National Institutes of Health
Office of the Director
Office of Biotechnology Activities

NATIONAL SCIENCE ADVISORY BOARD FOR BIOSECURITY

December 3, 2009
Held at the Pooks Hill Marriott Hotel
Bethesda, Maryland

MINUTES of MEETING

NSABB VOTING MEMBERS

Dennis L. Kasper, M.D., *NSABB Chair*
Kenneth I. Berns, M.D., Ph.D.
Arturo Casadevall, M.D., Ph.D.
Murray L. Cohen, Ph.D., M.P.H., C.I.H.
Susan A. Ehrlich, J.D., LL.M.
David R. Franz, D.V.M., Ph.D.
Claire M. Fraser-Liggett, Ph.D.
Christine M. Grant, J.D.
Michael J. Imperiale, Ph.D.
Joseph Kanabrocki, Ph.D., C.B.S.P.
Paul S. Keim, Ph.D.
Stuart B. Levy, M.D.
John R. Lumpkin, M.D., M.P.H.
Jeffery F. Miller, Ph.D.
Randall Murch, Ph.D.
Mark E. Nance, J.D.
Michael T. Osterholm, M.D., M.P.H.
David A. Relman, M.D.
James A. Roth, D.V.M., Ph.D., D.A.C.V.M.
Andrew A. Sorensen, Ph.D.
Anne K. Vidaver, Ph.D.

NSABB *EX OFFICIOS*/FEDERAL AGENCY DESIGNEES

Kay Briggs, Ph.D., U.S. Department of the Interior
Capt. Kenneth Cole, Ph.D., U.S. Department of Defense
Brenda Cuccherini, Ph.D., M.P.H., U.S. Department of Veterans Affairs

Amanda Dion-Schultz, Ph.D., Office of the Chief Scientist
Dennis Dixon, Ph.D., National Institute on Allergy and Infectious Diseases, National Institutes of Health
Elizabeth George, Ph.D., U.S. Department of Homeland Security
Maria Giovanni, Ph.D., National Institute on Allergy and Infectious Diseases, National Institutes of Health
Wendy Hall, Ph.D., U.S. Department of Homeland Security
Peter R. Jutro, Ph.D., U.S. Environmental Protection Agency
Joseph P. Kozlovac, M.S., R.B.P., C.B.S.P., U.S. Department of Agriculture
Mary Mazanec, M.D., J.D., U.S. Department of Health and Human Services
Janet K.A. Nicholson, Ph.D., Centers for Disease Control and Prevention
Christopher Park, U.S. Department of State
Gerald Parker, Ph.D., D.V.M., M.S., U.S. Department of Health and Human Services
Dana Perkins, Ph.D., U.S. Department of Health and Human Services
David G. Thomassen, Ph.D., Department of Energy
Joanne Tornow, Ph.D., National Science Foundation
Edward You, Federal Bureau of Investigation

NSABB EXECUTIVE DIRECTOR
ACTING DIRECTOR, OFFICE OF SCIENCE POLICY, NATIONAL INSTITUTES OF HEALTH (NIH)
Amy P. Patterson, M.D.

Call to Order and Review of Conflict of Interest Rules

Dr. Dennis Kasper, Chair of the National Science Advisory Board for Biosecurity (NSABB), convened the December 3, 2009 meeting of the NSABB at 8:30 a.m.

Dr. Amy Patterson read into the record the rules of conduct and conflict of Interest of NSABB members. She pointed out that the rules are explained in the report entitled “Standards of Ethical Conduct for Employees of the Executive Branch” which was received by each member when appointed to the NSABB. She reiterated that members of the NSABB are considered Special Government Employees and were requested to review the steps to ensure that conflicts of interest are addressed. Furthermore, Board members are required to recuse themselves in advance of any discussion in which they believe they have a conflict of interest. Dr. Patterson concluded by stating that issues relating to conflicts of interest should be brought to her attention during the meeting.

Introductions, Welcome to the New NSABB Members, and Overview of Agenda

Dr. Kasper reviewed the agenda and welcomed new and returning NSABB members, Federal Agency representatives, and members of the public in attendance, as well as those watching via webcast. Board members and *ex officio* representatives introduced themselves and stated their affiliations.

Dr. Patterson acknowledged the exemplary efforts of Mary Groesch, Ph.D. who has served the committee ably and brilliantly over its duration, but even more so since Dr. Patterson has taken on additional responsibilities. She then introduced Paul Lewis, Ph.D. who recently joined the Office of Biotechnology Activities staff and will be taking on the duties of managing the NSABB as Executive Director.

New Tasks for the NSABB and Swearing-in of New NSABB Members

Presenters: Gerald Parker, D.V.M., Ph.D., M.S.
Principal Deputy Assistant Secretary for Preparedness and Response
U.S. Department of Health and Human Services

Diane DiEuliis, Ph.D., Assistant Director, Life Sciences
Office of Science and Technology Policy
Executive Office of the President

Presentation by Dr. Parker

Dr. Parker expressed his appreciation for the work of the NSABB and noted that the Board's recommendations have been carefully considered and will continue to play an important role in helping to shape US Government (USG) policy. He conveyed sincere thanks from the Department of Health and Human Services to all NSABB members for their hard work, dedication, and commitment since the inception of the NSABB five years ago. He noted, retrospectively, that the NSABB has submitted four reports to the U.S. government on: (1) the synthesis of select agents (SAs); (2) a proposed framework for the oversight of dual use life sciences research (DUR); (3) a strategy for outreach and education on dual use research issues; and, (4) personnel reliability among individuals with access to biological select agents and toxins (BSATs). He further noted that a fifth report on synthetic biology was on the agenda to be considered during this meeting.

Dr. Parker stated that there has been unanimous agreement within the U.S. government that the NSABB has been of significant service and must continue with a new set of tasks. He noted that some of these new taskings are new issues and some are logical follow-on activities. Specifically, the overarching focus of NSABB activities is enhancing the culture of responsibility regarding biosecurity and dual use research of concern. He then presented an overview of the new taskings of the NSABB that encompass enhancing the culture of responsibility as well as advising the United States Government on the Select Agent Program.

- **Recommend strategies and guidance for enhancing personnel reliability among individuals with access to Biological Select Agents and Toxins (BSATs):**
    - This task is a followup to the personnel reliability report in which the NSABB delineated a number of ways to enhance the culture of responsibility at the local level. The Board should engage the scientific community on these issues and develop specific guidance that reflects broad input on how best to implement and train on critical practices such as self and peer reporting, including how to destigmatize such reporting and how to foster acceptance of this new responsibility.

