National Institutes of Health (NIH)
Office of the Director
Office of Science Policy
Office of Biotechnology Activities
NATIONAL SCIENCE ADVISORY BOARD FOR BIOSECURITY (NSABB)

October 22, 2014
NIH Campus
9000 Rockville Pike
Building 31, Room 6C
Bethesda, MD

MEETING MINUTES

VOTING MEMBERS

Samuel L. Stanley, Jr., M.D., Chair
Kenneth I. Berns, M.D., Ph.D.
Andrew Endy, Ph.D.
J. Patrick Fitch, Ph.D.
Christine M. Grant, J.D., M.B.A.
Clifford W. Houston, Ph.D.
Joseph Kanabrocki, Ph.D., C.B.S.P.
Gardiner Lapham, R.N., M.P.H.
Jan Leach, Ph.D.
Jeffrey F. Miller, Ph.D. (by phone)
Rebecca T. Parkin, Ph.D.
Susan M. Wolf, J.D. (by phone)

AD HOC VOTING MEMBERS[1]

Marie-Louise Hammarskjold, M.D., Ph.D.
Robert P. Kadlec, M.D., M.T.M.&H., M.S. (by phone)
Theresa M. Koehler, Ph.D.
Marcelle C. Layton, M.D.
James W. LeDuc, Ph.D.
Margie D. Lee, D.V.M., Ph.D.
Francis L. Macrina, Ph.D.
Joseph E. McDade, Ph.D.
Stephen S. Morse, Ph.D.
Jean L. Patterson, Ph.D.
David L. Woodland, Ph.D. (by phone)

ABSENT

Craig E. Cameron, Ph.D.

[1] Ad hoc voting members are incoming members who will participate in a non-voting capacity until their appointments to the Board are finalized.

I. Gary Resnick, Ph.D.

***EX OFFICIOS* / FEDERAL AGENCY REPRESENTATIVES**
Diane DiEuliis, Ph.D., U.S. Department of Health and Human Services
Amanda Dion-Schultz, Ph.D., Office of the Chief Scientist
Dennis M. Dixon, Ph.D., National Institutes of Health
Brendan Doyle, Ph.D., U.S. Environmental Protection Agency
Gerald Epstein, Ph.D., U.S. Department of Homeland Security
Richard Gordon, Ph.D., U.S. Department of Defense
Christopher J. Park, U.S. Department of State
Michael W. Shaw, Ph.D., Centers for Disease Control and Prevention
Eileen Thacker, D.V.M., Ph.D., U.S. Department of Agriculture
David G. Thomassen, Ph.D., U.S. Department of Energy
Edward H. You, Federal Bureau of Investigation

Welcome
Samuel L. Stanley, M.D., NSABB Chair, President, Stony Brook University

Dr. Stanley opened the meeting at 8:15 a.m. He welcomed the NSABB members and other meeting participants. The accomplishments of the NSABB are a testament to the dedication and hard work of the Board members, Dr. Stanley said, and he looked forward to continuing that work.

Biosafety and biosecurity are topics on everyone's mind at the moment, Dr. Stanley explained. Incidents in federal facilities this summer underscore the importance of laboratory safety and prompted calls for an assessment of laboratories working with dangerous pathogens, especially those conducting so-called gain-of-function (GOF) studies. Other events, such as the Ebola virus outbreak in West Africa and subsequent cases in the United States, highlight the importance of studying dangerous pathogens to develop the capacity to detect new strains rapidly and ultimately to develop more effective treatments and vaccines.

Dr. Stanley referred to the October 17, 2014, announcement by the White House Office of Science and Technology Policy (OSTP) and the U.S. Department of Health and Human Services (HHS) that the U.S. Government (USG) will launch a deliberative process to assess the potential risks and benefits associated with certain life sciences GOF studies and a concomitant pause of funding for new GOF research on influenza, severe acute respiratory syndrome (SARS), and Middle East respiratory syndrome (MERS) viruses. The announcement calls attention to the critical role that the NSABB plays, Dr. Stanley noted. Beginning with today's meeting, the NSABB will evaluate the benefits and risks of GOF research as well as the risks of not conducting such research, especially if a lack of knowledge inhibits the preparedness for responding to an epidemic. The issue of GOF studies has polarized the scientific community and the public, said Dr. Stanley, and a goal of the NSABB is to find a path forward.

Dr. Stanley summarized the agenda for the meeting, which included two public comment sessions. He said the Board has always sought broad input and public comments are appreciated, especially comments from the international community.

Introduction of NSABB Voting and Ex Officio Members and Recognition of Retiring NSABB Members
Mary E. Groesch, Ph.D., Executive Director, NSABB
Senior Policy Advisor, Program on Biosecurity and Biosafety Policy, Office of the Director, National Institutes of Health

Lawrence A. Tabak, D.D.S., Ph.D., Principal Deputy Director, National Institutes of Health

Dr. Groesch invited Board members and *ex officio* members to introduce themselves. On behalf of the NIH, she also recognized the dedication of the Board's retiring members, all of whom were appointed to the NSABB when it was created. Their advice was instrumental to the development of federal policy, and it was a pleasure to work with them, said Dr. Groesch.

Dr. Tabak added that the work of the Board is critical not just to the NIH but also to the whole federal government. The deliberations of the NSABB and the hard work of members have made a difference in how we think about complex and controversial issues. Each of the retiring members invested long hours and personal time to fulfill their responsibilities, said Dr. Tabak. As a token of appreciation, he presented retiring members who were in attendance with a certificate and a glass paperweight. Retiring NSABB members are listed below, with attending recipients denoted by an asterisk (*):

- *Arturo Casadevall, M.D., Ph.D.
- David R. Franz, D.V.M., Ph.D.
- Gen. John A. Gordon
- Michael J. Imperiale, Ph.D.
- Paul S. Keim, Ph.D.
- *Stanley M. Lemon, M.D.
- Stuart B. Levy, M.D.
- John R. Lumpkin, M.D., M.P.H.
- *Michael T. Osterholm, Ph.D., M.P.H.
- David A. Relman, M.D.
- James A. Roth, D.V.M., Ph.D., D.A.C.V.M.

Review of Conflict-of-Interest Rules
Mary E. Groesch, Ph.D., Executive Director, NSABB
Senior Policy Advisor, Program on Biosecurity and Biosafety Policy, Office of the Director, National Institutes of Health

Dr. Groesch explained that members of the NSABB are considered special government employees and as such are subject to federal rules of ethical conduct and proceeded to review the process for assessing and managing potential conflicts of interest.

U.S. Government Biosafety and Biosecurity Policy: A Review of the Changing Policy Landscape
Andrew M. Hebbeler, Ph.D., Assistant Director for Biological and Chemical Threats, OSTP, Executive Office of the President

Dr. Hebbeler presented an overview of the recent policy developments regarding oversight of dual use research of concern (DURC). He said that, for the past decade, the federal government has been considering how to implement comprehensive oversight of DURC, with active participation from the NSABB. Dr. Hebbeler also said that new policies announced by the OSTP this fall aim to foster consideration of the risks, benefits, and potential mitigation efforts of DURC as it is conceptualized, and throughout the research process, in keeping with the framework proposed by the NSABB in 2007.

The USG's 2012 policy established federal oversight of life sciences research involving high-consequence pathogens and toxins with potential to be DURC. The scope of the policy includes a list of 15 select agents and toxins and seven categories of experiments.

This September, the USG set forth a policy for institutional oversight of life sciences DURC, which will go into effect in one year. The two federal policies complement each other: both calling for the identification of DURC and mitigation of risks throughout the research life cycle. The policy for federal oversight describes the roles of funding agencies whereas the policy for institutional oversight lays out the oversight roles of principal investigators (PIs), institutions, federal funding agencies, and the USG.

To assist PIs and institutions, a companion guide to the policy was developed: *Tools for the Identification, Management, and Responsible Communication for DURC.* Other educational tools are also available online (S3 Dual Use Page), including case studies. In 2015, stakeholders will be convened to discuss their experiences with and strategies for implementing the policy for institutional oversight.

