessing an active and functional Select Agent. The aim is to avoid both the regulation of many key research reagents/products necessary for scientific advancement and unnecessarily hampering the pace of research, yet manage risk.

The WG considered additional options proposed by scientists and policy analysts for addressing biosecurity concerns including, but not limited to:

- restricting access to new sequence information about Select Agents;
- monitoring the sale of chemicals and lab equipment used to synthesize DNA;
- voluntary/involuntary surveillance/tracking of researchers/students using or trained to use synthetic genomics;
- modifying the SAR so that all select agent genomes are covered by the SAR; and
- modifying the SAR or create new regulations defining Select Agents in terms of their sequence.

The WG chose not to adopt such recommendations because they are either not feasible, likely to be ineffective, and/or would unduly hinder scientific research. In certain instances, science has not advanced to the point that such recommendations could be implemented.

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Recommendations:

The following recommendations are based upon the current state of the science as well as anticipated scientific advances enabled by synthetic genomics. (Attachment 3) Nevertheless, the WG recognizes that this technology is rapidly changing, thus, there is a need for continued oversight and review of this area.

Some issues surrounding the biosecurity concerns are more complex than others. Consequently, they will require different lengths of time to resolve. The WG was tasked to assess the adequacy of the current oversight framework for Select Agents, given advances in synthetic genomics. However, it is apparent that an agent generated from a genome that was synthesized so as to include fragments from Select Agent genomes, might not be classified as a Select Agent, despite the fact that such an agent might be just as dangerous as a Select Agent. Therefore the WG concluded that there is a need, not only to provide recommendations related to the extant framework for Select Agents, but to recommend longer term strategies for addressing biosecurity concerns related to the evolving field of synthetic genomics.

The recommendations below are listed in the order in which the WG suggests they might be addressed. Certain aspects of the longer term strategies rely on other shorter term recommendations to be fully resolved; however, the development of longer term strategies can begin in the near term.

Recommendation 1: The WG recommends that HHS and USDA collaboratively develop and disseminate harmonized guidance to investigators and nucleic acid/gene/genome providers concerning the SAR with respect to synthetically-derived DNA. Specifically,

1.1. provide clarification of what genetic elements or genomes are covered by 42 CFR 73.3c and 73.4c. This would include:
   1.1.1. a list of the organisms whose genomes are explicitly covered and where the reference sequence can be found; and
   1.1.2. instructions for whom to contact if an investigator or provider has questions about covered genetic material.

1.2. increase awareness among investigators and nucleic acid/gene/genome providers about their responsibilities to know what they possess, manufacture and/or transfer in order to comply with the SAR.

The WG recognizes that the language of the SAR is structured such that its coverage of nucleic acids will evolve as science advances. That is, any nucleic acids capable of producing a Select Agent are subject to the SAR; the identity of such nucleic acids is based upon the current state of science and expands as scientific understanding grows. Currently, such nucleic acids are understood to include the intact genomes of the positive-sense, single-stranded RNA viruses and of the herpesviruses on the Select Agent List. That is, the intact genomes of the following viruses are subject to the SAR: Tick-borne encephalitis complex viruses (European subtype, i.e. Central European encephalitis virus; Siberian subtype, i.e. Russian Spring and Summer encephalitis virus; and Far Eastern subtype, i.e. Far Eastern Tick-borne encephalitis virus),

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Kyasanur Forest disease virus, *Omsk hemorrhagic fever virus*, *Eastern equine encephalitis virus*, *Venezuelan equine encephalitis virus*, *Classic swine fever virus*, *Foot-and-mouth disease virus*, *Japanese encephalitis virus*, Swine vesicular disease virus, *Cercopithecine herpesvirus 1* (Herpes B virus), and *Alcelaphine herpesvirus 1* (Malignant catarrhal fever virus)[3]. In addition, the SAR govern the use, possession and transfer of the "reconstructed replication competent forms of the 1918 pandemic influenza virus containing any portion of the coding regions of all eight gene segments".[4] The SAR also cover nucleic acids capable of expressing functional SA toxins. However, this does not mean that other nucleic acids are not subject to the SAR.