    - Elaborate on the good hiring practices that will help to optimize personnel reliability and to recommend ways for local institutional leadership to communicate the value and priority of security and personnel reliability.

- **Develop strategies for enhancing interdisciplinary biosecurity:**
    - Advise on strategies for enhancing interdisciplinary biosecurity by recommending strategies for raising awareness among non-life sciences researchers about DUR issues and biosecurity concerns.

- **Recommend outreach strategies for nontraditional synthetic biology communities:**
    - The NSABB has noted that, increasingly, researchers not affiliated with universities or institutes are conducting life sciences research, notably synthetic biology research. Therefore, the NSABB is being tasked with identifying issues of concern regarding the conduct of synthetic biology research by nontraditional practitioners and to recommend strategies for effectively engaging these communities on biosecurity and biosafety issues.

- **Engage scientific journal editors on review of dual use research of concern (DURC) by lessons learned and future directions:**
    - **Engage science journal editors about the incorporation of policies for reviewing and responsibly publishing research that could be considered dual use research of concern.** A number of journals are already incorporating DURC review to some extent and likely have some experiences and best practices to share.

    - Obtain their input on how the existing NSABB guidance could be improved for this purpose and to continue raising awareness within the scientific community about dual use research (DUR).

- **Develop strategies for promoting codes of conduct:**
    - Engage scientific societies and other relevant professional organizations to identify strategies for refining and promoting the wider adoption of codes of conduct, both domestically and internationally. To be effective, resulting strategies must be implemented by the global scientific community, thus international dialogue is absolutely essential.

- **Continue international engagement on DURC :**
    Continue the critical work of raising awareness internationally about DUR issues and facilitating communication among countries regarding approaches to the oversight of dual use research, lessons learned, and challenges to addressing this issue.

- **Other duties as assigned**:
    - Advise the United States Government Select Agent Program, as requested.

    - Establishment of a subcommittee of the NSABB would be the most expeditious method of responding to such requests.

NSABB Discussion

A query was raised regarding the new subcommittee to advise the Select Agent Programs. Dr. Parker explained the need for an external advisory committee to provide guidance and advice in an expedient manner. The Department of Health and Human Services, Center for Disease

Control and the Department of Agriculture, Animal Plant Health Inspection Service, need to be able to reach out quickly to an advisory board to provide input and guidance, and this subcommittee would have its infrastructure already in place. Therefore, realtime guidance and advice would be provided. It is possible that revisiting the Select Agent List would be part of the subcommittee mandate. Drs. Casadevall, Imperiale and Keim volunteered to be on the subcommittee.

Questions and comments were elicited regarding the NSABB's continued role with respect to personnel reliability. It has been determined that the NSABB should continue to offer guidance and advice regarding the issue of personnel reliability. Although the NSABB issued a report on this topic approximately six months ago, the legislative and policy landscapes are rapidly evolving, making the Board's continued expert advice critical. The NSABB can assist in fleshing out the specifics for applying the recommendations in their previous report. The Board should respond to issues that have been raised in other reports and should be more specific regarding potential strategies at the local level. This might include engaging with research institutions and institutional officials to talk about what works, what does not work, and what model programs they are considering.

Letter from the Office of Science and Technology Policy and Swearing In of New NSABB Members

Dr. DiEuliis read a letter from John P. Holdren, Ph.D., OSTP Director and Assistant to the President for Science and Technology in which he conveyed his support and appreciation for the important work being done by the NSABB. She also presented a certificate from OSTP and an etched paperweight from the DHHS to NSABB members who recently retired from service on the Board. These members were unable to attend the meeting but included: Barry Erlick, Ph.D.; Adel Mahmoud, M.D., Ph.D.; Harvey Rubin, M.D.; Thomas Shenk, Ph.D.; and, Adm. William O. Studeman.

On behalf of the U.S. government Dr. DiEuliis then swore in the new NSABB members. All members participated in this ceremony with the existing members "renewing" their commitment to the NSABB.

Approval of the April 2009 Minutes

Judge Ehrlich and Dr. Imperiale reviewed the minutes of the April 2009 NSABB meeting in advance of this meeting, and their suggestions were incorporated.

NSABB Motion 1

Moved by Dr. Imperiale and seconded by Dr. Sorenson, the NSABB voted unanimously by voice to approve the April 2009 NSABB meeting minutes that had been distributed in advance of this meeting.

Update on Federal Responses to NSABB Reports

Presenter: Diane DiEuliis, Ph.D., Assistant Director, Life Sciences
Office of Science and Technology Policy
Executive Office of the President

Overview of U.S. Government Response to NSABB Reports

Dr. DiEuliis provided a broad overview of biosecurity policy actions in the Executive Branch and described where some of the NSABB reports have informed the USG process. Her slide presentation listed four NSABB reports and nine reports from other groups that have been under consideration by a working group that was put together to address an Executive Order from the previous administration that was tasked with strengthening the biosecurity of the United States. In July 2009, that working group completed its report and submitted it to the White House, and the Executive Branch currently is considering their recommendations.

The common themes across all of these reports are: to reduce and/or stratify the Select Agent List; to better coordinate inspections across agencies that manage contracts or facilities involving biological select agents and toxins (BSATs); to clarify standards and guidance across several areas of the Select Agent Regulations (SARs); to continue the assessment of personnel after BSAT access is granted; and the potential creation of an oversight or coordination body that would examine all of these issues. In response to the variety of recommendations, four different groups are working to address the policy recommendations.

NSS/OSTP Working Group on Optimizing BSAT Security. This working group has just begun its deliberations. Potential actions and activities include: establishing an interagency board and possibly an external board for advising the Select Agent Program (SAP), and the NSABB may be asked to assist in this activity; stratifying and/or reducing the list of Select Agents and Toxins; promulgating revised rules and guidance for compliance with the SAPs; simplifying U.S. government policies on BSAT security through centralization and coordination; and resolve key issues related to shipping and transport of BSAT. Personnel reliability issues will be covered throughout as is appropriate.