Some gain-of-function studies raise dual use concerns as well as concerns about the effectiveness of biosafety efforts. Questions raised include whether results of GOF research should be communicated (and if so, how they can be communicated responsibly), how to conduct such research safely, and whether it should be conducted at all. The Department of Health and Human Services has a framework for funding decisions about certain GOF research involving specified influenza viruses. In October of this year, the White House and HHS announced a new deliberative process to assess the potential risks and benefits of GOF studies. It also instituted a concurrent pause in USG funding for new research involving GOF experiments with influenza, SARS, or MERS viruses that may be reasonably anticipated to increase the transmissibility or pathogenicity of these viruses.

To support the deliberative process, the NSABB will be asked to draft recommendations on GOF research that will be reviewed by the broader life sciences community and to provide advice on oversight of GOF studies. The National Academies of Science (NAS) will convene scientific conferences to facilitate discussion of GOF research and the NSABB recommendations. The timeline of events is estimated to culminate in final recommendations from the NSABB in August 2015.

Discussion

Marcelle C. Layton, M.D., asked why the funding pause focuses on influenza, SARS, and MERS viruses. Dr. Hebbeler responded that recent laboratory incidents informed the decision to address pathogens with the highest pandemic potential and potential for transmission by aerosol. However, the USG does not want to compromise researchers' ability to prepare for seasonal influenza, so funding agencies can make exceptions as deemed appropriate.

Dr. Stanley asked what other mechanisms besides meetings are available to allow institutions to describe their challenges in implementing the USG policy for institutional oversight. Dr. Hebbeler replied that institutions generally interact closely with their funding agencies. Institutions not funded by the USG should contact the NIH. There is also a common e-mail address (DURC@ostp.gov) for submission of questions. The stakeholder meeting will be an important opportunity for face-to-face discussion. It will help bring the community together to facilitate linkages and harmonize implementation of the policy.

James W. LeDuc, Ph.D., asked whether any special activities are planned to address laboratory biosafety issues specifically. Dr. Hebbeler said that the NIH and the Centers for Disease Control and Prevention (CDC) investigated the causes of the incidents that arose this summer and implemented measures to address key contributing factors. The results of all these efforts will be made public. One long-term step is a holistic self-evaluation of areas for improvement in biosafety and biosecurity across the USG by the Federal Experts Security Advisory Panel, which will make recommendations in January 2015. Another is a review led by the White House National Science and Technology Council on the impact of the select agent regulations on science, technology, and national security; findings will be delivered in 2015.

Dr. Layton asked whether any consideration had been given to evaluating GOF research that looks at the ability of organisms to develop other modes of transmission, specifically airborne transmission, as that has been an area receiving a lot of attention from the media and scientists. Dr. Hebbeler said the funding pause focuses on three pathogens, but the NSABB's deliberative process is not limited to those. If the NSABB identifies other issues around GOF research that should be considered as the USG finalizes its policy, then those findings should be included in the recommendations.

Presentation of the Charge to the NSABB

Nicole Lurie, M.D., M.S.P.H., Assistant Secretary for Preparedness and Response, HHS

Speaking by phone, Dr. Lurie expressed her gratitude to the NSABB for its hard work and dedication in tackling difficult, complex issues. The NSABB's recommendations have guided the federal government's thinking about its policies.

For the GOF research issue, the USG will gather input and recommendations from the NSABB and the NAS, and it will commission formal qualitative and quantitative assessments of the risks and benefits from private firms. The charge to the NSABB is as follows:

- Advise on the design, development, and conduct of risk and benefit assessment studies
- Provide recommendations to the USG on a conceptual approach to the evaluation of proposed GOF studies

In developing the recommendations, the NSABB will consider the following:

- Results of the risk and benefit assessments
- Spectrum of potential risks and benefits associated with GOF studies
- Any alternative methods that may be employed to yield similar scientific insights or benefits, while reducing potential risks
- Discussions hosted by the NAS
- Any additional consultations with relevant subject-matter experts, as needed, to ensure that appropriate expertise is brought to bear on the issues

In its deliverables, the NSABB may take a broad approach; it is not limited to the three pathogens affected by the funding pause. Dr. Lurie stated that no research involving infectious agents is without risk. The efforts by the NSABB and others will guide future investments, maximize research benefits, and minimize risk for Americans and for the global community.

Discussion

Joseph E. McDade, Ph.D., asked whether the NSABB should limit its focus to the 15 select agents and toxins and the potential for certain outcomes as outlined in the 2012 policy. Dr. Lurie said the USG is seeking the NSABB's best thinking. If there are other pathogens or issues central to the discussion, Dr. Lurie suggested the NSABB members consider them and make recommendations as they see fit.

SESSION 1: BENEFITS, RISKS, AND ETHICAL CONSIDERATIONS ASSOCIATED WITH GOF STUDIES INVOLVING PATHOGENS WITH PANDEMIC POTENTIAL

Gain-of-Function Studies: Their History, Their Utility, and What They Can Tell Us about Pathogens with Pandemic Potential

Paul Duprex, Ph.D., Associate Professor of Microbiology, and Director of Cell and Tissue Imaging, NEIDL Institute, Boston University

Dr. Duprex noted that successful vaccination campaigns led to the eradication of smallpox and, in 2011, rinderpest. Measles had been close to eradication, but refusal to

vaccinate has led to a resurgence in Europe and in the United States. Dr. Duprex emphasized that the role of science is to inform and to educate, not to entertain or to scare, and the science community must communicate responsibly.

Among the key questions virologists address is how a virus spreads from animals to humans and among humans. Gain-of-function studies are one method for such research, but it is important to define clearly what is meant by gain or loss of function. The term "GOF research" can broadly be used to describe much of the work conducted in the course of basic virology research including, for example, growing virus in cell culture.

In recent years, Fouchier et al. have used reverse genetics to modify an avian influenza virus and determined that the modification enabled transmission of the virus between mammals via the respiratory route. The research provided important information about transmissibility but raised concerns about potential risks associated with some GOF studies.

In evaluating GOF research, it is important to consider the potential for unforeseen benefits in addition to any unforeseen risks. For example, cutting-edge research in oncolytic virotherapy is using the measles virus as a vector to put cancer into remission. The work of Peebles and Enders that led to the measles vaccine could also be considered GOF research. Both examples serve to demonstrate why use of the broad term "gain-of-function" is problematic. Furthermore, considerations about biosafety extend beyond influenza virus, so scientists working with other viruses should engage in the conversation as well.

Influenza GOF research has yielded important information about

- mechanisms (e.g., stability of receptor-binding proteins, replication, and the role of pH in viral stability),
- transmission (e.g., avian viruses can be transmitted from mammal to mammal),
- biosafety (e.g., experiments can be performed safely at biosafety level [BSL] 3 laboratories),
- vaccinology (e.g., mutations that can speed the growth of virus are needed to produce vaccine), and
- surveillance (e.g., public health policymakers are more informed).

Despite concerns about the so-called apocalyptic scenario, GOF research has not brought forth a catastrophe, and research continues to prompt global scientific progress. Finally, scientists understand the pathogens with which they work and routinely take steps to mitigate research risks for themselves, their colleagues, their families, and their communities. Communication and transparency are critical. Dr. Duprex concluded that GOF studies are just one element of a wider debate about safe, effective, and productive research involving dangerous pathogens.

Risks and Alternatives to GOF Studies
Marc Lipsitch, D.Phil., Professor of Epidemiology, Harvard School of Public Health

Dr. Lipsitch explained that insurers and regulators estimate risk by multiplying probability by consequence. Thus, the risk of GOF research could be calculated as the probability of a pandemic resulting from a GOF study times the consequences of such a pandemic. While that calculation may seem alarming, it highlights the point that there has been no quantitative evaluation of the risk of pandemic resulting from a pathogen release from a laboratory. While some believe such numbers do not exist, Dr. Lipsitch believes they do, and the challenge is to determine which numbers are most reasonable for evaluation.