Recommendation 2: The WG recommends that the USG should:

2.1. charge relevant federal agencies, in consultation with outside experts, to:
- 2.1.1. develop a process to be used by providers of synthetic DNA for determining the sequences for which to screen (Select Agents or otherwise);
- 2.1.2. develop and promote standards and preferred practices for screening orders and interpreting the results;
- 2.1.3. draft Points to Consider for determining whether genomic material that does not exactly match the genomes referenced in 1.1.1 should be considered covered under the SAR; and
- 2.1.4. develop standards and practices to be used by providers for retaining records of orders for gene-length or genome-length nucleic acids.

2.2 require federal grantees and contractors to order from providers that screen and retain information about requests for Select Agent sequences following standards and practices developed by relevant federal agencies. (See, 2.1.1 – 2.1.4)

2.3 foster an international dialogue and collaboration with the goal of developing and implementing universal standards and preferred practices for screening sequences and related matters.

The WG believes that establishing uniform and standardized screening practices among providers of synthetic DNA would help safeguard against the intentional or unintentional circumvention of the SAR. The WG realizes the magnitude of the effort involved and that establishing such practices requires the USG to fund the development of improved sequence databases and software tools, enhanced understanding of virulence, and improved framework for interpreting sequence screening results. While private initiatives to create such databases and software are currently underway, it is important that such efforts be harmonized with public efforts, the products be standardized, and that they be vetted by a broad range of experts to ensure scientific consensus. Furthermore, as best practices are defined and demonstrated to work for gene- and genome-length DNA segments, the application of such methods and

[3] Species names are in italics whereas strain and colloquial names are not.

[4] "Possession, Use, and Transfer of Select Agents and Toxins—Reconstructed Replication Competent Forms of the 1918 Pandemic Influenza Virus Containing Any Portion of the Coding Regions of All Eight Gene Segments" **Federal Register** / Vol. 70, No. 202 / Thursday, October 20, 2005 / Rules and Regulations

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standards of practice should be considered for shorter oligonucleotides. Such a strategy will become even more important as methods for assembly of DNA improve.

If there is to be a review or use of the screening effort, records will need to be retained. The least intrusive way to accomplish this would be for the providers to retain records; accordingly, record-keeping will need to be standardized for effective implementation and compliance. Effective compliance requires provider acceptance and may also require audits, fines and/or other legal actions.

To best achieve these goals, the USG should work with recognized experts from the gene-synthesis industry and research communities, and integrate international expertise into the process. The NSABB can provide a forum for convening such experts and facilitating collaboration among these experts and the federal agencies responsible for implementing and enforcing the SAR.

Recommendation 3: The WG recommends that the USG:

3.1 repeal 18 U.S.C. 175(c)[5] because current scientific insight precludes meaningful definition of an agent based solely on sequence homology;

3.2 examine the language and implementation of current biosafety guidelines and regulations to ensure that such guidelines and regulations provide adequate guidance for working with synthetically-derived DNA and are understood by all those working in areas covered by the guidelines; and

3.3 continue to reconcile the genetic elements language in the CCL[6] with that in the SAR.

At the present time, arriving at a meaningful definition of variola virus or any other agent on the sole basis of sequence homology is a profoundly difficult scientific problem, yet the definition of "variola virus" in 18 U.S.C. 175(c) is based on genome sequence similarity. The WG found this problematic because current scientific understanding does not permit an adequate correlation of sequence with function, the definition allows for multiple interpretations of what is covered, and thus, the sequence homology stipulation is arbitrary. There are many regions of the variola major virus genome and variola minor genomes that are significantly greater than 85% similar to sequences found in related but relatively harmless viruses. The current definition of variola virus, as provided in the statute, could be interpreted to include other less harmful naturally-occurring poxviruses such as vaccinia virus which are vital to beneficial research, thereby inadvertently restricting and potentially criminalizing many types of beneficial research, such as the development and production of smallpox vaccine. For these reasons, the WG recommends that 18 USC 175(c) be repealed, particularly because the misuse of variola virus is adequately covered by other criminal legislation already in place.

Discussions with stakeholders revealed that some practitioners of synthetic genomics are educated in disciplines that do not routinely entail formal training in biosafety. Additionally,

[5] This statute deems it unlawful, unless explicitly so authorized, to knowingly produce, synthesize or engineer variola virus, which is defined in the Code to include "any derivative of the variola major virus that contains more than 85% of the gene sequence of the variola major virus or the variola minor virus."