Working Group on Dual Use Research Oversight (DURO). The charge of this working group is to analyze the framework proposed by the NSABB to identify any gaps, overlaps, or unresolved issues; to identify policy options and recommendations for oversight and; to promote opportunities for interagency coordination. The NSABB's report on a framework for the oversight of dual use research is being considered by the Biotechnology Subcommittee of the Committee on Science within the National Science and Technology Council, which is the OSTP's policy arm. This working group will likely develop guidelines for oversight of DUR (as opposed to any kind of rulemaking)and a list of additional tools and guidance documents.

Synthetic Genomics. The USG is undertaking numerous policy actions involving synthetic genomics including harmonizing guidance concerning the Select Agent Regulations (SAR) with respect to synthetically-derived DNA (in progress); establishing a screening infrastructure for use by commercial providers and users of synthetic nucleic acids (a request for information was released in late November 2009); and coordinating international outreach on synthetic biology issues. The Department of State has drafted an outreach strategy to elevate the topic internationally. These policy actions have been informed by the NSABB's recommendations in its 2006 report on synthetic genomics.

Other actions include:

- Amendment of 18 U.S.C 175c (variola virus research) and issuance of an opinion letter by the Department of Justice addressing the applicability and scope of the definition of "variola virus." A copy of this letter was sent to all the Select Agent officials and institutions and has been posted on the CDC Select Agent Web site;

- Proposed update/revision of the *NIH Guidelines for Research Involving Recombinant DNA Molecules* (*NIH Guidelines*) to address synthetic biology;
- Reconciling the Commerce Control List (CCL) with Select Agent Regulations. This will be addressed after completing the task on the SAR guidelines; and
- Identifying the scientific advances necessary for a predictive oversight system, which is being addressed by a National Academy of Science study.

Biosecurity Outreach and Education Working Group. The goal of this working group, in addition to responding to recommendations made by the NSABB and others, is to develop a unified U.S. government message on biosecurity. This working group is developing educational materials, websites, and booths for scientific meetings regarding dual use research; it is hoped that the website <biosecurity.gov>, when developed, will be an active source for policies as well as comments on proposed policies.

Applicability of the Select Agent Regulations to Issues of Synthetic Genomics

Presenter: Tru Twedt, D.V.M., C.B.S.P.
Associate Director for Science
Division of Select Agents and Toxins
Centers for Disease Control and Prevention

Dr. Twedt noted that an advanced notice for proposed rulemaking relating to the Select Agent list would be published in the *Federal Register* in mid December 2009 to start the biennial review process for the list.

He reviewed the document entitled "Applicability of the Select Agent Regulations to Issues of Synthetic Genomics," a copy of which was provided in each meeting packet and is available on on the website www.selectagents.gov. The purpose of this document is to provide guidance regarding the application of the current SARs to those who create and use research products using synthetic genomic methods. The first three pages of the document discuss the regulatory background and the last three pages include six sample scenarios that address frequently-asked questions in this area.

Because the SAPs do not regulate information, they do not regulate sequence information on biological select agents and toxin. However, end products are regulated by the SAP. For example, if an entity wants to synthesize a complete and functional Select Agent such as Marburg virus, that end product (the virus) would be regulated by the SAR and that entity ideally would work with the CDC SAP beforehand to ensure it was acting in a manner consistent with the regulations throughout the process. The CDC SAP regulates functional viable bacteria, viruses, toxins, and some genetic material. If an entity proposes to synthesize the complete genome of a single-stranded RNA virus, a positive-stranded RNA virus, one of the herpes viruses on the Select Agent List, or a gene that encodes for one of the select toxins, the CDC SAP would regulate that material whether or not it was functional.

Screening Framework Guidance for Synthetic Double-Stranded DNA Providers

Presenter: Jessica Tucker, Ph.D.
AAAS Science and Technology Fellow
Office of Medicine, Science, and Public Health
Contractor for Department of Health and Human Services

Dr. Tucker stated that the draft screening framework guidance was published as a *Federal Register* notice on November 27, 2009, for a 60-day public comment period. Emphasizing that these recommendations are still a draft, she provided background about the guidance, a brief overview of the goals of the guidance, and a summary of key recommendations, focusing on the U.S. government efforts to develop a process to be used by synthetic DNA providers for determining sequences for which to screen. This process is in response to recommendations issued in the NSABB's 2006 report on synthetic genomics. Development of an oversight mechanism should balance the need to minimize the risk of misuse with the need to ensure that science and innovation are encouraged, and also to engage the synthetic nucleic acid industry, the scientific community, and other stakeholder communities.

The overarching goal of developing a screening framework is to minimize the risk that unauthorized individuals or individuals with malicious intent will gain access to toxins and organisms of concern through the use of nucleic acid synthesis technologies, while simultaneously minimizing any negative impacts on the conduct of research and business operations. Key elements of the screening framework, include:

- Identification of the appropriate sectors of the synthetic nucleic acid industry for these efforts (determined to be the double-stranded DNA, gene, and genome synthesis sector)
- Mechanisms by which a screening framework should be pursued. A voluntary approach was pursued, as opposed to a regulatory approach due to the global nature of the nucleic acid synthesis industry and the proactive measures already taken by the industry.
- Principles and objectives of screening. Notably, providers should know their customers and the products they are selling.
- Process for enabling timely response to orders of concern — including how and when to contact the U.S. government.
- Tools to facilitate implementation of the screening guidelines (*still under development*).
- Ways to evaluate implementation and impact (*still under development*).

The foundation of this draft guidance is that the U.S. government recommends that all orders for synthetic double-stranded DNA of 200 base pairs in length or greater be subject to a screening framework that incorporates both customer and sequence screening. The recommended approach is to begin with a customer-screening step that would involve verification of the customer's identity, screening customers against several lists of proscribed entities, and checking for "red flags," with the goal of looking for suspicious activity and behavior of customers. If customer screening raises a concern, followup screening is recommended.

The next step is to pursue a sequence screening step. In this step, the U.S. government recommends that nucleic acid sequences be screened against GenBank using a best-match approach to identify nucleic acids that are unique to Biological Select Agents and Toxins. For foreign orders, nucleic acids should be screened using a "Best Match" approach to identify nucleic acids that are unique to pathogens and toxins on the Commerce Control List. Sequence screening should be performed for both DNA strands and the resultant polypeptides derived from the alternative reading frames on each DNA strand. Also recommended is that the sequence alignment methods used by providers should detect sequences of concern as small as 200 base pairs that may be embedded within large orders. In any case in which sequence screening raises a concern, followup screening is recommended.