For the purpose of demonstration, Dr. Lipsitch defined one "unit" of GOF research as one year's worth of research in a BSL3 laboratory. The probability of risk would be the sum of one unit of GOF research times the number of laboratory-acquired infections (LAIs) that occur in that year. Outside of a massive research program, the number of LAIs is small, and the probability of such infections resulting in a pandemic low. However, because the consequences are potentially so large, the resulting product can be significant.

Using CDC data on accidents resulting in LAIs, Dr. Lipsitch calculated a conservative estimate of 0.2% LAIs per year in a BSL3 laboratory. The probability of a pandemic can be estimated using modeling. For example, there is a 5% to 60% likelihood that an influenza-like infection will spread. Multiplying these factors yields a probability ranging from 1 in 1,000 to 1 in 10,000 per BSL3 laboratory-year of GOF research on influenza.

The probability estimate can be adjusted by factoring in control measures, the extent of vaccination and other prophylaxis among laboratory workers, conduct of research in BSL3-enhanced laboratories, and the use of molecular biocontainment. However, it is important to note that the CDC data on LAIs undercount infections and overcount laboratory-years. In addition, other countries do not apply the same biosafety standards as U.S. laboratories.

To estimate the consequences portion of the equation in terms of pandemic mortality rates, multiply the attack rate (e.g., 24%–38% on the basis of historical data) by the case-fatality rate (e.g., about 60% for wild-type H5N1 influenza virus or 1% for highly attenuated H5N1 virus) by the global population (7 billion). That results in a consequence ranging from 2 million to 140 million fatalities. The consequence estimates can be adjusted by a reduction in virulence (although the result of reduced virulence cannot be predicted in advance of GOF research). The estimate does not take into account the costs of diminished health in nonfatal cases, school closures, loss of scientific credibility, and so forth.

Given the potential consequences as determined by this calculation, even if 99% of transmissions could be prevented through vaccination and prophylaxis, the number of fatalities would still be significant in relation to a single unit of GOF research. Dr. Lipsitch called for more discussion of this approach to risk assessment.

Gain-of-function research is just one method for studying influenza; others include using defective virus in vitro, comparative analysis of natural bird and natural human strains, and GOF experiments on seasonal strains not likely to cause pandemic even if LAIs occur. Notably, the costs of conducting GOF research are high (in part because of animal biocontainment requirements). While alternative approaches may not answer the same questions as GOF studies, they typically have higher throughput and higher generalizability.

To assess the value of GOF research, it may seem logical to weigh the risks and benefits, but that is not how scientists or funders make decisions. Scientists consider, for example, various study designs, the likelihood of producing reliable data, the likelihood of achieving an adequate sample size, and the budget and staff required. Funders take into account the broad portfolio of research.

Dr. Lipsitch recommended comparing two portfolios—one with GOF studies as well as alternative approaches (research on surveillance, and research on universal influenza vaccines, for example), and one with all of those approaches except GOF studies—to assess which is more likely to yield useful results. This approach involves weighing the evidence of research with and without GOF studies and then weighing the risks of GOF studies themselves. The risk of the alternative approaches is minimal, as none are likely to cause a pandemic. Dr. Lipsitch said the portfolio-based assessment allows a comparison of the marginal benefits and opportunity costs of displacing some alternative approaches with GOF studies in a portfolio of research against the unique insights that GOF research provides.

The Ethics of GOF Studies: Considering Risks and Benefits in the Context of Uncertainty
David B. Resnik, J.D., Ph.D., Bioethicist and IRB Chair, National Institute of Environmental Health Sciences

Dr. Resnik said the ethical questions underlying the debate are whether GOF research should be conducted, who should fund it, and whether results should be classified, redacted, or published in full. He described some approaches to addressing these questions when the benefits and risks are uncertain.

The expected utility theory, a quantitative approach, calculates probability times the likely outcome to determine the utility, which can be positive or negative. Regulators at the U.S. Food and Drug Administration (FDA), for example, might use the approach to compare the number of lives potentially saved by a new drug with the number of people who might die from its use; that finding would also be compared with the likely outcomes of not approving the drug (which carries minimal or no risk). The calculations could be applied to the risks and benefits of publishing results of a GOF study on H5N1 influenza virus, for example. Dr. Resnik's model (using arbitrary assumptions) suggested that full publication would likely cause more harm than redacted publication, while not publishing the results at all would result in no harm.

The expected utility theory assumes that we can assign probabilities to the different outcomes. In terms of GOF research, one of the most significant concerns—terrorism—is a low-probability/high-impact event that cannot be estimated without more data. Models could be developed to estimate the probability. The assumptions required for such models could be mistaken—sometimes by orders of magnitude—which significantly alters the estimates of expected utility.

Another approach, dubbed "maximin," is used for decision making when the probabilities of outcomes are unknown. The maximin strategy lays out the possible outcomes so that the worst possible outcome can be avoided. It is very risk-averse, but also leads to forgoing potential benefits. The maximin strategy would likely suggest that, to avoid the risk of misuse or accidental exposure, GOF research should not be conducted.

The precautionary principle is an approach to making decisions under uncertainty when neither the expected utility, nor the maximin strategy is desirable. It considers how to make reasonable choices that maximize benefit while minimizing risk. The precautionary principle has been criticized for being unscientific, vague, subject to political manipulation, and excessively risk-averse. Dr. Resnik proposed a version of the precautionary principle that addresses some of those criticisms that involves taking reasonable measures to prevent, minimize, or mitigate risks that are plausible and serious. He posited that a precautionary measure is reasonable if it (1) is proportional to the severity of the risk, (2) carefully balances the competing values, and (3) is effective.

This approach is quantitative and requires users to make value judgments, set priorities, and balance competing values. For GOF research, the competing values would be avoiding harm, promoting public health, and advancing scientific freedom and openness. Returning again to the example of whether to publish the results of a successful GOF experiment, Dr. Resnik's precautionary principle would suggest that a redacted publication aims for a compromise that addresses all of these values but may also pose practical problems.

Discussants

W. Ian Lipkin, M.D., John Snow Professor of Epidemiology, Professor of Neurology and Pathology, and Director of the Center for Infection and Immunity, Columbia University

Dr. Lipkin said that GOF research is essential and incredibly important as we identify more pathogens. It can provide valuable insights into pathobiology and inform drug and vaccine development, but should be closely monitored to ensure public health. Dr. Lipkin said his primary concern is the inadvertent release of a high-threat pathogen, not the publication of GOF research.

It is important that risky research be identified before investigators or taxpayers invest in it. Dr. Lipkin did not believe that all scientists can adequately assess the value of their own work. Individual institutions should not be responsible for identifying unduly risky GOF research, because many do not have the range of expertise for such rigorous review, and they may have conflicts of interest. Dr. Lipkin advocated for a second level of

review, preferably by the USG, through a group with appropriate expertise in science, ethics, and other relevant issues.

Dr. Lipkin stated the two "laws" of his laboratory:

1. Potential high-threat GOF research should not be pursued without access to drugs or vaccines to prevent or treat disease.
2. GOF research that may eliminate the activity of existing drugs or vaccines should not be pursued without a backup plan.

Yoshi Kawaoka, D.V.M., Ph.D., Professor of Virology, University of Wisconsin–Madison

Dr. Kawaoka described the extensive preventive measures in place to protect against accidental release of pathogens in BSL3 and BSL3-Agriculture (BSL3-Ag) laboratories as well as the thorough oversight of his laboratory. Such laboratories are required to have mechanisms for protecting individuals and facilities and backup resources in case of power failures, as well as security clearance and training of staff.

Dr. Kawaoka said experiments at his laboratory must be approved by the institutional biosafety committee, and the program is reviewed by his institution's biosecurity task force. It is also subject to annual and unannounced inspections by the U.S. Department of Agriculture and CDC personnel to ensure compliance with safety protocols. The USG has several regulatory and guidance documents that address H5N1 influenza research. Dr. Kawaoka stressed that studies of H5N1 influenza are highly regulated.

