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

NATIONAL SCIENCE ADVISORY BOARD FOR BIOSECURITY

October 25, 2006
National Institutes of Health Campus
Building 31, 6C, Room 10
9000 Rockville Pike
Bethesda, Maryland

MEETING SUMMARY

VOTING MEMBERS (Present)

Dennis L. Kasper, M.D., NSABB Chair
Arturo Casadevall, M.D., Ph.D.
Murray L. Cohen, Ph.D., M.P.H., C.I.H.
Susan A. Ehrlich, J.D.
Barry J. Erlick, Ph.D.
David R. Franz, D.V.M., Ph.D.
Michael J. Imperiale, Ph.D.
Paul S. Keim, Ph.D.
Stuart B. Levy, M.D.
Mark E. Nance, J.D.
Michael T. Osterholm, Ph.D., M.P.H.
David A. Relman, M.D.
James A. Roth, DVM, Ph.D.
Harvey Rubin, M.D., Ph.D.
Andrew A. Sorensen, Ph.D.
Anne K. Vidaver, Ph.D.

EX OFFICIOS and FEDERAL AGENCY REPRESENTATIVES (Present)

Irma E. Arispe, Ph.D., Executive Office of the President
Kenneth Cole, Ph.D., Department of Defense
Natalia Comella, Ph.D., Department of State
Brenda A. Cuccherini, Ph.D., M.P.H., Department of Veterans Affairs
Dennis M. Dixon, Ph.D., National Institute of Allergy and Infectious Diseases
Dan Drell, Ph.D., Department of Energy
Maryanna P. Henkart, Ph.D., National Science Foundation
Peter R. Jutro, Ph.D., Environmental Protection Agency

Janet K.A. Nicholson, Ph.D., Centers for Disease Control and Prevention
Stuart L. Nightingale, M.D., Department of Health and Human Services
Caird E. Rexroad, Jr., Ph.D., Department of Agriculture
Ronald A. Walters, Ph.D., Intelligence Community

NSABB EXECUTIVE DIRECTOR

Amy P. Patterson, M.D.

WELCOME
Dennis L. Kasper, M.D.

National Science Advisory Board for Biosecurity (NSABB) Chair Dr. Dennis L. Kasper welcomed everyone, introduced himself, and asked NIH Office of Biotechnology Activities Director Dr. Amy Patterson to proceed with "Review of Conflict of Interest Rules" prior to the "Call to Order."

REVIEW OF CONFLICT OF INTEREST RULES
Amy P. Patterson, M.D.

Dr. Patterson noted the "Standards of Ethical Conduct for Employees of the Executive Branch" document received by all Board members, who, as Special Government Employees, are subject to conflict of interest regulations therein. She noted that before each NSABB meeting, Board members provide information about their personal, professional, and financial interests. This information is used to assess real, potential, or apparent conflicts of interest that would compromise members' ability to be objective in giving advice during Board meetings.

Dr. Patterson noted that Board members must be attentive during meetings to the possibility that an issue may arise that could affect or appear to affect their interests in a specific way. Should this happen, Dr. Patterson asked that the affected member recuse himself or herself from the discussion by refraining from making comments and leaving the room.

Dr. Patterson invited Board members to direct any questions to Board Management Officer Kimberly Cuozzo.

CALL TO ORDER, INTRODUCTIONS, AND APPROVAL OF JULY 2006 MEETING SUMMARY
Dennis L. Kasper, M.D.

Dr. Kasper called to order the sixth meeting of the NSABB and welcomed NSABB members, ex officio members, federal agency representatives, members of the public in attendance, and those observing remotely via Webcast.

Dr. Kasper asked Board members, ex officios, and federal agency representatives present to introduce themselves, and they did so.

Dr. Kasper asked Board members for comments on the Summary of the July 13, 2006 NSABB Meeting.

Dr. Anne Vidaver noted that in paragraph 3 of page 22, the reference to "plum box" should be "plum pox." Dr. Vidaver also noted that on page 26, paragraph 3, an invited participant stated that no Select Agent (SA) had been removed from the SA list; however, the fact is that plum pox and soy bean rust have both been removed. The first correction will be made, and the second matter will be handled in a footnote, which will be denoted as a subsequent addition to the Summary.

The summary of the July 13, 2006 NSABB Meeting was then unanimously approved by all members present.

AGENDA OVERVIEW
Dennis L. Kasper, M.D.

Dr. Kasper reviewed the rest of the meeting agenda, noting that most of the meeting would be devoted to the Working Group (WG) on Synthetic Genomics' draft recommendations. When these draft recommendations are accepted by the Board, they will be communicated to the U.S. Government (USG).

Dr. Kasper added that, after Dr. Relman's presentation, Dr. David R. Franz would give a Status Report on the WG on International Collaboration, and then Dr. Kasper would provide a Status Report on the WG on Oversight Framework Development. Before or after Dr. Franz's and Dr. Kasper's presentations, he said that public comments would be taken at or around the set time of 2:15 p.m.

Dr. Kasper noted that the WG on Communication is continuing to develop its draft Statement on the Importance of Open Communication in Science, so Dr. Paul S. Keim's report on that topic was deferred.