[6] Includes genetic elements defined to include, among other matter, chromosomes, genomes, plasmids, transposons and vectors, whether genetically modified or unmodified, and genetically modified organisms.

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scientists employing synthetic genomics are unclear as to the circumstances under which they should consult an IBC and providers of synthetic DNA may not be using appropriate laboratory procedures that ensure biosafety. Therefore, there is a need for the USG to work with the scientific research community to ensure that the current biosafety guidelines and regulations are appropriate, adequate and easily understood.

The WG recognizes that the effectiveness of any oversight system relies upon activities across U.S. government agencies which share the oversight responsibility. The DOC should continue efforts to reconcile the SAR and the CCL such that there is consistency between the Select Agent genetic material that can be imported and used domestically, and the genetic material that can be exported.

Recommendation 4: The WG recommends that the USG, after taking into account the results of implementing Recommendation 2,

4.1 convene a group of experts from the scientific community to conduct an open and in-depth examination of the Select Agent classification system to determine if it is possible to reconcile the current controls for Select Agents with the anticipated scientific advances enabled by synthetic genomics;

4.2 assemble a group of experts from the scientific community to determine if an alternative framework based on predicted features and properties encoded by nucleic acids, such as virulence or pathogenicity, can be developed and utilized in lieu of the current finite list of specific agents and taxonomic definitions; and

4.3 consider the potential international implications of any proposed changes to the current oversight framework for synthetic DNA and synthetic genomes, and foster an international dialogue and collaboration on these issues.

Current studies of human pathogens using genomics-based approaches have revealed an enormous level of strain diversity that has challenged our notion of microbial species as discrete entities with well-defined properties. This diversity in large part reflects the fact that microbial genomes are dynamic entities shaped by multiple forces, including acquisition of new functions via lateral gene transfer. One implication of these observations is that in some instances the assignment of a genus/species name to an organism may be difficult, and of limited utility in predicting the phenotypic properties of a particular isolate, in particular with regard to virulence and pathogenicity. Therefore, the genus/species based approach that is currently used in Select Agent classification is imperfect, since it does not take into account the great degree of genetic variability that can exist within species as they are currently defined.

Advances in the science of synthetic genomics and synthetic biology will further confound this already murky situation. It is increasingly easy to produce synthetic genomes that encode novel and taxonomically unclassified agents with pathogenic properties equivalent to, or possibly more harmful than, current Select Agents. Reliance on taxonomic definitions for Select Agents becomes increasingly irrelevant in an age of synthetic or engineered genomes that can produce biological agents with novel features and properties that might render them as harmful as Select

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Agents. The development of a new oversight framework should be supplemented through the issuance of guidance as information becomes available that with which to define the genetic sequences that form the basis for an organism's pathogenic properties.

Given recent scientific advances in recombinant DNA technology and synthetic genomics, and the wide spectrum of potential agents with the possibility for causing harm, future standards for regulating agents should be based on presumed/predicted functionality rather than sequence homology or taxonomy. Recent efforts by the USG to assess and quantify risks associated with a wide variety of naturally-occurring agents has revealed significant degrees of uncertainty in the estimates of risks, and difficulty in distinguishing among a large subset of these agents, based on their associated risks. This subset of agents includes some that are currently on the Select Agent List and some that are not. In order to facilitate the development of an improved oversight framework for natural, engineered, and synthetic agents, the USG should continue to fund research in a variety of relevant disciplines, including pathogenesis, genomics and bioinformatics, so as to understand and recognize sequences that are responsible for properties such as virulence, tropism and transmissibility. Future oversight for infectious agents and toxins should consist of a tiered system of levels of control and associated burdens, based on upon scientifically based projections of risk. Such controls should be less onerous and more effective since they would be titrated to the projected degree of risk.

The group assembled to identify the attributes of an alternative framework should include researchers with expertise in microbial pathogenesis, genomics, computational molecular biology, structural biology, evolutionary biology and risk analysis. While a broad range of expertise is represented on the NSABB, additional types of expertise would be required if this group were to assume this charge. Nevertheless, the NSABB is appropriately composed so as to identify and convene such experts, as well as facilitate the development options to guide the USG in developing standards, practices and an alternate framework.