Highly pathogenic avian influenza viruses can replicate faster than other viruses and can grow in organs other than respiratory tissues. Experiments with less-pathogenic viruses may not be applicable to highly pathogenic viruses and results may be misleading. Thus, research on highly pathogenic viruses is necessary.

The poor growth of virus strains has led to insufficient amounts of virus needed to produce a vaccine. Dr. Kawaoka said GOF studies in his laboratory have generated a high-yield H5N1 influenza virus for vaccine production. This high-yield virus is slightly more pathogenic in mice than the wild-type virus and replicates more than 10-fold better than wild-type virus. However, the research has been voluntarily suspended in light of recent regulations. Dr. Kawaoka concluded that influenza GOF studies are critical to public health and scientific progress.

Michael Osterholm, Ph.D., M.P.H., McKnight Presidential Chair of Public Health, Director of the Center for Infectious Disease Research and Policy (CIDRAP), Professor of Environmental Health Sciences, School of Public Health, University of Minnesota

Dr. Osterholm said that while there is no simple answer to the questions posed, the scientific community can develop a common approach and then make decisions on a case-by-case basis about what makes sense for science and for humans. What is needed is a method for measuring the risks and benefits of GOF research. The risk–benefit calculation must assume that all humans make mistakes, which is not a value judgment.

The benefits of GOF research are not clearly defined. At least one patient in Cambodia had the H5N1 influenza strain identified by the ferret laboratory research, but no pharmaceutical company has expressed interest in developing a vaccine for the new strain. He added that the risk of laboratory release of pathogens is not hypothetical; H1N1 influenza originated from a laboratory in the late 1970s.

Dr. Osterholm pointed out that when the NSABB addressed the question of publication, the choices seemed to be full publication or no publication; however, now it is clear that redacted publication is an option. In addition, the scientific community should acknowledge that discussion about classified information may be necessary—physicists have done so for years. Dr. Osterholm called for more discussion on how to share data safely.

Dr. Osterholm said there was discussion in the 1980s about destroying smallpox samples; he and others advocated for sequencing the samples. At the time, no one had the tools to create virus *de novo*, and scientists did not anticipate that they would ever have such capability. Part of the risk–benefit assessment involves understanding or anticipating the future of technology.

Janet Peterson, C.B.S.P., Senior Biosafety Officer, University of Maryland

Ms. Peterson outlined numerous methods of risk mitigation in place for individuals and institutions involved in high-risk research:

- Federal regulations and guidelines on biosafety and biosecurity
- Required institutional oversight procedures for those with NIH funding (including risk assessments applicable to most GOF research)
- Facility features, policies, and procedures to ensure containment (at least BSL3-Ag or BSL3-enhanced required for working with highly pathogenic avian influenza virus)
- Education and competency assessment (including annual biosafety, biosecurity, and incident response training and occupational health planning)

Ms. Peterson said that it is imperative to study viruses to develop vaccines and treatments in case of an outbreak. Decreased funding over the past 10 years for Ebola virus research has resulted in a lack of treatment approaches. By comparison, current treatment for human immunodeficiency virus—which emerged at about the same time as Ebola virus—is extremely effective. Ms. Peterson said these contrasting situations demonstrate that impeding science because of fear of the unknown or lack of funding hurts everyone. While it is impossible to reduce the risk of GOF research to zero, it can be carried out safely with appropriate containment, she concluded.

Stacey Schultz-Cherry, Ph.D., Member, Department of Infectious Disease, Deputy Director, St. Jude Children's Research Hospital World Health Organization Collaborating Center

Dr. Schultz-Cherry explained her institution's role in the World Health Organization's (WHO's) global influenza surveillance and response system. This system monitors influenza worldwide in humans and in animals and then identifies candidate virus strains for seasonal influenza vaccines. Decisions are made on the basis of monitoring and analysis to reveal functional changes in viruses, particularly changes associated with increased transmission and especially in animal viruses that have begun infecting humans. Thus, GOF studies are crucial for identifying virus strains that pose the highest risk.

The list of candidates is long, and new candidates are added frequently, because viruses change quickly in nature. Creating a seed vaccine costs $50,000. With limited resources, suggestions for vaccine candidates must be made very judiciously and responsibly.

Beyond candidate selection, GOF studies are also crucial to public health. Researchers conducted a lot of work around multiphasic cleavage sites in high-pathogenicity H5 influenza viruses to better understand pathogenicity, without a particular public health goal in mind. Those findings became incredibly important in public health with the advent of reverse genetics, said Dr. Schultz-Cherry. Without that knowledge, we would not know how to make H5 vaccines safely. Likewise, laboratory efforts to improve virus replication have been instrumental to vaccine development. This happened in 2009, when the lack of a high-yield virus for vaccine production will lead to vaccine shortages.

Dr. Schultz-Cherry pointed out that the White House hopes the voluntary moratorium on research will not impact seasonal influenza vaccine development, but it does. The moratorium captures vaccine escape studies, which are necessary to build vaccines, including universal influenza vaccines, which are many years away. It also prevents research to understand and address why even vaccine-targeted H3 viruses change so rapidly in nature, resulting in lower-than-desired efficacy of vaccines. Dr. Schultz-Cherry implored the NSABB to think about how decisions trickle down to public health issues.

Bill Sheridan, M.B., B.S., Senior Vice President and Chief Medical Officer, BioCryst Pharmaceuticals Inc.

Mr. Sheridan emphasized that drug development is time-consuming, arduous, and risky. Peramivir, for example, took 15 to 20 years to go from the laboratory to FDA approval. It is not a foregone conclusion that pharmaceutical companies will be able to create antivirals for the next strain of influenza (or other infectious viruses) or that they can successfully identify the superior host targets for drug development. The system should not rely on any particular technology to come up with new antiviral drugs. Mr. Sheridan said that one limitation of a portfolio approach as described by Dr. Lipsitch is that it relies on the potential to develop antiviral drugs or a universal vaccine, neither of which is easy to do.

Mr. Sheridan described the many steps involved in developing an antiviral and the ways in which efficacy of drugs is tested in the laboratory and in clinical studies, both before and after FDA approval. If research that deliberately induces resistant mutations to test

drugs is classified as GOF research and comes to a halt, it will not be possible to develop any antiviral drugs under the current regulatory formats. Mr. Sheridan said classifying such research as GOF research would be a serious error. He urged the NSABB to think about the use of GOF studies in the drug development process.

Daniel Perez, Ph.D., Professor of Virology, University of Maryland

Dr. Perez summarized his laboratory's efforts to understand what changes would have to occur for avian influenza viruses to become transmissible to and among mammals. There was a belief that certain highly pathogenic avian influenza viruses would only affect poultry, until those viruses began infecting humans in 1996. The research demonstrated that remarkably few changes are needed to enable airborne transmission of some of these viruses.

Gain-of-function research provides insight on how pathogens work and how they differ from one another. While not exactly the same as field conditions, such research provides lessons on a pathogen's behavior. For risk mitigation, training is key to working safely in the laboratory.

Research has clarified that at least three influenza subtypes that have not been established in humans have the potential to become airborne transmissible. A switch in receptor specificity is required by some but not all subtypes. In the more than 100 years since the description of highly pathogenic influenza virus, not a single outbreak in poultry occurred as a result of a U.S. laboratory release, Dr. Perez noted. Birds are the species that are most sensitive to such viruses, and countries are required to report such infections, so an outbreak would have been recognized.

Some results cannot be predicted using sequence or structure analysis. In 2009, there were concerns that H1N1 influenza virus would reassort and become more virulent. Research showed that the virus has a biological advantage in transmission and thus has no need to reassort. Five years later, the virus is still circulating as such in the human population. Also, in 2009, laboratories working with H1N1 virus had to maintain strict BSL3 conditions. However, there was not a single outbreak of the virus related to a laboratory release during the year that such conditions were required.