Dr. Kasper concluded by noting that, at its July meeting, the NSABB approved a set of work products that include (1) Criteria for Identifying Dual Use Research of Concern, (2) Tools for the Responsible Communication of Research with Dual Use Potential, and (3) Considerations in Developing a Code of Conduct for Dual Use Research in the Life Sciences. These have since been communicated to the USG. The documents can be accessed from the NSABB Web site.

SYNTHETIC GENOMICS WORKING GROUP: RECOMMENDATIONS
David A. Relman, M.D.

Synthetic Genomics WG Chair Dr. Relman gave a presentation on the WG's charge, deliberative process, and draft recommendations contained in a document entitled

"Addressing Biosecurity Concerns Related to the Synthesis of Select Agents." He also outlined the WG's next steps.

The WG's charge reflects two phases. Phase I of the charge reads as follows: "Examine the potential biosecurity concerns raised by synthesis of SAs, assess the adequacy of the current regulatory and oversight framework and recommend potential strategies to address any biosecurity concerns." Phase II involves identifying and assessing any dual use concerns related to synthetic biology and recommending how to address these concerns.

Dr. Relman noted that, in fulfilling the first phase of its charge, the WG found that issues related to DNA synthesis technology transcend concerns about generating SAs *de novo* and pertain as well to the generation of entirely novel agents. Since it is possible that novel agents could be just as dangerous as the current SAs, the WG concluded that there is a need not only to provide recommendations related to the extant framework for SAs but also a need to reflect on the adequacy of any list-based framework for biological threat agents in general.

In conducting its work, the WG informally consulted with other key stakeholders to examine the state of the science and of technology, as well as of the oversight system. These stakeholders included industry experts, who were consulted about the current technological capabilities for synthesizing nucleic acids and the resources needed to do so; eminent researchers, who were consulted 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 the Department of Agriculture (USDA) on the extant legal/regulatory framework for controlling SAs; and key stakeholders regarding their perspectives about biosecurity concerns related to the ability to synthesize SAs.

Dr. Relman then summarized the Group's key findings:

- Technological Capability:
    - 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 presently, but not all DNA synthesis companies have this capability.
- State of Science:
    - It is possible to recover and reconstruct from DNA certain SAs; however, successful use of such reverse genetic systems currently requires that one be "skilled in the art";
    - Researchers have successfully created infectious chimeric viruses using combinations of genomic material from various SAs; these novel organisms do not fit current taxonomical classification schemes.

- Biosecurity Concerns:
    - Synthetic SA nucleic acids are easy to acquire;
    - There is a need for additional regulatory clarity in specific areas;
    - Developing a suitable regulatory framework will be difficult.

Dr. Relman added that there is difficulty in developing a suitable framework for pathogenic agents due to 1) a lack of consensus among scientists regarding an appropriate approach and methods for identifying and defining SAs and for screening sequences, and 2) current capabilities for constructing new pathogens.

Policy Options Considered

Prior to reading the WG's four recommendations, Dr. Relman summarized key portions of the recommendations report, as detailed below:

- The WG recognized that various groups outside NSABB have been grappling with issues pertaining to the potential misapplication of synthetic genomics. Therefore, it sought outside input on biosecurity concerns and possible solutions through consultations with stakeholders, including practicing synthetic biologists, representatives from the intelligence community, organizations that have conducted or are conducting relevant policy studies, and federal agencies responsible for implementing and enforcing the Select Agent Rules (SAR).
- Also considered were strategies proposed by scientists and policy analysts in workshops and conferences not associated with the NSABB.
- In general, most individuals consulted believed that the major biosecurity concerns stemmed from advances in synthesis technology that make manipulation and creation of DNA sequences simpler, faster, and more accessible. The WG was also advised to recognize that synthetic genomics is an internationally accessible technology with major primary sources of key material located outside of the United States. In addition, the WG learned that 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 regulation.
- An additional issue raised was that synthetic genomics is being embraced by communities not always familiar with biosafety guidelines or closely associated with institutions with Institutional Biosafety Committees (IBCs). In addition, many practitioners of synthetic genomics are generally educated in disciplines that do not routinely include formal biosafety training, such as engineering.
- Stakeholders recognized the value of screening requested sequences for homology with the known sequences of pathogens, but also emphasized the need for guidance in identifying the specific sequences for which current regulations require prior authorization for use, possession, or transfer. Stakeholders provided suggestions how screening could be used to guard against misuse of synthesis technologies. It was noted that the USG could provide incentives to encourage providers to screen by requiring grantees to acquire synthetic DNA only from suppliers that screen and by investing in improved screening software and in enhanced understanding of sequences associated with pathogenicity and virulence.

- The WG was also advised to consider the spirit of any proposed regulations in assessing their adequacy. The aim is to manage risk while avoiding unnecessary regulation of many key research reagents and products necessary for scientific advancement.

Dr. Relman noted that the WG's recommendations are based on the current state of the science as well as anticipated scientific advances enabled by synthetic genomics. Nevertheless, the WG recognized that because this technology is rapidly changing, there is a need for continued oversight and review of this area of activity.