Synthetic genomics and synthetic biology are already widespread; emerging biosecurity issues will be increasingly global in scope. International cooperation encourages standard practices across the industry worldwide. Harmonized international standards will encourage organizations, industry and researchers to conform their research activities to the applicable guidelines. International guidelines that are scientifically or technically-based will be more feasible to implement than those that are more conjectural and/or political.

While these recommendations focus on Select Agents they touch on some of the broader potential biosecurity issues related to synthetic biology. The WG will build upon these findings in carrying out the second phase of its charge--which is to identify, assess, and recommend strategies that address potential dual use concerns which may arise from work in the nascent field of synthetic biology.

Salient points the WG will address include: How can possible risks associated with the generation of novel organisms be addressed? What strategies can be employed to safeguard against the misuse of synthetic biology and associated technologies? How can global cooperation in addressing related biosecurity concerns be encouraged?

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ATTACHMENT 1

Current U. S. Authorities

Current USG laws, regulations, and policies include related to oversight of Select Agents:

- The Public Health Security and Bioterrorism Preparedness and Response Act of 2002 and Agricultural Bioterrorism Protection Act of 2002, which are implemented by the Select Agent Rules (42 CFR part 73 (threats to human health), 7 CFR part 331 (threats to plant health and plant products) and 9 CFR part 121 (threats to animal health and animal products)). These Acts and Regulations govern the possession, use, and transfer of "select agents," which are biological agents and toxins that have been determined to have the potential to pose a severe threat to human, plant and/or animal health. The Acts provide for penalties for violations of the Rules.

- The USG Policy on Biosecurity in Life Sciences Research, which was announced in Spring 2004 and (1) established a biosecurity advisory body (the NSABB) to advise NIH, HHS and other federal agencies on specific strategies for the effective oversight of federally conducted or supported dual-use biological research, taking into consideration both national security concerns and the needs of the research community; and (2) mandated several actions to promote the development and implementation of biosecurity principles throughout the national and international scientific communities.

- 18 USC 175, which mandates fines and/or imprisonment for: (1) individuals who knowingly develop, produce, stockpile, transfer, acquire, retain or possess any biological agent, toxin, or delivery system for use as a weapon; and (2) individuals who knowingly possess any biological agent, toxin or delivery system of a type or in a quantity that, under the circumstances, is not reasonably justified by a prophylactic, protective, bona fide research or other peaceful purpose.

- 18 USC 175(b), which mandates fines and/or imprisonment for: (1) a restricted person shipping, possessing, or receiving a Select Agent in or otherwise affecting interstate or foreign commerce through the use of a Select Agent; or (2) transferring a Select Agent to a person who the transferor knows or has reasonable cause to believe is an unregistered person; or (3) knowingly possessing a Select Agent for which the person has not obtained registration.

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ATTACHMENT 2

Classification of Select Agent Viruses

	Single-stranded positive RNA[7]	Single-stranded negative RNA	Double-stranded RNA	Double-stranded DNA
CDC Select Agent Viruses	▪ Tick-borne encephalitis complex (flavi) viruses: - Central European Tick-borne encephalitis - Far Easter Tickborne encephalitis - Russian Spring and Summer encephalitis - Kyasanur Forest Disease - Omsk Hemorrhagic Fever	▪ Crimean-Congo haemorrhagic fever virus ▪ Ebola viruses ▪ Lassa fever virus ▪ Marburg virus ▪ South American Haemorrhagic fever viruses: - Junin, - Machupo, - Sabia, - Flexal, - Guanarito		▪ Variola major virus (Smallpox virus) and Variola minor virus (Alastrim) ▪ Cercopithecine herpesvirus 1 (Herpes B virus)[7] ▪ Monkeypox virus
CDC/USDA Overlap Select Agent Viruses	▪ Eastern Equine Encephalitis ▪ Venezuelan Equine Encephalitis virus	▪ Nipah virus ▪ Hendra virus ▪ Rift Valley fever virus		
USDA Select Agent Viruses	▪ Classical swine fever virus ▪ Foot-and-mouth disease virus ▪ Japanese encephalitis virus ▪ Swine vesicular disease virus	▪ Akabane virus ▪ Avian influenza virus (highly pathogenic) ▪ Newcastle Disease virus (velogenic) ▪ Peste des petits ruminants virus ▪ Rinderpest virus ▪ Menangle virus ▪ Vesicular stomatitis virus (exotic)	▪ African horse sickness virus ▪ Blue tongue virus	▪ African swine fever virus ▪ Camel pox virus ▪ Goat pox virus ▪ Lumpy skin disease virus ▪ Malignant catarrhal fever virus (Alcelaphine herpesvirus type 1)[7] ▪ Sheep pox virus