Tom Inglesby M.D., CEO and Director, UPMC Center for Health Security, Associate Professor of Medicine and Public Health, University of Pittsburgh

Dr. Inglesby expressed serious concerns about GOF research and believes it is appropriate to pause for deliberation and risk assessment, because the risks are potentially extraordinary. The benefits described by other speakers may not warrant the risks.

Notably, DURC and GOF research are not the same thing, and different solutions address each. While DURC oversight policies in the U.S. focus on 15 select agents and toxins, a lot of GOF research occurs with agents not included in that list. Also, DURC hinges on

intent and deliberate misapplication, while the dangers of GOF research also include the risk of accidents.

As the events at CDC this summer demonstrated, accidents are possible. Research is generally safe, but human error is part of science. There are no international rules about the acceptable settings for GOF research or who has the infrastructure or skills to do such research safely. Around the world, more BSL3 laboratories are being constructed. Without international rules, scientists have an incentive to pursue such research, and a few years from now, hundreds of institutions could be conducting GOF research if no rules are established. There is no consensus in the biosafety or life sciences communities about how to gauge the risk of misapplication. There are no guidelines about how to share information.

The following steps may be helpful in furthering the conversation:

- Proponents of GOF research should acknowledge more directly the potential risks up front. In doing so, they should address how serious the risks are. Ideally, proponents would make their case by clearly stating the potential risks and the corresponding mitigation efforts along with the rationale for the research.
- The GOF case studies already collected and assessed by the NIH should be made available to the community. Although local control and responsibility is generally important, institutional review bodies do not have sufficient local institutional knowledge to address the issues, and the case studies could be helpful.
- The process over the next year should include the broader scientific community to reach a consensus about how to proceed.

Arturo Casadevall, M.D. Ph.D., Leo and Julia Forchheimer Chair in Microbiology & Immunology, Director of the Center for Immunological Sciences, Chair of the Department of Microbiology, Albert Einstein College of Medicine

Dr. Casadevall emphasized that he is strongly opposed to moratoriums. The findings of the research on H5N1 virus transmissibility were very important; the only other way to learn such information would have been from an actual pandemic. Gain-of-function experiments are powerful tools for inquiry: they are normative in molecular microbiology, yield cause–effect results, directly imply causality, and are reproducible. Such research is essential for probing certain questions, and no alternatives are available.

The debate focus should shift to consideration of the scientific questions rather than focusing on particular methods. There should be some consensus about what we need to know—such as transmissibility across mammals, the relationship between transmissibility and virulence, and the relationship between laboratory-engineered and naturally selected virus in terms of pathogenicity.

The influenza research community is humanity's best defense against pandemics. The so-called pause will have negative effects on research and will have a cost. The White House announcement is vague; it does not define what is meant by "reasonably anticipated" to result in a gain of function. Moratoriums are disruptive; they weaken the field by

discouraging investigators and eliminating research tools. More creative thinking is needed around safety. For example, it may be possible to create vaccine strains specifically for laboratory personnel.

Dr. Casadevall urged all the stakeholders to avoid invoking the apocalypse, which is a strategy that proposes consequences so dire that it quashes innovation. Humans are a risk-taking species. Further contributing to polarization is the oversimplification of the debate. There is already a lot of common ground and room for more.

Discussion

Dr. Stanley asked Dr. Hebbeler to address the risks to public health of the moratorium and what research may continue under the moratorium. Dr. Hebbeler said the White House recognizes the pause comes with a cost, but that cost is counterbalanced by some of the potential risks witnessed by recent lab incidents at federal facilities. The first line of inquiry about whether to move forward with research should be directed to program officers, but a USG framework is needed so that answers will be consistent across federal agencies. The White House is committed to transparency. Dr. Hebbeler hoped the pause allows time for robust deliberation that covers the range of views and complexity of the topic.

Dr. Schultz-Cherry said she was very concerned that surveillance efforts across the world may be halted until researchers are able to consult with their program officers about whether their research is covered by the pause. Dr. Perez asked what the government includes in its risk and benefit assessments. He pointed out that people may die because of a lack of influenza vaccine, but no one has died because of a laboratory-release of influenza virus. Dr. Layton asked for more clarification of how surveillance is defined in the new regulation. Dr. Stanley asked Dr. Hebbeler to describe broadly the thinking about the pause and the analysis of risks and benefits.

Dr. Hebbeler said the idea for the pause originated in the midst of the federal laboratory incidents. Most of the deliberation occurred in a joint interagency group—one that is focused on biological select agents and toxins and one that focuses on life sciences and DURC. Leadership across the agencies recognize that the incidents raised fundamental questions about safety assumptions that have underpinned decisions about funding and conducting certain research. The deliberative process over the next year is important to reach a final answer. Surveillance is vital to preparedness, and exceptions are built into the process to make determinations on a case-by-case basis, said Dr. Hebbeler. Discussions with program officers do take time, but everyone is committed to make such determinations about exceptions as quickly as possible.

Joseph Kanabrocki, Ph.D., C.B.S.P., raised concern about combining and confusing issues. The incidents at the government laboratories were missteps in biosafety, but they represent the kinds of incidents that can happen at any laboratory working with pathogens, not just those conducting GOF research or DURC. The culture of safety can be improved, as can dialogue among the research community, the public, and politicians.

Dr. Kanabrocki worried that GOF studies are being targeted when the problems identified do not necessarily reflect GOF research.

Dr. Osterholm added that he is not convinced that the definition of GOF research is adequate or that any of the research discussed so far actually constitutes GOF research. He hoped the administration would reconsider its definitions. Dr. Duprex agreed, saying that taking an organism from its natural host and manipulating it results in a gain or a loss of function. Such imprecise language only causes more confusion within and outside of the research community. The challenge is what to call the issue and how to address miscommunication and misunderstanding.

Dr. Lipsitch said that the moratorium focuses on the risk of enhanced pathogenicity when the real concern should be enhanced transmissibility. Surveillance does not enhance transmissibility, and pausing surveillance efforts is an overreach by the USG. In advocating for a focus on virulent, transmissible and novel pathogens, Dr. Lipsitch said that the research community cares about the risk of laboratory personnel exposure to dangerous pathogens. However, he emphasized there was a different level of concern about the risk of laboratory personnel who have been exposed to a virulent, transmissible pathogen, spreading it to others.

Dr. Inglesby said that until about five years ago, researchers used the term “novel, human-transmissible pathogens” to get at the issue. If the definition of GOF research encompasses surveillance and antiviral development, it should be revised and narrowed to the issue of concern. Because of the potential consequences, said Dr. Inglesby, it does seem fair to single out novel, transmissible strains.

Dr. Casadevall said scientific research is not like a factory that can shut down and reopen. The work under way is the best defense against a pandemic. The cost of a moratorium includes the people who leave the field or drop their studies, which can pose tremendous risks for the future.

Dr. Schultz-Cherry said researchers accept that there is some risk, but even when research was conducted in laboratories that had less regulation and fewer precautions, there were no cases of seroconversion. Risk can be mitigated, and oversight is already fantastic. Dr. LeDuc said data about the absence of seroconversions should be captured to help quantify the real risks. There is likely other such data that can be captured.

> **Follow-Up Item**
> Dr. Stanley suggested that the NSABB might craft a statement to the White House spelling out the concerns expressed about the moratorium and the inclusion of surveillance, as well as the need to speed up the process for granting exceptions to the moratorium..

Dr. McDade said some concepts to cover in the statement to the White House or in later deliberations are as follows:

- Multiple strains are candidates for vaccine, and no one knows which will be needed, according to Dr. Schultz-Cherry.
- The mechanisms underlying various strains are poorly understood, according to Dr. Perez.
- It is important to make recommendations that last, as Dr. Osterholm previously stated.
- Focus should be on the questions that need to be answered, not the methods, as Dr. Casadevall suggested.
- The potential for use of less pathogenic strains to answer some questions should be explored.

All research proposals include proof of concept and likelihood of success, said Dr. McDade. It appears that some research outcomes in this field were not anticipated. A lot of recommendations are being made on a foundation that is not firm. There is no simple answer as to how to define GOF research.