Whenever customer or sequence screening reveals "red flags" or sequences of concern, the U.S. government recommends that providers ask for additional information about the customer's proposed end use and take additional steps to verify the customer's identity and need. Providers are also reminded to check orders against various lists of restricted entities before filling every order; these lists vary for domestic and foreign customers. In cases in which follow-up screening cannot resolve concerns raised by customer or sequence screening, or when providers are otherwise unsure about whether to fill an order, the U.S. government recommends that providers contact relevant U.S. government agencies.

In this draft document, the U.S. government recommends that providers select a sequence screening software tool that uses a global as well as a local sequence alignment technique. Additionally, the USG recommends that providers have the necessary human expertise in-house to perform sequence screening, to analyze results, and to conduct appropriate follow-up. It is also recommended that providers retain electronic copies of customer orders for at least eight years.

Public engagement regarding the guidance will continue. At the conclusion of the public comment period for the *Federal Register* notice, the U.S. government will review and consider those comments for potential incorporation into the guidance and will release final guidance as a result of that review. An interagency group will be working to find tools to monitor the implementation of the guidance and to evaluate its effectiveness as different providers implement it.

Revising the *NIH Guidelines* To Address Synthetic Nucleic Acids

Presenter: Jacqueline Corrigan-Curay, J.D., M.D.
Executive Secretary, NIH Recombinant DNA Advisory Committee (RAC)
Acting Director, Office of Biotechnology Activities
National Institutes of Health

Dr. Corrigan-Curay provided an update on the status of revising the *NIH Guidelines* with regard to biosafety and synthetic nucleic acids. The original NSABB report on synthesizing Select Agents noted that a number of practitioners of synthetic genomics are educated in disciplines that do not routinely entail formal training in biosafety and thus they may not be aware of when to consult institutional biosafety committees (IBCs). She mentioned that the NSABB recommendation was to ensure that the biosafety principles and practices are applicable to synthetic genomics and easily understood. That recommendation was adopted by the U.S. government with the understanding that it would be implemented through modification of the *NIH Guidelines*, as appropriate, and then those modifications would be referenced in the *Biosafety in Microbiological and Biomedical Laboratories* (*BMBL*). The *NIH Guidelines* apply to institutions that receive NIH funding for recombinant DNA research as a term and condition of the grant, and other governmental agencies also require adherence. However, it does not cover RNA viruses or synthetic DNA that is synthesized *de novo*. The *BMBL* is agent specific. It is not technology driven, and it references the *NIH Guidelines* with respect to recombinant molecules.

Because the Recombinant DNA Advisory Committee (RAC) has been advising the NIH Director on all aspects of recombinant DNA research for the past 30 years, a charge to the RAC was to consider the application of the *NIH Guidelines* to synthetic biology. Specifically, the RAC was asked to consider the degree to which this technology is covered by the *NIH Guidelines* and whether the scope of the *NIH Guidelines* needs to be modified to capture synthetic biology

research. The RAC was also to develop draft recommendations regarding principles and procedures for risk assessment and management of research involving synthetic biology.

A subcommittee of the RAC, the Biosafety Working Group, developed the initial proposal, and the full RAC reviewed and approved the proposed revisions in March 2008. After extensive review, a proposal was published in the *Federal Register* on March 4, 2009, with a 90-day public comment period during which comments were generally supportive. The comments were taken to a stakeholders' conference which convened in June 2009. The final proposal was submitted to and approved by the full RAC on December 1, 2009.

The overarching themes of the proposal were to capture the same products made by synthetic techniques that are currently covered under the *NIH Guidelines* for recombinant DNA research, provided that the same biosafety concerns are raised; to develop a risk management framework based on the current science and what appears to be feasible in the foreseeable future; and, to recognize that not all future scientific developments can be anticipated so that the *NIH Guidelines* will need periodic review and updating.

Dr. Corrigan-Curay reviewed the specifics of the RAC's proposed changes. The RAC added a definition of synthetic nucleic molecules as being "…molecules that are chemically, or by other means, synthesized or amplified, including those that are chemically or otherwise modified but can base-pair with naturally occurring nucleic acid molecules…" Other proposed changes include a new Section F-1 that exempts from the *NIH Guidelines* certain synthetic nucleic acids that cannot replicate, provided they are not used in human gene transfer. After extensive consultation, the Biosafety Working Group concluded that the risk assessment for synthetic nucleic acids is not fundamentally different from that of recombinant DNA. However an IBC must be conscious of the possibility that chimeras might be generated by synthetic means and those chimeras might be more complex than what has been generated by recombinant methods and the parent organism may not be obvious. Consequently, the proposed framework advocates a conservative approach to reviewing such research.

The Biosafety Working Group concluded, and the full RAC agreed, that research with synthetic nucleic acids in most cases present biosafety risks that are comparable to recombinant DNA research and, therefore, should be brought under the recombinant DNA guidelines which will be renamed The Framework. The current risk assessment framework can be used with attention to the unique aspects of this technology. Certain work with nonreplicating synthetic nucleic acids may not require oversight under the *NIH Guidelines*, although other biosafety standards would apply.

NSABB Discussion

Dr. Relman commented that the wording of the proposed screening guidelines was thoughtful and created an appropriate balance between cautiousness in not wanting to do harm to the scientific enterprise and the concerns about potential risks. He also expressed the importance of the ability to review on a frequent and periodic basis the impact of effectiveness and potential costs. Dr. Relman also asked about whether there are plans to measure the added burdens associated with the proposed screening guidelines, namely whether there are proposed metrics to measure costs or detrimental impacts on research. Dr. DiEuliis stated that a review that is flexible and responsive to changes in technology was important in crafting the guidelines. Many ideas are currently being explored and the close working relationship with most of the synthetic nucleic acid industry providers will be key in deciding the most effective method of review and evaluation of the guidelines.

Dr. Casadevall noted the importance of attempting to measure, quantitatively if possible, the amount of research that does not get conducted, which is the price society pays for regulation.

Dr. Patterson asked about the delta between the proposed screening guidelines and current practices of synthetic nucleic acid industry providers. Dr. Tucker responded that extensive outreach to the providers showed that minimal differences exist, most of which could be worked out easily.