The recommendations are listed below in the order that the WG suggests they might be addressed:

Recommendation 1: The WG recommends that HHS and USDA collaboratively develop harmonized guidance on the application of the SAR to synthetically derived DNA and disseminate this guidance to investigators working with, and providers of, synthetic genes and genomes. Specifically:

1.1. Provide clarification of what genetic elements or genomes are covered by 42 CFR 73.3c and 73.4c, including:
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 materials

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.

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 (SAs 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 SA sequences following standards and practices developed by relevant federal agencies (See 2.1.1.-2.1.4); and

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.

Dr. Relman commented that the WG appreciates the magnitude of the effort involved and realizes that establishing such practices requires that the USG support development of improved software tools, an enhanced understanding of virulence from a sequence perspective, and an improved framework for interpreting sequence screening efforts. He further stated that the WG also thinks that it is important for the USG to develop guidance, such as "Points to Consider," describing the standards to be used to determine if genomic material is subject to the SAR. Furthermore, the WG recognized that records of orders will need to be retained if any entity is going to review or use the information that results from the screening of sequences.

To achieve these goals in the most effective manner, Dr. Relman noted that the USG should work with recognized experts from the gene synthesis industry and from the research communities, integrating international expertise into this process. The NSABB can provide a forum for convening such experts and for facilitating collaboration among these experts and the federal agencies responsible for implementing and enforcing the SAR.

Dr. Relman also said that the WG noted that while private initiatives to create databases in software are currently underway, it will be important that such efforts be harmonized with public efforts, that the products be standardized, and that the products be vetted by a broad range of experts to ensure scientific consensus. Furthermore, he said that, once these standards and practices are in place in the United States, the USG can promote the screening of ordered sequences (1) by requiring that federal grantees and contractors order from providers that screen and retain information about requests for SA sequences and (2) by fostering an international dialogue regarding best practices and standards for screening sequences.

Prior to articulating Recommendation 3, Dr. Relman provided some background. During examination of the extant oversight framework for SAs, the WG found there is a need for the USG to amend certain laws and regulations. Specifically, the WG recommended that 18 U.S.C. 175c be repealed. This statute deems it unlawful, unless explicitly authorized, to knowingly produce, synthesize, or engineer Variola virus, the causative agent of smallpox, which is defined in the code to include "any derivative of the Variola major virus that contains more than 85 percent of the gene sequence of the Variola major virus or the Variola minor virus." At the present time, to arrive at a meaningful definition of Variola virus or any other agents on the sole basis of sequence homology is a profoundly difficult scientific problem, yet the definition of Variola virus in 18 U.S.C. 175c is based on genome sequence similarity. In addition, misuse of Variola virus is adequately covered by other statues.

Dr. Relman noted the WG also recommends that current biosafety guidelines and regulations be examined to ensure that they apply to the use of synthetic genomics and provide adequate guidance for working with synthetically derived DNA and that the DOC continue its efforts to reconcile the genetic elements language in the Commerce Control List (CCL) with that in the SAR to achieve consistency between SA genetic

material that can be imported and used domestically and the genetic material for which authorization is needed for export.

Recommendation 3: The WG recommends that the USG:

3.1 Repeal 18 U.S.C. 175c 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 with that in the SAR.

Addressing Recommendation 4, Dr. Relman noted that, in terms of the adequacy of the current oversight framework for SAs, given advances in synthetic genomics, it is apparent that an agent generated from a genome that was synthesized to include fragments from SA genomes might not be classified as an SA despite the fact that such an agent might be just as dangerous. Therefore, the WG concluded that there is a need to recommend longer term strategies for addressing biosecurity concerns related to synthetic genomics. Key to these longer term strategies are the needs to examine the current classification system for SAs and to determine if an alternate framework can be developed so as to be useful.

He further noted that recent studies of pathogens using genomics-based approaches have revealed an enormous degree of strain diversity, challenging notions of microbial species as discrete entities with well-defined properties. Additionally, one implication of these observations is that in some instances the assignment of a genus or 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- and species-based approach that is currently used in SA classification is imperfect and increasingly problematic since it does not take into account the great degree of genetic variability that can exist within species as they are currently defined and presumes a clear understanding of species boundaries. Advances in the science of synthetic genomics and synthetic biology will further confound this already murky situation. As a result, reliance on taxonomic definitions for SAs will become increasingly irrelevant in an age of synthetic or engineered genomes.

Finally, Dr. Relman noted that synthetic genomics and synthetic biology are technologies that are being employed globally and that emerging biosecurity issues will increasingly be global in scope. Therefore, he stated that it is important to consider the potential international implications of any proposed changes to the current oversight framework for synthetic DNA and synthetic genomes. Because international cooperation encourages standard practices worldwide, he said that the WG recommends that the USG foster international dialogue and international collaboration on these issues.

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 SA classification system to determine if it is possible to reconcile the current controls for SAs 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.

Dr. Relman thanked WG members, past and present, and also Drs. Andrew Robertson and Dan Drell for their contributions.