Kenneth I. Berns, M.D., Ph.D., raised concerns about program officers making exceptions on a case-by-case basis without a framework that narrows down the definition of GOF research as it currently appears in the regulations. Some program officers will be reluctant to allow questionable research. Dr. Stanley agreed that definitions must be improved, and that doing so may resolve some of the concerns raised.

Dennis M. Dixon, Ph.D., said the question about the inclusion of surveillance in the moratorium is an example of the kind of confusion that will arise as the new policy is implemented. He also said that transmissibility is easy to identify, but pathogenicity is harder to pinpoint.

Edward H. You of the Federal Bureau of Investigation (FBI) asked for clarification of the baseline, when talking about risk. Many of the issues raised by presenters address occupational health, not national security, and there are threats other than pandemic. The security community faces challenges educating the scientific community about how to assess risk. Mr. You highlighted a previous NSABB report on outreach and education regarding dual use research and encouraged additional ways to empower the scientific community to make more thorough risk assessments.

Dr. Osterholm said the real concerns are with the apocalyptic issue (or worst-case scenario) and what might happen in laboratories outside of USG authority, if information is shared openly. Problems can be addressed by focusing on these two issues.

Dr. Lipsitch said the debate that began 10 years ago about GOF research petered out, and in 2011, such research resurged without consideration of the risks and benefits. Because the debate about GOF research did not continue in 2004, the community now has a moratorium.

Dr. Lipkin reiterated that not all institutions have the expertise to provide the rigorous, fair, efficient review that is needed to ensure that work is not delayed unnecessarily and

that it is done safely. The availability of mitigation techniques (treatments and vaccines) should also be highlighted.

Chris Park of the U.S. Department of State suggested the NSABB not focus on terminology, which could lead down a rabbit hole. Efforts at definition always lead to some perverse effects. The current process allows for exceptions that are determined at the senior leadership level, which aids with consistency and removes program officers from the final decision process. Dr. Stanley countered that the timeliness of response matters very much to people doing research, and inappropriate definitions should be addressed.

Dr. Casadevall said the debate will bring together the virology and influenza research community as well as generate lots of ideas from the outside, which may improve science and safety. However, the requirement for risk and benefit assessments is being proposed by those who are against GOF research, because they believe it will quantify the risk in a way that sways the debate in their favor. In scientific research, the benefits are not clear for many years. No figure determined by risk and benefit assessments will settle the debate, but talking about risk assessment may help identify more variables to address.

Dr. Perez said mitigation efforts should always be in place to prevent exposure or release. Halting research out of fear about how others will use the information generated is not a tenable approach. Marie-Louise Hammarskjold, M.D., Ph.D., added that it is clear that risk can be mitigated by doing a better job in biosafety, in every laboratory, and through education and surveillance.

Dr. Layton said that researchers do not always know what is going on in other laboratories. Establishing connections with local and state health laboratories to improve information sharing is another issue that the NSABB should address.

Dr. Inglesby said there may be some threshold of experimentation to create novel, human-transmissible, virulent strains that should not be pursued, and he did not believe that line of thinking constituted an apocalyptic approach. Dr. Casadevall disagreed, and noted that researchers could learn something from such experimentation that could prove to be tremendously important.

Dr. Perez clarified that current research has not sought to make human-transmissible virus, rather, the viruses are transmissible in non-human, mammalian model organisms such as ferrets. Dr. Layton said that clarification affects the assessment of risks and benefits; if researchers do not think an experiment could be generalized to humans, then it would be of little benefit, and the findings could potentially be misleading. Dr. Kawaoka said animal research offers the best model available; if its validity is negated, then why are there concerns about transmissibility studies in these animals? he asked. Dr. Osterholm said the discussion exposes a semantic problem. He said he is willing to accept a researcher’s case that the work is important for humans as long as the researcher acknowledges the potential for human transmissibility.

Lunch
The meeting adjourned for lunch from 12:25 p.m. and resumed at approximately 1 p.m.

SESSION 1: BENEFITS, RISKS, AND ETHICAL CONSIDERATIONS ASSOCIATED WITH GAIN-OF-FUNCTION STUDIES INVOLVING PATHOGENS WITH PANDEMIC POTENTIAL

Discussion (continued)
Margie D. Lee, D.V.M., Ph.D., asked for clarification about the WHO animal surveillance system. Dr. Schultz-Cherry said that veterinary and agricultural scientists are an incredibly important part of the vaccine candidate selection process. They monitor and conduct screening in animals, and their reference laboratories submit information. Dr. Schultz-Cherry said GOF research that provides a better understanding of transmissibility is important for animal and agricultural science as well as for humans and could reduce the impact of disease on humans. The surveillance includes wildlife; wild birds have been part of surveillance for four years.

Francis L. Macrina, Ph.D., hoped that throughout the deliberative process, discussion would be as precise as possible. Instead of suggesting that institutions talk with their funding agencies, it would be helpful to be clear about whom to contact and who should be involved. Dr. Stanley asked Dr. Macrina and others to point out areas that need more clarification as the NSABB communicates its thinking to others.

Andrew Endy, Ph.D., asked Dr. Perez and Dr. Kawaoka whether pathogens created in their laboratories have a genetic signature or mark that could be traced back to their laboratories. Dr. Kawaoka said that a virus registry can be searched to identify the source. Dr. Perez said it is possible to embed a signature in a virus to track it.

Dr. Endy said the charge to the NSABB seems to be to recommend how to secure an open, distributed network. Information networks are structured to encourage reporting. In addition to quantifying risks and benefits, consideration should also be given to understanding the ongoing evolution of processes. Dr. Endy asked Dr. Schultz-Cherry how close we are to an ideal framework, either in surveillance or laboratory settings, for getting the information needed to identify viruses and whether the NSABB should think about how to improve the pace of information exchange or the connections. If a researcher knows that sharing information would help the public health system improve its response, he or she may not be so reluctant to share it.

Dr. Schultz-Cherry responded that systems can always be improved and made faster. Surveillance takes place all year, and anyone can see the results online in real time. The results of laboratory work are slower, but the laboratories communicate preliminary information as it unfolds, such as markers. In addition to informal sharing, the surveillance network is a formal mechanism for exchanging information. The development of the Centers of Excellence for Influenza Research and Surveillance network has changed how influenza virus is studied in the United States. There is also frequent, weekly communication with international research partners. Dr. Kawaoka

added that, since 2009, there have been weekly calls organized by the NIH for researchers to share information long before they publish their results.

Dr. Lipsitch supported the need to continue improving the speed and scope of surveillance. Efforts to improve influenza risk assessment now are motivated by the idea that strains acquired by humans sporadically from animals, pose a higher risk of pandemic than viruses that have not been shown to infect humans. However, none of the four most recent pandemics have followed that pattern of sporadic zoonotic infection; that is, none were detected in humans before they emerged in pandemic form. More and better surveillance is needed, but Dr. Lipsitch cautioned against saying that surveillance is predictive.

Dr. McDade asked whether less-pathogenic avian influenza strains can be used to assess some basic concepts without so much strain on laboratories. Dr. Kawaoka said many researchers are working on many things, and only a few laboratories are working at the end of the spectrum where research on highly pathogenic viruses is needed to assess transmissibility. Foundational work can provide insights, but research involving highly pathogenic strains is needed to answer some key questions. Dr. Perez added that the growing body of information will help researchers tease out what information could be important for further assessment.

Dr. Schultz-Cherry said much research is built on historic data using laboratory-adapted viruses and predicts certain changes in transmissibility, but viruses in the field behave differently. Dr. Duprex agreed, saying research on non-laboratory-adapted viruses reveals new information.

Dr. Stanley asked for input on the pros, cons, and feasibility of the concept of engineering viruses to make them safer. Dr. Kawaoka pointed out that an attenuated virus can provide information, but some things cannot be learned from attenuated strains. Dr. Perez agreed and indicated that while engineering a safer virus is feasible, scientists still lack the ability to produce the desired effects with certainty and without introducing the ambiguity that any results observed could be due to the artificial modifications introduced.