Dr. Patterson queried whether these guidelines would put restrictions on U.S. providers, companies, and investigators that might create imbalance within the international scientific community; in particular, whether the guidelines would be applicable to U.S. investigators ordering reagents from other countries. Dr. Petrillo answered that the vast majority of the output of this industry internationally is from providers who are already actively pursuing codes of conduct. The industry is setting its own international standards at this relatively early stage, with major providers located in Germany and the United States, and significant attempts are being made to include new industries and new providers in locations such as India, China, and Canada.

In response to Dr. Fraser-Liggett's question relating to monitoring noncompliance, Dr. Tucker stated that ideas, such as seals of approval, have been considered. However, no decisions have been made and the input from public comments will assist in determining whether industry views the guidelines as onerous.

Dr. Miller asked what process would determine a sequence's legitimacy of use, to which Dr. Tucker responded that customers would be able to look at the select agent regulations and determine for themselves whether it would be regulated. Since industry currently asks questions to determine legitimacy of end use during its screening process, the U.S. government could provide further guidance with regard to what proposed end uses would be considered legitimate, if the providers would find such information helpful.

Judge Ehrlich wondered whether the U.S. government had considered providers turning their orders over to the government in order to discern patterns of orders or parts of orders that might pose the possibility of a malevolent use. Dr. Tucker explained that, while discussions have taken place, a "clearinghouse" of orders is not part of the draft proposed guidance. Some nervousness exists about creating a government clearinghouse for this information, in terms of intellectual property and other issues. This idea may continue to be considered based on the public comments received.

NSABB Draft Report on Synthetic Biology

Presenter: David A. Relman, MD
Chair, NSABB Working Group on Synthetic Biology
Professor of Microbiology & Immuology and of Medicine
Stanford University

Background Remarks

Dr. Relman discussed how the NSABB Working Group on Synthetic Biology is addressing biosecurity concerns related to synthetic biology. The two-part charge to the NSABB covered synthetic genomics as well as synthetic biology: (1) to address whether synthetically derived Select Agents are adequately covered by the current regulatory framework and (2) to identify,

assess, and recommend strategies to address any biosecurity or dual use research concerns that may arise from work being performed in the nascent field of synthetic biology. He noted that his presentation would focus on the second part of the charge.

Dr. Relman began by noting that policymakers have embraced, in nearly intact form, the 2006 NSABB report entitled "Addressing Biosecurity Concerns Related to the Synthesis of Select Agents." That report included recommendations to develop and disseminate harmonized guidance, to develop standards and practices for sequence providers, to review current biosafety guidelines, and to continue consultation with experts to develop a framework for predicting pathogenicity.

The new NSABB report "Addressing Biosecurity Concerns Related to Synthetic Biology," presented here by Dr. Relman, focused on synthetic biology more broadly. The NSABB Working Group on Synthetic Biology considered the ability to synthesize new genes, metabolic pathways, and/or proteins and approaches that enable the design of new genetic systems and potentially organisms with specified functions. As part of its deliberations the working group co-hosted (with the NIH Recombinant DNA Advisory Committee) a scientific roundtable on October 11, 2007, that addressed topics such as the state of the science of synthetic biology, goals of research, predicting biological function from sequence, and risk assessment and management. The Group also considered the existing oversight frameworks that are relevant to these considerations including the NSABB's proposal for DURC oversight and the *NIH Guidelines*.

Dr. Relman highlighted the key aspects of the report entitled "Addressing Biosecurity Concerns Related to Synthetic Biology." The defining characteristics of synthetic biology include the design and construction of new biological parts and devices, the redesign of existing natural biological systems for specific purposes, and the synthesis of self-replicating entities or the synthesis of independent life forms from scratch – with the last aspect receiving the greatest public attention. Synthetic biology is sometimes referred to as "engineering biology" because it often involves the use of parts to construct novel forms and biologic systems. Synthetic biology relies on the ability to predict the behavior of biologic systems. Predicting biological function is still incredibly challenging but a hallmark of synthetic biology research is to understand the properties and functions of the underlying parts so that they may be utilized in a predicable manner. Synthetic biology research can be described as being conducted in two ways: a top-down and a bottom-up approach. The top-down approach begins with an existing organism whose genome is re-engineered to perform functions of value. This approach uses many of the traditional approaches of recombinant DNA engineering; examples include metabolic engineering of microbes and genome shuffling. The bottom-up approach involves assembling nonliving biological parts into novel systems with predictable properties; examples include biofabrication and synthetic organisms made from scratch. Synthetic biologists come from different educational, scientific, and philosophical backgrounds, including biologists who readily self-identify as part of this community as well as people who have not considered that they might be viewed as synthetic biologists.

He concluded his presentation by asserting that the promise of this area of science cannot be understated. The potential benefits from synthetic biology, when defined broadly, will serve important functions and activities that will produce important products and that will teach important scientific principles. Before presenting the NSABB's recommendations, Dr. Relman invited Dr. Jay Keasling to present an overview of synthetic biology.

Overview of Synthetic Biology

Presenter: Jay Keasling, Ph.D.,
Professor of Chemical Engineering and Bioengineering
University of California, Berkeley (UC Berkeley)
Director, Synthetic Biology Engineering Research Center (SynBERC)

Dr. Keasling highlighted the important benefits of synthetic biology from an engineer's perspective. He discussed how other fields have developed and how the synthetic biology community believes this field should develop.

In microelectronics, the computer was developed from off-the-shelf parts; standards are widely used for characterizing components and connections, and manufacturers are able to fabricate devices to fit new computers because of standardization. In the chemical industry, styrene is one of the most widely used and manufactured bulk chemicals and is made in a chemical synthesis facility that uses unit operations like reactors and distillation columns that are connected with standard components like pipes. These fields have in common the independent parts and devices that are standardized and that function as well-characterized standards for connections of components, along with the ability to design and fabricate. Dr. Keasling contrasted this type of standardization with the fields of biology, in which the standardization of parts is almost non-existent.

Synthetic biology can reduce the cost and time to engineer biological systems and increase their reliability. One example is the microbial synthesis of artemisinin, which is the treatment for malaria that is approved by the World Health Organization (WHO). The natural source of artemisinin is a plant, and there are significant shortages of this treatment for malaria due to economic factors and variations between growing seasons. Because availability, quality, and price are seriously problematic, it was decided to attempt to use a microbe to synthetically produce artemisinic acid. The approximately 40 needed components could be obtained through genome sequencing or from colleagues, but the parts are not standardized and may not always provide reliable results. One of the major aims of synthetic biology is to characterize components and standardize them so that they can be used more readily.