Next Steps:

- Consider input from the Board.
- Seek broader public input on the recommendations, particularly from "part-time" users.

Discussion

Dr. Kasper congratulated the WG for its extremely thoughtful work. He invited Board members and ex officio members to make comments.

Dr. Murray L. Cohen asked how the activities and findings of this WG may affect the report of the Criteria WG. Specifically, he wondered whether the latter WG should explicitly consider synthetic genomics in the criteria for identifying dual use research of concern.

Dr. Relman replied that there were no plans to cite synthetic genomics in the dual use criteria, adding that they emphasize functional characteristics.

Dr. Arturo Casadevall asked how the Board might tackle issues regarding susceptible hosts. For example, Variola major could not be used as a biologic weapon if everyone were immunized.

Dr. Relman replied that the point is well taken, and it is relevant not just for synthetic genomes but for any threat defined by whatever perspective or metric chosen. Dr. Relman added that such considerations need to be part of the WG's Phase II discussion.

Dr. Michael T. Osterholm observed that it is not always possible to identify a sequence or genetic element that makes something a pathogen. Even with high-consequence pathogens, many sequences are present that are not known to be associated with their pathogenicity. Sometimes it is a combination of genetic elements that needs to be

considered, as opposed to a particular genetic element. Dr. Osterholm asked what the WG discussed in this area and how it will tackle the question of sequences whose function is yet to be discerned. Dr. Relman replied that the WG made brief forays into this area of uncertainty. No group has a crisp answer at present, but the science in this arena is rapidly advancing.

Dr. Cohen asked whether the WG looked at what might be happening in this nascent field beyond our borders, given that the WG's recommendations are very focused on the United States. Dr. Relman replied that the WG received the views of several stakeholders from the gene synthesis industry, which is based primarily outside of the United States. From the perspective of users, the WG heard from a reasonable but small sampling of the domestic community. He added that the International Collaboration WG may want to address this in more depth.

Dr. Barry J. Erlick asked whether the WG received feedback from user groups, particularly commercial groups, that they would be amenable to the WG's draft recommendations. Dr. Relman replied that the WG heard a wide spectrum of perspectives, ranging from ardent requests for more guidance to concerns, including concerns about commercial proprietorship and intellectual property.

Dr. Kasper asked if anyone other than Board members, including members of the public, had any comments.

Alan Pearson, from the Center for Arms Control and Nonproliferation in Washington, D.C., asked two questions: First, with respect to Recommendation 3, he asked why the WG recommended repeal of 18 U.S.C. 175c as opposed to an amendment. Second, with respect to Recommendation 2**,** he asked why the WG called for "Points to Consider" for determining if genomic material is subject to the SAR rather than the development of actual guidelines.

Dr. Relman responded that, in the first instance, the WG was guided in part by whether repeal or amendment would create additional risk to the public. The WG was assured that the current regulatory guidelines, rules, and statutes provide adequate protection against misuse of the Variola virus. Repeal was chosen for two reasons: at present, the science does not allow the definition to be based solely on sequence; and repeal might be grounds for greater public debate on, for example, the utility or propriety of using the U.S. Code for this purpose.

In the second instance, Dr. Relman noted that Recommendation 2 has several components. Development of "Points to Consider" is one, but there is also a subrecommendation that calls for the development and promotion of standards and preferred practices for screening orders and interpreting the results.

Discussion of Proposed Amendments Prior to Vote
Dr. Kasper asked if Board members had any changes to propose.

Dr. Casadevall asked for some acknowledgement of the concept that virulence depends in part on the host and cannot be defined on the basis of the organism alone. If that is acknowledged, he said, one can begin to acknowledge the limits and challenges inherent in this task.

Judge Susan A. Ehrlich proposed that Dr. Casadevall's concern could be addressed in the WG's work on Phase II of its charge. Dr. Casadevall agreed.

Dr. Relman suggested another possibility: that some relevant, supporting text could be added to the materials in the WG report that follow Recommendation 4.

There was further discussion of the issue.

Dr. Osterholm commented that while he agrees with Dr. Casadevall's comment, any discussion of virulence has to be combined with the concept of infectivity and pathogenicity because the relationship between a host and an agent is the ability to be transmitted, and that can be altered by any number of genetic components of the host and the agent. Virulence is the ability to cause severe or debilitating disease, which can be altered by any number of combinations of genetic components of the host or the agent. In conclusion, Dr. Osterholm suggested that these factors be discussed in the WG document because they are all relevant to the host-agent relationship. Dr. Kasper responded that he was somewhat concerned about the relevance of a textbook definition of virulence for the document at hand. Dr. Osterholm clarified that he is not asking for further additions to the document, particularly as it has already been agreed that the WG will consider the issue in Phase II of its charge. Dr. Andrew Sorenson suggested that the body of the WG's report not be modified but, rather, text be added to an appendix that discusses the matter at hand. Dr. Kasper and other Board members agreed with this solution. Dr. Relman will consult further with Drs. Casadevall and Osterholm.

Dr. Kasper called for a vote on the WG's report and draft recommendations as they stand, with the commitment to consider modification of its supplementary materials as discussed. Dr. Kasper reminded Board members that a vote to move the report and its draft recommendations forward will result in conveyance of the report and its draft recommendations to the USG for broader comment and posting on the NSABB Web site.