Dr. Casadevall said the issue goes back to defining the question you want to answer. To evaluate virulence and transmissibility, wild-type virus is needed. Other questions could be assessed using safer strains. Much of what is known about the current Ebola virus comes from work on other viruses outside of BSL4 laboratories. Dr. Kawaoka said the final work on Ebola virus was always done with wild-type virus.

Dr. McDade asked how researchers could quantitate the public health benefit of their work. That is, in assessing their research and weighing the risks and benefits, how can the benefit to public health (e.g., vaccine development) be measured, and how can researchers be confident that their work is important enough to justify the risks. Dr. Perez said influenza research can answer specific questions that contribute to understanding but that does not predict anything. Dr. Stanley said the question speaks to the NSABB's task,

which should eventually result in guidance on how to assess whether research should proceed.

Dr. Osterholm took the question a step further, noting that there is no mechanism that compels the pharmaceutical industry to use the important findings gained from research on highly pathogenic viruses to make vaccines. So in the assessment of risks and benefits, it is reasonable to acknowledge that there may be no benefits.

Dr. Sheridan said that in the field of infectious disease, animal models are more predictive of human results than in other areas of medicine. To create antivirals and vaccine, wild-type virus is needed, and clinical testing in humans is also needed. Dr. Inglesby agreed, but said the debate is concerned specifically with GOF research. He hoped the NSABB would gather input from industry representatives about the contributions of such research, as well as from those who do surveillance in the field, about whether such research affects their work.

> **Follow-Up Item**
> The NSABB members should consider the types of expertise needed to inform its deliberations and invite relevant participants to working group or future NSABB meetings.

Dr. Lipsitch echoed Dr. Osterholm's point about the gap between research findings and real-world actions. In 2012–2013, there was awareness that H7N9 avian influenza virus had shown up in humans, that an unmodified virus from humans could be transmitted efficiently between ferrets in laboratories. There were four cases of probable human-to-human transmission, but the only response was a temporary shutdown of poultry markets, despite extensive knowledge.

Dr. Schultz-Cherry countered that the WHO responded immediately to that situation, and that there is a vaccine prepared to address that virus. It is not up to the WHO to decide whether the vaccine is used. If another wave of that virus occurs, there will be discussion about making the vaccine available. The fact that a vaccine is not released does not mean we are not prepared, Dr. Schultz-Cherry said.

Dr. Casadevall urged the group to think beyond influenza and coronavirus. J. Patrick Fitch, Ph.D., asked Dr. Casadevall to expand on the generalizing principles the NSABB should consider to make its recommendations more broadly applicable. Dr. Casadevall said the NSABB should address influenza, as charged, but focus on the relationship between virulence and transmissibility, which can provide answers to research questions beyond influenza. Dr. Hammarskjold added that the charge to the NSABB also includes SARS and MERS.

To close the session, Dr. Stanley asked each presenter and discussant to give his or her advice to the NSABB. Their remarks are summarized here:

Dr. Sheridan: Clarify the charge; GOF research may be caught up in the reaction to biosafety and biosecurity concerns related to laboratory accidents. Consider the potential impact of recommendations on the development of countermeasures, which requires studying transmissibility.
Dr. Perez: Make an effort to bring safety up to the same level across the globe, and incorporate surveillance and training across medical laboratories to increase safety and reduce risks.
Ms. Peterson: Do not be so draconian in your recommendations that the resulting regulation or guidance scares researchers away. Do not create unfunded mandates. Recognize that laboratories already struggle to keep up with the myriad requirements. Enhanced or additional training is important, but it should not be so hard that it drives researchers away.
Dr. Osterholm: Stick with the big issues. Consider what will happen if research results are widely disseminated such that certain GOF experiments can take place in laboratories all over the world. Some of these may not have the same standards for safety.
Dr. Schultz-Cherry: Keep in mind that your decisions impacts public health. Engage the larger microbiology community, which is unaware of the issues raised here.
Dr. Kawaoka: Remember that this topic has international dimensions. Research in the United States is already highly regulated.
Dr. Casadevall: Consider how to ameliorate the effects of the moratorium, because it could hinder drug discovery, surveillance, and vaccine preparation. Without swift action, the effects of the moratorium could linger and some work could shut down. It is okay to acknowledge that current biosafety efforts are fine; processes are already tremendously regulated, and there were no releases even when practices were less stringent.
Dr. Inglesby: Slowing down surveillance is an unintended consequence of the policy that could be undone. The United States is setting a precedent, and other nations will follow. If there are negative consequences of this research, who will take responsibility for it, and how does that play out?
Dr. Lipsitch: The terminology is complicated, and lists of pathogens are not useful because they do not take into account the three factors that together raise concern: transmissibility, virulence, and novelty. Evaluating benefits will be the hardest part; to do so, consider the portfolio evaluation approach suggested earlier to determine how GOF research fits in.
Dr. Duprex: Realize that the benefits of basic science research can take years to manifest. Remember that virology is bigger than influenza; the recommendations will translate to other areas of virology. To understand pathogenesis, one must understand transmission and virulence.
Dr. Resnik: As Aristotle said, “It is the mark of an instructed mind to rest assured with that degree of precision that the nature of the subject admits.”

Public Comment

Dr. Stanley invited those interested in making comments to do so.

Peter Hale of the Foundation for Vaccine Research said that he has been hearing for years that GOF research will help develop better vaccines. Some senior vaccine researchers disagree. The benefit of GOF research in the immediate future is tiny. Vaccine companies also do not see the benefit; the first step they take in their process is to attenuate the virus. The Foundation for Vaccine Research polled vaccine manufacturers, and all of the respondents said they saw no advantage to GOF research in helping develop vaccines. Because they are polite, and because they receive federal funding through U.S. agencies such as the Biomedical Advanced Research and Development Authority and through European governments, these companies do not speak up, and they have not been consulted. The NSABB should hear the views of vaccine manufacturers on the value of GOF research.

Mr. Hale continued, saying GOF research has diverted attention and resources away from other productive areas of study, such as the following:

- The search for a universal influenza vaccine. Encouraging work is under way, and some candidates work against potential avian strains.
- Improving effectiveness of seasonal influenza vaccine. On average, the seasonal vaccine is only 55% to 60% effective, and sometimes lower. (Two years ago, the seasonal vaccine was only 9% effective in seniors.) Many people die as a result.
- Speeding up vaccine manufacturing and production. Increased surveillance gets us halfway there.

Kanta Subbarao, an intramural researcher at the NIH's National Institute of Allergy and Infectious Diseases, said MERS is an ongoing outbreak, and there are no robust small-animal models in which to evaluate MERS therapies or vaccines (although marmosets may be an option). Dr. Subbarao said her laboratory created a mouse model for evaluating MERS, but work will be halted with the moratorium, which is concerning. In addition, for influenza, research on the development of monoclonal antibodies as immunotherapy or prophylaxis will focus on whether the virus can escape. It is necessary to evaluate immunotherapy, because it would establish proof of principle of whether a universal vaccine would work.

Regine Aalden, health counselor of the Dutch Embassy, said the same policy debate is playing out in the Netherlands. This issue is global, and concerns are mutual. This administration has moved forward with a global health security agenda in which the Netherlands takes part. Ms. Aalden hoped the NSABB would consider how to provide more clarity for international organizations to address their own concerns.

> **Follow-Up Item**
> International institutions should be engaged in the discussion about assessing GOF research.

Matt Frieman, of the University of Maryland School of Medicine, said there was little discussion about SARS and MERS at the meeting. He asked that the NSABB have representation at its next meeting to talk about the ongoing research on SARS and MERS and the risk and benefit assessment that SARS and MERS researchers all do. Dr. Frieman also questioned the moratorium's inclusion of SARS and MERS in the context of GOF work on transmission model systems that may enhance pathogenicity. He said that there is no transmission model for SARS or MERS currently in use in the laboratory.