The research on artemisinin began in 2001 and the basic science was finished in December 2007; it was eventually licensed to SanofiAventis which is doing the final process development. It is anticipated that this treatment for malaria will be in the hands of underprivledged children in Africa in one or two years, with the hope of filling the entire 200-million-dose treatment gap that is expected in 2012.

Much of the foundational work in synthetic biology is being done in the SynBERC and is a collaboration of synthetic biologists from the Massachusetts Institute of Technology (MIT); Harvard University; the University of California, San Francisco; University of California Berkeley; Stanford University; and Prairie View A&M University. These researchers are developing foundational components and tools that will improve the speed, cost, and reliability of applications. The basic molecular units of synthetic biology such as DNA binding proteins, enzymes, DNA sequences, promoters, and RNA structures are being developed to physically implement complex biological functions. These parts will be combined to develop well-characterized functional devices such as metabolic pathways and gene expression control systems.

A biotechnology foundry (biofab) is being developed in the San Francisco Bay area with the goal of streamlining the development, standardization, and characterization of components to make them available to the research community; patent and other intellectual property issues would not encumber the achievement of these goals. Biofab components might include parts characterization, parts registry, cell envelope synthesis, robotic DNA assembly, parts repository, and evolution and screening.

Biological parts will be deposited in registries, one of which has already been developed at MIT. The characterization of those components will be used in a computer-aided design program that would allow designing these devices to function as needed. Such a program would be similar to Bio-SPICE (Biological Simulation Program for Intra-and Inter-Cellular Evaluation), which is an open-source framework and software toolset for systems biology that assists biological researcher in modeling and simulating spatio-temporal processes in living cells.

Dr. Keasling also describe the promise of synthetic biology using examples of metabolically engineered microbes that could someday aid in the production of a broader array of crops that can fix nitrogen, produce biofuels, and synthesize specialty and commodity chemicals that could replace those currently produced from petroleum.

Presentation of the NSABB Draft Report on Synthetic Biology

Dr. Relman reiterated the significant uncertainties of synthetic biology that stem from the present state of the science, the rapidly evolving nature of synthetic biology, and the diverse practitioners attracted to synthetic biology, noting that these uncertainties could present some biosecurity risks. Synthetic biology relies heavily on the ability to predict biological function from nucleic acid or protein sequence and structure; however, accurately predicting biological properties from sequence or structure is difficult and a better understanding of how biological context determines function is needed. In addition, it will continue to be difficult to predict the biological risk of a synthetic entity that bears little resemblance to natural organisms. Science is evolving rapidly, cost is decreasing, and information is being generated at increasing rates; thus, it will remain challenging to predict the new discoveries, information, and technologies generated by such a rapidly changing field. Synthetic biology is attracting a growing number of diverse practitioners from diverse disciplines and interdisciplinary collaborations, with different research interests and goals that are discovery based, application driven, and focused on technology optimization and development.

Because of these significant uncertainties, it is impossible to predict the information, technologies, and new applications that will be developed by or applied to this field. Therefore, greater awareness of biosecurity (and biosafety) risks will be crucial, and methods should be pursued to predict functions associated with DNA constructs and engineered proteins and organisms. Current oversight paradigms include the *NIH Guidelines* with proposed updates and the NSABB proposed framework for oversight of dual use research, which provides the tools, perspective, and criteria for managing risk and communicating responsibilities.

The Working Group on Synthetic Biology offered the following four recommendations:

1. Synthetic biology should be subject to institutional review and oversight. The Working Group noted that many (but not all) of the dual use concerns associated with synthetic biology would be adequately covered in the NSABB's proposed framework for the oversight of dual use research.

2. Because of the large numbers of synthetic biology practitioners who come from backgrounds that are not traditionally considered the life sciences, oversight of dual use research should extend beyond the boundaries of life sciences and academia. The aim of this regulation would be to engage, sensitize and educate, not regulate or constrain.

3. Outreach and education strategies should be developed that address dual use research issues and engage the research communities that are most likely to undertake work under the umbrella of synthetic biology, including communities that are not currently subject to federal requirements and that may not be knowledgeable about guidelines, those that are not formally affiliated with universities or research institutions, and students at all levels.

4. The U.S. government should include advances in synthetic biology and advances in our understanding of virulence and pathogenicity in "tech-watch" or "science-watch" endeavors.

NSABB Discussion

Dr. Levy asked about the potential effectiveness of the industry forming its own international organization to watch over itself. He also expressed concern that deterring the science beyond a certain point would take the industry outside the United States but still subject the United States to the risks and consequences. Dr. Relman agreed that an unintended consequence could be dislocation of effort and added that individualization of this work might also result, a trend that has already been noticed. The provider industry is self-organized and users of parts have begun to organize. It will be important to think about those who are not yet involved in this discussion, as there are many others who are eagerly and productively engaged in this work.

Dr. Casadevall expressed concern about the longterm impact on U.S. security. He asked everyone at the meeting to do a "thought experiment" – imagining in the mid-19th century a committee that envisions future pollution and worker safety issues and therefore implements too much restriction during the Industrial Revolution, resulting in no industrial base in the United States. He observed that synthetic biology research is the "industrial base" of tomorrow. If this research is not conducted within the United States, it will be done elsewhere. Dr. Relman agreed, proposing that the ideal solution might be that everyone who participates in this science sits on a board like the NSABB for one year, thus having to think through the key issues.

Dr. Levy noted that, although there are consequences of this technology and possible dangers, it is critical not to hinder the science going forward.

Dr. Casadevall reminded NSABB members about the importance of considering that some of the emerging properties may not be predictable, and that inherent risk will always be present.

Public Comment

Meredith Wattman, a reporter with *Nature*, asked about the framework screening guidance published in the *Federal Register*. She noted that Steve Maurer at the University of California Berkeley has stated that the proposed guidance is very different from what the two industry groups have developed so far, proposing a lower standard than what the industry is willing to provide. One specific problem he notes is that no human would be required to consider what a gene does before that gene is shipped. She wondered if this is an outlier opinion or a legitimate concern. Dr. Tucker stated that a role exists for both automatic screening steps as well as

human follow-up. Beyond that, she preferred to wait until the full comment period is over before judging whether or not this opinion is outlying.