Before the vote was taken, Attorney Mark E. Nance recused himself by physically leaving the meeting room.

Vote on "Addressing Biosecurity Concerns Related to the Synthesis of Select Agents: Draft Recommendations," Prepared by the Working Group on Synthetic Genomics

Board members present approved the report and draft recommendations unanimously without abstention.

Dr. Kasper asked that the meeting move on to the WG on International Collaboration's Status Report.

INTERNATIONAL COLLABORATION WORKING GROUP: STATUS REPORT
Dr. David R. Franz

International Collaboration WG Co-Chair, Dr. David R. Franz, noted that the WG's general purpose is to take the products of the Board and to work with scientists, policy makers, and others internationally to encourage them to take under consideration the Board's work and to get their input to facilitate working together on a wide range of very difficult problems.

Dr. Franz further observed that the value of the WG's work will sometimes lie as much in process as in product. Formed later than the other WGs, in part because it depends on the products of the other WGs, the International Collaboration WG is just beginning to implement its charge, which, very broadly, is to "recommend strategies for fostering international collaboration for the effective oversight of dual use biological research."

After noting the WG's roster of Board members, including WG Co-Chair Dr. Stuart B. Levy, and federal agency representatives, Dr. Franz presented the WG's recent activities:

- Preparing for a two-day International Roundtable in early 2007 as the first in a series of meetings with the international science and policy communities.
- Planning to invite a fairly small group of representatives of 14-15 nations and 5-6 Non-Government Organizations (NGOs) to the Roundtable, in co-sponsorship with the World Health Organization (WHO), with representatives from the World Organisation for Animal Health (OIE) and the Food and Agriculture Organization of the United Nations (FAO) in order to cover the entire spectrum of biology.
- Presentations by Dr. Keim and Dr. Franz at the Royal Society meeting in the United Kingdom in September 2007, along with the National Academy of Sciences (NAS) and International Academy of Pathology (IAP).
- Presentations by Dr. Janet K.A. Nicholson on the NSABB at the Lab Network WG meeting of the Global Health Security Action Group in Canada in June 2007.
- Informal involvement by Dr. Franz in the NAS Center for International Security and Cooperation (CISAC) meeting in Moscow and with a variety of Chinese entities during his visit to Beijing in June 2006, as well as presentations on NSABB by Dr. Franz at the WHO WG meeting on Life Science Research and Global Health Security in Geneva in October 2006.
- Discussion of NSABB activities by Dr. Cohen at the American Biological Safety Association (ABSA) meeting in October 2006.
- An overview presentation on NSABB by Dr. Harvey Rubin at the Infectious Diseases Society of America (IDSA) meeting in Toronto in October 2006.
- A presentation on NSABB Dual Use Science by Dr. Rubin at the Student Pugwash meeting at NAS in October 2006.

Next steps include holding the planned Roundtable with the goal of soliciting input on common principles with regard to dual use research and on the work of the Board to date. Other Roundtable goals are to work with international colleagues to understand:

- How they see dual use research as a problem;
- What challenges they face in addressing this issue;
- How important this issue is to them;
- Any activities that they have been involved in this area; and
- Ways in which the NSABB and international colleagues can work together now and in the future.

Next steps in addition to the planned Roundtable are to:

- Continue to build a database of international contacts in science and science policy, and
- Participate in the following meetings:
  - Drs. Levy and Kasper will present "Dual Use Science" at BIO 2007 annual conference in Boston.
  - Dr. Franz will participate in the European Union's meeting on Codes of Conduct in Berlin in December 2006.
  - Dr. Lynn W. Enquist will continue to be involved in preparations for the NSABB Symposium at the American Association for the Advancement of Science (AAAS) Meeting in San Francisco in February 2007.

Dr. Franz asked members of the Board to pass along relevant international contacts they might have in science and science policy.

Concluding his presentation, Dr. Franz made general comments about the significant interest he has experienced abroad in the draft products of the NSABB. Specifically, he heard a number of comments about the NSABB's draft guidance documents and about how useful it was that the Board focused on principles rather than trying to fashion a one-size-fits-all code.

Dr. Franz said making the communities aware of the work that the NSABB is doing and educating them about it is useful. A good approach may be to use common tools such as biosecurity and biosafety for their intrinsic and practical value and the opportunity they afford for the communities to work together, he said.

Dr. Franz further noted that the technical problem that the Synthetic Genomics WG is tackling is very difficult, but by working internationally, the Board can attract good minds and build on the understanding and transparency that the Board seeks as it works toward not just solutions for the United States but for solutions that may have an international impact as well.

Discussion

Dr. Kasper asked for questions or comments.

Dr. Levy noted that the WG is trying to draw international attention to the NSABB's documents, which were nonetheless developed primarily for an American context. The WG believes that international attention to the issue is key to addressing it effectively, and that this Roundtable will be an opportunity to learn how to get acceptance of the legitimacy and importance of the dual use issue.