[7] The intact genomes of these viruses are subject to the SAR

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FIGURE 1

Process for Deriving Select Agents De Novo Using Mail-Ordered DNA

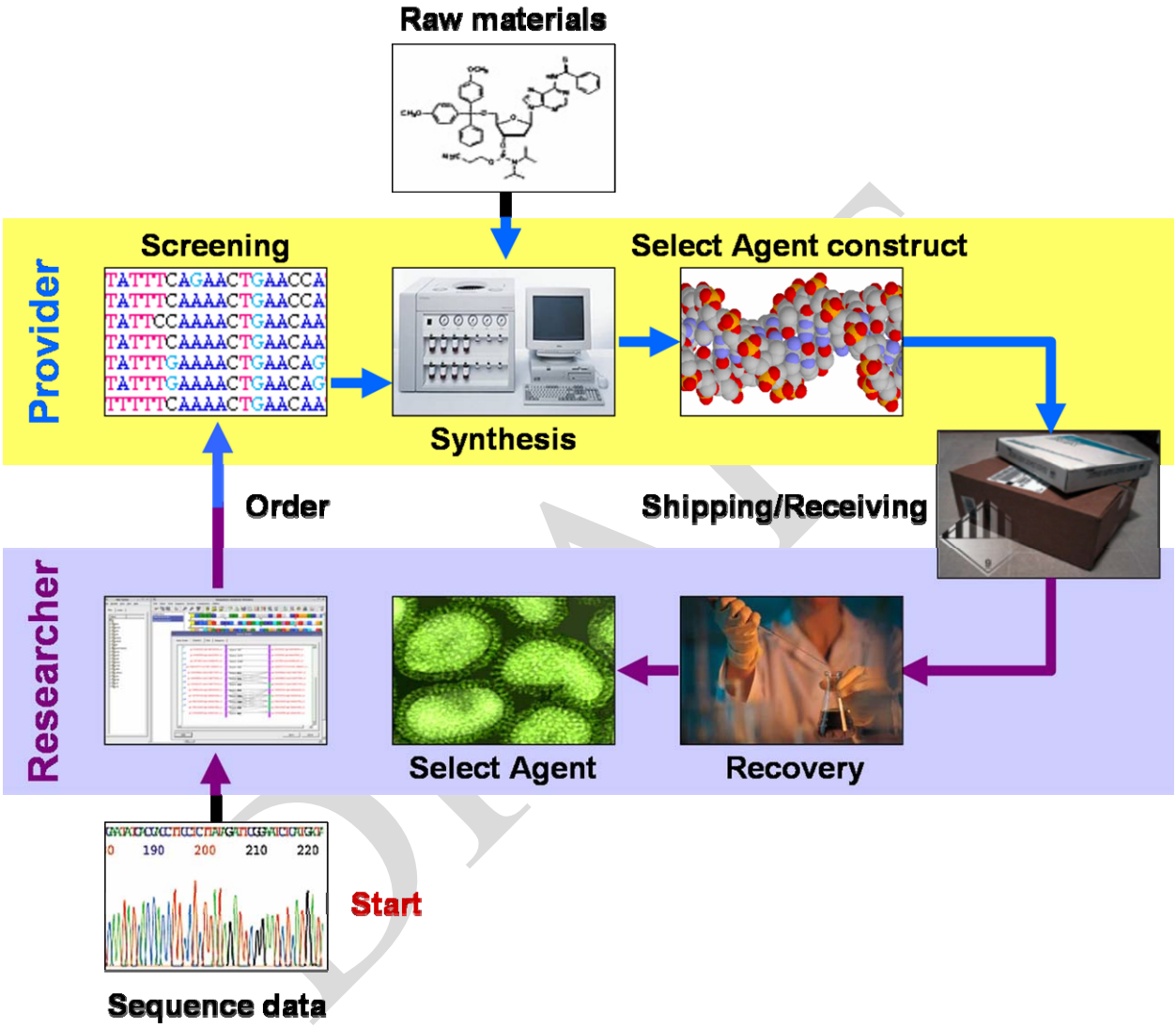

FIGURE 2

Biosecurity Concerns Mapped to Process

Synthesis of DNA						
Access Sequence Data	**Screen Orders**	**Use Raw Material**	**Use Equipment**	**Derive Genetic Material**	**Transfer Material**	**Recover/ Reconstruct**
	Need for additional regulatory clarity			Difficulty developing a suitable regulatory framework	Non-compliance with SAR	Ease of acquisition of synthetic SA nucleic Acids Construction of new pathogens

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ATTACHMENT 3

Recommendations of the NSABB Working Group on Synthetic Genomics

Recommendation 1: The WG recommends that HHS and USDA collaboratively develop and disseminate harmonized guidance to investigators and nucleic acid/gene/genome providers concerning the SAR with respect to synthetically-derived DNA. Specifically, the Departments should provide clarification of what genetic elements or genomes are covered by 42 CFR 73.3c and 73.4c. Such clarification should include a list of the organisms whose genomes are explicitly covered and where the reference sequence can be found, and instructions for whom to contact if an investigator or provider has questions about covered genetic material. There is also a need for HHS and USDA to increase awareness among investigators and nucleic acid/gene/genome providers about their responsibilities to know what they possess, manufacture and/or transfer in order to comply with the SAR.

Recommendation 2: The WG recommends that the USG should charge relevant federal agencies, in consultation with outside experts to 1) develop a process to be used by providers of synthetic DNA for determining the sequences for which to screen (Select Agents or otherwise); 2) develop and promote standards and preferred practices for screening orders and interpreting the results; 3) draft Points to Consider for determining whether genomic material that does not exactly match the genomes referenced in Recommendation 1 should be considered covered under the SAR; and develop standards and practices to be used by providers for retaining records of orders for gene-length or genome-length nucleic acids. The WG also recommends that the USG require federal grantees and contractors