NSABB Motion 2

Moved by Dr. Sorenson and seconded by Dr. Imperiale, the Board voted unanimously by voice to approve the recommendations of the NSABB Working Group on Synthetic Biology with the proviso that the OBA staff incorporates the minor changes to be enumerated in writing by Dr. Vidaver. Dr. Patterson promised that the final wording would be sent to the NSABB members for a final review. Judge Ehrlich suggested that the vote be subject to a later motion to reconsider if the final review turned up any substantial changes, which Drs. Sorenson Imperiale accepted as a friendly amendment.

NSABB Outreach and Education Activities

Presenter: Michael Imperiale, Ph.D.
Chair, NSABB Working Group on Outreach and Education
Professor, Department of Microbiology and Immunology
University of Michigan

Dr. Imperiale provided an update on the activities of the NSABB Working Group on Outreach and Education and offered a preview of two new initiatives implemented by the Office of Biotechnology Activities (OBA). He reviewed the impetus for the formation of this working group and reminded attendees about the strategic plan approved by the NSABB one year ago that is currently under consideration by the U.S. Government.

Prior and ongoing outreach efforts include ensuring stakeholder input into NSABB work products, electronic communications and websites, exhibits at major meetings, and presentations to and workshops with key constituency groups. He provided a sample list of organizations to which NSABB members and staff have made presentations; a list of outreach efforts during 2008 and 2009 accomplished by NSABB members and OBA staff; and, a representation of one of the exhibit posters put together by the OBA regarding the dual use issue. These efforts constitute Phase 1 of the strategic outreach plan.

Phase 2 of the outreach efforts on input into federal policymaking, which includes publication of proposed requirements and policies for public comment and input. In addition, public consultation meetings were suggested and have occurred. Phase 3 of the plan is to educate the scientific community and other stakeholders once the federal government implements policy. A multipronged approach is suggested, including electronic and print materials, model curricula, workshops, and exhibits.

Four key points must be considered when developing outreach and education initiatives. The target audience encompasses the scientific community as well as a broader group of researchers among whom understanding and educational needs vary. Members of these groups must be engaged in dialogue in order to include their views and to ensure buy-in to the process and the end result. Message development will vary because key points need to be conveyed differently to diverse stakeholder communities. Another consideration is determining the most effective means of communicating about dual use research issues in addition to

assessing who would be the most credible and effective communicators. Also, there is a need to coordinate communication efforts in order to ensure consistency of the messages and to avoid confusion.

A number of groups outside the U.S. government have already begun education efforts, including online educational modules from the Federation of American Scientists as well as the Policy, Ethics, and Law Core of the Southeast Regional Center for Emerging Infections and Biodefense. At a conference organized by the Inter-Academy Panels in Poland in November 2009 about education on dual use issues, Dr. Imperiale took away three major points: (1) champions of this issue are needed in order to make the dual use research issue widely known and understood; (2) there remains a high degree of lack of awareness of the dual use research issue in the scientific community as well as a high degree of denial about its existence; and (3) care must be taken not to overemphasize the risks, especially when teaching to audiences at the college level and below, because doing so might scare away these young people from doing the research.

Dr. Imperiale then discussed two recent initiatives undertaken by the OBA into which the working group has provided input: an educational brochure on the dual use issue and a dual use educational video. The aim of the brochure, which is currently being developed by the OBA, is to:

- Present a general conceptual overview of dual use research
- Distinguish between dual use research and dual use research of concern, and
- Introduce the work of the NSABB

When completed and printed, the brochure will receive wide distribution at meetings and exhibits.

The purpose of the educational video is to initiate a dialogue among scientists about the dual use research issue and to present the issue from the point of view of various different stakeholders, including experts in infectious disease, molecular biology, plant pathology, human biology, animal sciences, research administration, policy analysis, and the public perspective. Divided into four parts, the video defines the dual use research issue, describes the nature of the potential threat from dual use research, talks about the responsibility of the scientific community and the government to minimize the risks, and discusses how to move forward on a common path. Perceived uses of this video include awareness building and as an opening segment to future educational materials; as yet there are no specific policies that can be included. The dissemination plan calls for making the video available on the OBA website, distributing DVDs of the video at meetings and presentations, and incorporating the video into ongoing dual use education efforts, such as courses on the responsible conduct of research.

Noting that it was in near-final form and that background shots dealing with plant science would be incorporated in the final version, Dr. Imperiale showed the “world premiere” of the video.

NSABB Discussion Regarding the Video

Dr. Fraser-Liggett asked whether a study guide was being prepared. Allan C. Shipp, Director of Outreach in the OBA, responded that the OBA is putting together a set of packaging materials that will suggest how the video could be used and its intent. Advice will be sought from the working group on how best to package the video and what kind of information would be most helpful to the end user.

Dr. Murch noted that this video begins to pull together the personnel reliability, education, and outreach issues, which will be an effective way to perfuse the system so that awareness, education, responsibility, and ownership comes together and persists.

Judge Ehrlich suggested that materials should be prepared by the OBA to educate the public that not only are scientists responsible but about the importance of basic research and scientific progress for biodefense, commerce, health and the future in general.

Dr. Cohen asked whether discussions had occurred about adding subtitles or having other versions of the video that could be used for international outreach. Mr. Shipp responded that the primary goal was to finish the domestic product and judge the success with the video domestically, but that subtitles and other versions for use internationally have been discussed.

Dr. Casadevall asked if there were any plans for web-based refresher courses. Mr. Shipp responded that courses in the responsible conduct of research that are required for trainees and fellows supported by NIH are incorporating this subject matter fairly routinely. This video would be a key tool for that purpose.

It was queried whether focus groups had been used in developing the video. Mr. Shipp replied that a series of focus groups were done when the outline for the video product was being developed. It was tested on working scientists, research administrators, people who worked for professional associations, leaders of courses on responsible conduct of research, and others. These focus groups helped shape the messages, the questions, and the order of the statements.

Dr. Wendy Hall, Department of Homeland Security, offered to facilitate introductions to more of the national security and law enforcement communities that need to know the work being done by the NSABB and by this outreach effort, in particular.