Dr. Franz noted that this first International Roundtable is deliberately limited in size, but the next workshop will involve more countries, including those not already involved in activities related to dual use research of concern and dual use potential.

Dr. Stuart L. Nightingale asked if the International Collaboration WG is formally capturing comments heard by WG members during their travels and presentations abroad and suggested a template could be used. Dr. Franz responded that the comments heard have been mostly general.

Dr. Keim noted that when he and Dr. Franz attended the Royal Society meeting it was obvious that people in the developed world are thinking a lot about the issues and are receptive to them. However, the developing world will be a different audience. He asked if the International Collaboration WG has discussed the different strategies for working with developed and developing countries. Dr. Franz responded that the WG has discussed those issues generally and that he has seen them play out many times at meetings. For example, he attended a meeting in a developing country last summer, and developing country representatives were more concerned about malaria, HIV, hepatitis, and multiple drug resistant tuberculosis than dual use research of concern. Sensitivity will be required, he said. The first Roundtable will be an opportunity to focus on NSABB products and on the WG's mission as an international subgroup.

Dr. Vidaver asked for a compilation of relevant presentations given by other Board members.

Dr. Kasper responded that the Board could discuss those presentations next.

General Discussion of Board Member Presentations

Dr. Vidaver noted that approximately two or three weeks ago, she gave a presentation at the University and Industry Consortium meeting in Indianapolis about the NSABB's activities and draft products. Attendees were extremely interested and also concerned about the impact of the NSABB's work on what they were doing, both in research and in industry. They want to be kept informed. Dr. Vidaver indicated to them that what the NSABB decides will be available for public comment.

Judge Ehrlich noted that she had spoken about NSABB at a conference at the Biodesign Institute at Arizona State University, where excitement was expressed about the NSABB's work, in particular the draft guidance documents.

Dr. Relman noted that he had given a presentation to the University of California Biological Safety Officer's Working Group. His presentation had the potential to cause

great anxiety, given that he was introduced as someone who would tell "us more about the burdens that will be thrust upon us by the federal government." However, at the end of his presentation, the audience seemed reassured, and there was greater understanding of the sensitivities involved in NSABB's work and that the Board is undertaking its work in a thoughtful and considered manner.

Dr. Keim noted that he has presented several times recently. Once was at a symposium sponsored by the College of Law at Arizona State University, which seems particularly interested in dual use research. One reaction came from a USG representative who asked what regulations NSABB would be putting into effect. His comment was, of course, that the Board does not regulate; rather, it makes recommendations to the USG.

Dr. Keim commented that the Royal Society meeting in London was very interesting because he and Dr. Franz found that the level of awareness was higher than at meetings in the United States. At the Royal Society meeting, there was some interest in how the NSABB would handle recommendations regarding commercial entities that keep everything secret.

Dr. Cohen commented that there was keen interest in the NSABB's draft guidance documents at the ABSA meeting last week. The ABSA science program chair for next year's conference asked about the possibility of workshops specifically on codes. On another point, European scientists in the audience were confused about how the NSABB's work relates to the Biological Weapons Convention (BWC).

Dr. Franz responded that how the work of the NSABB relates to the BWC will be addressed in the upcoming Roundtable. He noted that on the one hand, there are scientists who are interested in regulation but, for the most part, who also want to be free to conduct scientific research. Among those interested in regulation are those interested in putting teeth into mechanisms such as the BWC. NSABB needs to carefully mark its boundaries; i.e., the NSABB mission is not to give the BWC teeth; rather, it is to engage in a spectrum of activities that reduce the misuse of biology intentionally or unintentionally. A keynote speaker for the Roundtable in early 2007 will discuss that concept.

Dr. Michael J. Imperiale noted that he had given a presentation a few weeks ago in a course on the responsible conduct of research that the University of Michigan offers to graduate students and postdocs. More than 100 people attended the presentation. At the beginning of his presentation, Dr. Imperiale had asked who was familiar with the term "dual use." Fewer than a handful of people raised their hands. This is an issue the NSABB will have to address. In the end, the course director told him that the topic of dual use research generated more discussion than any other course topic. Clearly, advanced students are interested in the issue and want to discuss it more. Well over 90 percent of the discussion dealt with publications—what should be published and how—leading Dr. Imperiale to conclude that the Communication WG's work will be key.

Dr. Rubin recounted three general audiences that he had addressed recently. The first was alumni of the University of Pennsylvania. It was clear that while approximately half of the audience did not understand initially what was under discussion or its importance, the university community subsequently became very interested in dual use research and, hence, the work of the NSABB. The second audience was students at the Student Pugwash conference. The NSABB should focus on these younger scientists because they will have to live with whatever system is ultimately put in place as a consequence of the NSABB's recommendations. The third audience was working scientists who asked that NSABB members engage them in deliberations on such topics as synthetic biology. In addition, a number of working groups are asking how they can help the NSABB as well as share what they are doing.

Dr. Casadevall commented that four or five NSABB members will be presenting the work of the Board at the American Society for Microbiology (ASM) Biodefense Meeting that will take place in Washington, D.C. in February 2007 before an audience very focused on biodefense.