to order from providers that screen and retain information about requests for Select Agent sequences following standards and practices developed by relevant federal agencies, and foster an international dialogue and collaboration with the goal of developing and implementing universal standards and preferred practices for screening sequences and related matters.

Recommendation 3: The WG recommends that the USG repeal 18 U.S.C. 175(c)[8] because current scientific insight precludes meaningful definition of an agent based solely on sequence homology; examine the language and implementation of current biosafety guidelines and regulations to ensure that such guidelines and regulations provide adequate guidance for working with synthetically-derived DNA and are understood by all those doing work in areas covered by the guidelines; and continue to reconcile the genetic elements language in the CCL[9] with that in the SAR.

Recommendation 4: The WG recommends that the USG, after taking into account the results of implementing Recommendation 2, 1) convene a group of experts from the scientific community to conduct an open and in-depth examination of the Select Agent classification system to determine if it is possible to reconcile the current controls for Select Agents with the anticipated scientific advances enabled by synthetic genomics; 2) assemble a group of experts from the scientific community to determine if an alternative framework based on predicted features and properties encoded by nucleic acids, such as virulence or pathogenicity, can be developed and utilized in lieu of the current finite list of specific agents and taxonomic definitions; and 3) consider the potential international implications of any proposed changes to the current oversight framework for synthetic DNA and synthetic genomes, and foster an international dialogue and collaboration on these issues.

[8] This statute deems it unlawful, unless explicitly so authorized, to knowingly produce, synthesize or engineer variola virus, which is defined in the Code to include "any derivative of the variola major virus that contains more than 85% of the gene sequence of the variola major virus or the variola minor virus."

[9] Includes genetic elements (defined to include, among other matter, chromosomes, genomes, plasmids, transposons and vectors, whether genetically modified or unmodified) and genetically modified organisms.