NSABB International Activities

Presenter: Stuart Levy, M.D.
Co-Chair, NSABB Working Group on International Engagement
Director, Center for Adaptation Genetics & Drug Resistance
Tuft University School of Medicine

Dr. Levy provided an update on the activities of the NSABB Working Group on International Engagement, noting that the goal of this working group is to expand the message of dual use research of concern to the international community by reaching out to the international community who will champion these issues. Major activities to date have been three international roundtables: in February 2007 on dual use research in the life sciences, in October 2007 on strategies for fostering international engagement, and in November 2008 on sustaining progress in the life sciences and strategies for managing DURC. After the third roundtable, a total of 37 countries had been engaged in these discussions.

On October 22, 2009, the working group piloted a webinar, in English and in Spanish, entitled "Dual Use Concerns in Life Sciences Research: An International Dialogue." Objectives were to foster international discussion on issues related to dual use research and dual use research of concern, expand the global network of country representatives engaged in this area, and test the feasibility of webinar technology as an outreach vehicle for dual use research. If the pilot

was successful, the plan was to engage global participants region by region using this technology. There were two sets of viewers – individuals who were participating as part of the webinar and those who were invited to look at it as part of the webcast. This pilot webinar was limited geographically to the Americas in order to minimize difficulties due to time-zone differences. People were allowed to send in questions ahead of time and observers from around the world were invited to be part of the Webcast. Invitees were from South America, Central America, the Caribbean, Mexico, and Canada, and represented broad professional expertise.

The panelists for this first Webinar were Luis Gabriel Cuervo, M.D., representing the Pan-American Health Organization; David Franz, D.V.M., Ph.D., Dennis Kasper, MD, and Stuart Levy, MD represented the NSABB; and Amy Patterson, M.D. represented the U.S. government. The program lasted for approximately 90 minutes and consisted of four presentations and a question period that included numerous questions from five countries. Participants and observers numbered 166 from nine countries in the Americas including the United States, ten participants/observers from three other countries, and seven of unknown origin, for a total of 183 viewers. This total is a minimum as it was unknown whether more than one individual was viewing the Webinar at each of these viewing locations. The videocast and related information is archived on the OBA website.

A "postmortem" meeting following the webinar was conducted where two key pieces of information were identified. First, didactic presentations were useful but discussions of opinions among the panelists were the most interesting segments and second, slides and speakers should be shown simultaneously. It was also noted that future events should be advertised more widely and DVDs of the webinar would be useful for training and at exhibits. The working group is considering two or three webinars in 2010, and is contemplating how to select future target regions and what the content of those Webinars should be.

Other activities that resulted from the third international roundtable include an international biosecurity listserv hosted by the Federation of American Scientists, a summary of the country presentations at the third roundtable published in *Biosecurity and Bioterrorism*, a statement on how to approach dual use research by the Council of Science Editors, and a presentation of some of the dual use research of concern material to the NIH Global Bioethics Network at the Fogarty International Center.

The WHO partnered with the NSABB for all three roundtables. Key WHO messages regarding responsible life science research are parallel to NSABB goals:

- *Preserve good science.* A culture of scientific integrity and excellence is the best protection against accidents and potential misuse of life science research, and the best guarantee of progress and development.

- *Responsible management.* Responsible management of life science research goes with increasing capacities in three areas: research, ethics, and laboratory biosafety/biosecurity.

- *One size does not fit all.* No single solution or system will suit all countries or laboratories. A self-assessment questionnaire has been developed to identify and build on respective strengths and weaknesses in research, ethics, and laboratory biosafety/biosecurity.

Main activities of the WHO with regard to responsible life science research include training programs and regional meetings, as well as a guidance document, entitled "Responsible Life Science Research and Global Health Security," that is likely to be released in Summer 2010. The guidance document is expected to be a key complement to additional webinars organized by the Working Group on International Engagement.

NSABB Discussion

Dr. Murch suggested a possible toolkit for individuals to generate interest in dual use research issues among their colleagues and in their respective countries. Dr. Levy acknowledged that the working group has discussed a toolkit that would consist of NSABB documents that could be used to help develop documents needed in other countries.

Dr. Imperiale encouraged development of a "DUR 101" course that would combine a didactic approach with discussions.

An audience member from the Department of State noted that the general issue of biosecurity is a compilation of many different issues, including the conduct of individual scientists, the role of government, the roles of intervening organizations such as professional associations, the functions of the scientific press, and the issues of laboratory biosafety and biosecurity. Therefore, because of these "market segments," it might be useful to think about the appropriate target audience not only by geographic region but also by sector. These different communities do not interact much but cut across country lines. Dr. Levy added that the working group has decided that it would not be appropriate to use the same message for everyone.

Mr. Tim Trevan from the International Council for the Life Sciences talked about his organization's experiences in working with Middle East countries with vastly different agendas and interests. He suggested that the working group think about addressing issues that are of immediate concern to different audiences, rather than addressing more generic and theoretical issues that do not affect their lives directly. He also suggested a blog for participation after the Webinars. Dr. Levy stated that the working group understood that some of these concerns might be a little too esoteric in countries where, for example, clean drinking water is a major issue. Mr. Trevan's idea for a blog was noted as possible.

Dr. Keim expressed concern that the Webinar may have been interpreted as the United States telling the rest of the Americas what to do, especially since four of the five presenters were U.S. citizens. Dr. Levy noted that the working group is highly sensitive to this issue.

Closing Remarks

Dr. Patterson stated that the OBA would be contacting NSABB members to ascertain their interests in serving on additional working groups as per the new charges delineated at this meeting by Dr. Parker. To facilitate the process, the OBA will prepare a draft charge, work plan, and set of deliverables for each working group that can be refined by the group. She explained that the currently constituted working groups would continue, likely with new members because the NSABB membership has changed and expanded, and each of the current working groups would take up portions of the new charges as appropriate. However, new working groups would likely need to be constituted.

Adjournment

Dr. Kasper thanked the members of the NSABB and the audience for their insightful comments. He adjourned the meeting at 2:30 p.m.

Date: _____ _____

Amy P. Patterson, M.D.
Executive Director
National Science Advisory Board for Biosecurity,

and

Acting Director
Office of Science Policy
National Institutes of Health

I hereby acknowledge that, to the best of my knowledge, the foregoing Minutes and Attachments are accurate and complete.

These Minutes will be formally considered by the NSABB at a subsequent meeting; any corrections or notations will be incorporated into the Minutes after that meeting.

Date: _____ _____

Dennis L. Kasper, M.D.
Chair
National Science Advisory Board for Biosecurity