Dr. Franz noted that at the WHO meeting last week, there was significant discussion about the terms "dual use" and "misuse." It is something for the NSABB to think about as it moves forward. A number of attendees indicated they prefer the concept of "misuse," yet "dual use" is what the NSABB has been discussing.

Clarification of the NSABB's Mission—To Address Dual Use or Misuse—and Discussion of "Dual Use Research of Concern"

Dr. Kasper noted that the purpose of the NSABB is to address dual use, not misuse. He added that this confusion was present at an ASM meeting he recently attended.

Dr. Erlick noted that the Criteria WG has adopted the term "dual use of concern."

Dr. Kasper clarified that the term should be "dual use research of concern" and stated that the NSABB would from this time forth use that term.

Judge Ehrlich commented that the term "dual use" is in the NSABB's charter, as opposed to the term "misuse."

OVERSIGHT FRAMEWORK DEVELOPMENT WORKING GROUP: STATUS REPORT

Dr. Dennis L. Kasper

Dr. Kasper noted that he has served as Chair of the Oversight Framework Development WG. He cited the WG members and observed that the WG is a very creative group that has held several meetings since its inception.

The NSABB's ultimate task is to recommend a comprehensive system of federal and local oversight for dual use research. Toward this end, the WGs have been developing some of the key components of such a system, namely criteria for identifying dual use

research, tools for the responsible communication of dual use research, and a code of conduct for life scientists.

The next step, and the task of the Oversight Framework Development WG, is to describe the oversight framework into which these components will fit and to develop specific guidance for the various steps within the oversight process. The actual task for the WG will be to recommend the features and characteristics of an oversight framework, delineating the relevant attributes of local review entities and proposing processes for the local and federal review and oversight of dual use research.

Introducing his presentation entitled "Conceptualizing an Oversight Framework for Dual Use Research," Dr. Kasper said the WG has tried to take a systematic approach. Toward that end, it explored extant models of oversight of biomedical research, looking at:

- Recombinant DNA and the structure and function of IBCs;
- Human subjects research; and
- Animal research.

From this exploration, the WG approach was to identify common features of these extant models of oversight that might be relevant to oversight of dual use research and principles that underlie these features.

Next, the WG has been articulating principles to guide the oversight of dual use research and identifying:

- Key features of an oversight system;
- Specific elements of an oversight framework, including purpose, roles and responsibilities, and attributes; and
- Tools needed for oversight.

The WG is still discussing the key features and elements of a proposed oversight system for dual use research and still developing its work product.

So far, WG discussion has resulted in identification of a number of shared principles in features of extant oversight systems that might be examined further and included when appropriate in the WG's work:

- The significant stewardship role of the USG;
- Distributive responsibilities (sometimes unique and sometimes overlapping responsibilities on the part of institutions, investigators, and federal agencies);
- Public trust, accountability, and transparency, such as including public members on review entities and permitting public access to meetings and meeting summaries;
- Expert scientific review;
- Ethical review;
- Consideration of social consequences; and
- Employment of principles of risk assessment and risk management involving risks to individuals and risks to community/environment, with degree of oversight titrated to risk.

Dr. Kasper then showed a slide delineating key features and activities of federal oversight systems. These features are presented below with underpinning principles noted in parentheses:

- Guidelines and regulations (public input; revision as science advances);
- Principal investigator (PI) identification of research projects subject to guidelines/regulations (researcher responsibility and accountability);
- Risk assessment and risk management (expert review; authority within institution; degree of oversight titrated to risk—levels of review and local monitoring; and public input);
- Institutional oversight—education and compliance (fiduciary responsibility; stewardship; compliance a condition of funding; registration with federal entity; establishment of a local expert review body; and provision of resources); and
- Federal oversight—policy development and interpretation; adjudication; education; compliance; and expert consultation (fiduciary responsibility; stewardship; public input; revision as science advances; and degree of oversight titrated to risk).

The goal, Dr. Kasper said, is for the degree of oversight to correspond to the degree of risk in order to minimize slowing the pace of discovery. Public input as well as expert consultation are key components of the development of federal policies as is ongoing assessment of guidelines and regulations to ensure currency and relevance.

Next, Dr. Kasper showed a slide that, instead of mapping underlying principles to the general features of core activities of research oversight, maps these functions to the oversight of dual use research. He stressed that the diagram is still very much in draft form.

Proceeding through the diagram, Dr. Kasper noted that, starting at the bottom, dual use research guidelines would provide a basis for oversight, both local and federal. They would include some of the guidance the NSABB has already developed, for example, criteria for identifying dual use research and tools for the responsible communication of dual use research. At the local level, PIs would utilize the guidelines in identifying subsets of life sciences research with dual use potential of concern. Other institutional entities may play key roles in the review of such research. This would likely include risk assessment and assignment of risk management strategies. These or other institutional entities might also play a role in educating about dual use research issues and policies and ensuring compliance with dual use research policies.

Certain types of research may warrant review at the federal level, Dr. Kasper continued, possibly because the findings could be associated with a high degree of risk of misuse or because they are so novel that existing guidance does not address them adequately. An advisory body such as the NSABB could provide for one aspect of expert consultation and public input in such instances and could also continue to advise on the development and interpretation of federal policies. In rare cases, administrative approval at a senior

federal level (such as that of the Secretary) might be deemed necessary for certain types of dual use research.

The WG's "Draft Principles" to underpin oversight of dual use research are:

1. Life sciences research is essential for improvements in health and safety (with potential for producing information with dual use potential):
    - Therefore, it is appropriate to have a framework and tools for oversight, conduct, and communication.
    - Oversight must address needs for both security and research progress.
    - Scientific community awareness of the dual use potential of research is key to effective oversight.

2. Effective oversight will help maintain public trust:
    - By demonstrating that the scientific community recognizes the implications of dual use research;
    - By demonstrating that scientists are acting responsibly to protect public welfare and security; and
    - With responsibility to be shared by federal funding agencies, recipient institutions, and researchers.

3. To be effective, such oversight requires ongoing dialogues among scientific communities, government agencies, and the public.

4. The foundation of oversight of dual use research is investigator awareness, peer review, and local institutional responsibility (which facilitates direct input from investigators), timely review, and personal responsibility on the part of scientists.

5. Because research is dynamic and can yield unanticipated results, it should be periodically evaluated for dual use potential.

6. The oversight process should be evaluated periodically for effectiveness and impact on the research enterprise.

7. Responsible communication of dual use research of concern is essential to maintain public confidence in the scientific community.

Dr. Kasper noted that the WG is in the process of formulating the various features and elements of a dual use research oversight system, including:

- Guidelines for institutional review of dual use research of concern;
- Risk assessment and management, with oversight correlated with the likelihood and possible consequences of misuse of researching findings;
- Compliance with dual research policies—mandatory for federally funded institutions and voluntary for other institutions;
- Investigator awareness of dual use concerns and policies;
- Training and education;
- Appeals processes; and

- Evaluation of the system.

Possible specific components of the oversight framework are:

- The federal government;
- National review bodies, such as the NSABB;
- Dual use research biosecurity guidelines;
- Institutions receiving federal support for life sciences research;
- Institutional dual use research biosecurity review entities;
- Institutional dual use research biosecurity officers; and
- Research staff.

In addition to tools already developed by the NSABB, the WG anticipates needing, at a minimum, to develop tools for risk assessment, risk management, and evaluation. This will likely be in the form of "Points to Consider" documents and case studies.

.

Next Steps include:

- Continuing to refine key features of oversight;
- Continuing to flesh out specific elements of the oversight framework (i.e., purpose; roles and responsibilities; and attributes); and
- Identifying the array of tools needed for oversight and, as necessary, developing needed tools.

Discussion

Dr. Cohen asked about use of the term "biosecurity" in local oversight, wondering whether it was purposefully used in lieu of the term "biosafety.[1]"

Dr. Kasper responded that the use of the term "biosecurity" was very purposeful and that the WG has evolved to subdividing its use of the term because there is a lock box type of biosecurity versus the type of biosecurity that the WG is concerned about regarding the dual use potential of research.

Dr. Rubin asked what tools might be recommended for risk assessment.

Dr. Kasper responded that this is a very good topic. Where the rubber really hits the road regarding the whole oversight system is defining risk assessment, how you do that, and then, ultimately, how you manage the risks that have been defined. This has not been a WG focus to date, but the WG recognizes it as an extremely important issue.

PUBLIC COMMENTS
Dr. Dennis L. Kasper Presiding

Dr. Kasper opened the meeting for public comments.

[1] Clarifying note from the NSABB: Biosafety is generally used in the context of protecting the investigator working with microorganisms or chemicals, whereas biosecurity is more encompassing with an emphasis on protecting populations of people, animals, plants, or the environment.

There were no public comments.

Dr. Kasper declared an end to the public comments session.

MEETING CONCLUSION
Dr. Dennis L. Kasper

Dr. Kasper reminded meeting attendees that the Synthetic Genomics WG Draft Recommendations will be posted on the Web site for public review.

Dr. Kasper announced that the next NSABB meeting will focus on further developments involving the Draft Oversight Framework, with follow-ups on the proceedings of the Synthetic Genomics WG and plans for the International Roundtable. NSABB Outreach and Education activities will also be discussed.

Dates for upcoming NSABB meetings are on the Web site. The next Board meeting is scheduled for January 31st through February 2nd, 2007. Subsequent meetings are scheduled for June 25th through June 27th, 2007; October 10th through October 12th, 2007; and February 25th through February 27th, 2008[2].

On behalf of the NSABB, Dr. Kasper thanked all of those who attended the meeting or who watched via Webcast. He again thanked all who provided comment and input on the topics of today's meeting, in particular with regard to the work of the Synthetic Genomics WG. He thanked Board members and the NSABB staff for their work in helping the NSABB move forward and concluded the meeting.

Date: _____

_____
Amy P. Patterson, M.D.
Executive Director, NSABB/Director, OBA

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

[2] Note: *The next public NSABB meeting was subsequently scheduled for April 19, 2007; the January-February meeting was closed for a security briefing.*