Dr. Frieman went on to say that the mouse models and pathogenic studies undertaken for SARS, informed research on MERS when it emerged. In turn, more research around MERS will inform the approach to the next pathogen. Inhibiting such research, through the pause or any other methods, leaves us less prepared for future events. From a public health perspective, MERS surged in the spring and then leveled off, but it seems to be resurging now. Thus, now is potentially the worst time to pause research. Laboratories working on MERS are developing some small-animal models to test therapeutics, some of which may be published soon. The pause hurts the next endeavor.

> **Follow-Up Item**
> Dr. Stanley acknowledged the concerns expressed about the inclusion of SARS and MERS in the moratorium and indicated that the NSABB should hear more from those involved in research on SARS and MERS.

SESSION 2: BIOLOGICAL RISK ASSESSMENTS: THEIR STRENGTHS AND LIMITATIONS

Dr. Stanley introduced the session by noting that the purpose of risk assessment in the life sciences is to identify the risks associated with the research and the likelihood of realizing those risks. Major risks are exposure to pathogens from laboratory accidents (biosafety concerns) or malevolent use of research. Other risks include potential harm to agriculture (crops or animals), and the economy, among others. Some risks can be modeled quantitatively, while others cannot. Uncertainty is an inherent part of risk assessment. The assessment can be based on models or assumptions; sometimes detailed data are available but not always. A risk assessment can give us a sense of the associated risks yet not address whether a study should be performed. Potential benefits must be carefully weighed against the risks.

Modeling and Biological Risk Assessments

Stephen Eubank, Ph.D., Deputy Director of the Network Dynamics and Simulation Science Laboratory at the Virginia Bioinformatics Institute, and Professor, Department of Population Health Sciences, Virginia Tech

Dr. Eubank explained that modeling aims to understand impact—in this case, how GOF research will affect the probability of morbidity and mortality. Ideally, a model can describe the distribution of outcomes with and without GOF research, but the likely outcomes in this case are not known. Even a conditional distribution of outcomes does not indicate whether an experiment should be done. It may not be necessary to know the

distributions, only the differences between them (although this conclusion also may not be true). The difference is due to things that can only happen with GOF research.

In determining the possible negative outcomes, or costs, the first step is to throw out the "worst-case scenario," which is usually highly improbable. However, doing so results in vague language, such as "reasonably foreseeable" events and "prudent person" rule. However, it is possible to better define the scope of the effort by focusing on identifying certain negatives, such as bad actors, accidents, poor procedures, natural disasters, and publication of DURC.

In determining the potential positive outcomes, or benefits, the first step is to throw out the "best-case scenario," which is difficult to predict. Instead, the assessment can focus on specifics, such as lower morbidity and mortality (which would not occur spontaneously). Potential benefits also include improvements in situation assessment and forecasting as a result of better surveillance and preparedness, for instance. Many of the positive outcomes related to GOF research can be measured by mathematical models.

Modelers want a lot of data, so that their models will quantify morbidity and mortality, compare benefits with risks, and estimate the impact of control measures. Using a range of inputs into a model, the NIH blue ribbon panel to advise on risk assessment of the National Emerging Infectious Diseases Laboratory (NEIDL) concluded that one or more transmissions of Ebola virus following a needlestick event, would be expected to occur once in every 550 to 18,000 years.

In terms of assessing benefits, it is not possible to create parameters for emerging disease, but the results of GOF research can identify credible ranges. Also, GOF research could lead to better threat estimates, allowing for targeted surveillance, for example. However, it is not clear that these benefits can only be achieved with GOF research.

The precautionary principle, summarized as "first, do not harm," involves a Catch-22. It holds that, if there is no scientific consensus that the action is not harmful, then the action should be avoided. On the other hand, inaction may cause harm, and action is a prerequisite for achieving scientific consensus (to understand the risks and consequences).

Dr. Eubank predicted the NSABB would hear advice, particularly at the upcoming National Research Council symposium, to focus on qualitative analysis, and reserve quantitative analysis for areas with sufficient data. He disagreed, suggesting that quantitative analysis should be conducted for all areas to understand the uncertainties. Where the uncertainties are too large, research should aim to address them.

Risk assessment is not cheap or quick. It should be conducted by a disinterested party. The costs of risk assessment should be factored into the research; otherwise, it will not be done properly.

In summary, Dr. Eubank suggested that if GOF research does proceed, efforts should be made to prioritize the research that best informs the risk models, so that the laboratory data can be used as quickly as possible. As with a two-armed clinical trial, if in the course of a GOF study, the risk is found to be much higher than anticipated, it should be halted. There should not be a moratorium to determine whether the risks can be re-estimated. Conversely, if the benefits are significantly higher than anticipated, research should proceed.

Dr. Stanley noted that one challenge of prioritizing GOF research and conducting studies to address uncertainty is that there may be no ethical way to do such research.

Uncertainty
Scott Ferson, Ph.D., Senior Scientist, Applied Biomathematics, New York

Dr. Ferson pointed out that, even if risk assessment of GOF research involves more numbers, uncertainty will remain. Uncertainty can arise from incertitude, or incomplete knowledge, which can be reduced with empirical effort. Uncertainty can also come from variability, which is natural variation that cannot be reduced.

There is general agreement that probability theory is the appropriate method for propagating variability. In a drug trial, for example, subjects may receive different doses, and each subject will have different responses. These variable results can be modeled by probability distributions, either mapped as density distribution (which results in a bell curve) or as cumulative distribution (which results in a slope).

Probability theory is not ideal for accumulating gross uncertainty. The precision of the answer of a probability model depends on the number of inputs—the more inputs, the tighter the answer. But when the inputs are grossly uncertain, adding more inputs yields an answer that appears to be very tight or precise. Dr. Ferson gave an example in which the sum of two intervals can be described as an interval. Mapping that finding according to probability theory leads to a triangular-shaped distribution, which in turn leads to the erroneous conclusion that the middle point is somehow “more right” than the end points.

Variability and incertitude are different types of uncertainty that should be propagated differently. Probability theory is appropriate for propagating variability when random variation is involved. For incertitude, other techniques that apply some sort of bounding are needed. Imprecise probability theory encompasses both at once. For example, joining the cumulative probability distribution (that characterizes randomness and variability) with an interval analysis (that characterizes incertitude) results in a sort of sloped-box shape that describes a range of potential distributions. Furthermore, this model can accommodate a lack of assumptions about dependence between the probability distribution and the interval analysis.

If efforts were made to generalize a deterministic calculation to do probabilistic risk assessment, inputs that can be described in point values would be transformed into uncertain values. Thus, uncertain inputs, dependencies, and drivers all feed into a

deterministic model that yields point estimates. However, those estimates would all feed into a stochastic model (i.e., one that allows for random variation), which would yield risk estimates.

Dr. Ferson described various sources of incertitude, from doubt about the appropriate mathematical model to lack of data. He emphasized that variations and their relationships matter. For instance, the frequency of serosurveillance may depend on the quality of laboratory worker training. Thus, dependencies arise, and they make a difference. Mapping out the relationships between variations results in the sloped-box shape that allows the user to look more closely at the uncertainty of a risk or the probability of the risk under certain circumstances. The sloped-box shape characterizes both types of uncertainty (variability and incertitude) at the same time.

In applying the results of this imprecise probability theory, the bounding gives some confidence in the reliability of a decision when the results are clear enough that the uncertainty no longer makes a difference. When uncertainty obscures the decision, the results of this approach identify where to invest in empirical efforts to find answers. Uncertainty can, however, overwhelm the answer. If the uncertainty is huge and the bounds too wide, the reliability of the results are misleading.

Comparing the utility of the two common approaches reveals that interval analysis (or traditional worst-case scenario analysis) is good for addressing incertitude but bad for addressing frequency and dependence. In such cases, because the analysis ignores some information, the results say less than what is known. Probability theory is good for expressing likelihoods and dependences but bad for incertitude. It can lead to results that seem to say more than what is known.

Everyone makes assumptions, Dr. Ferson pointed out, but not all sets of assumptions are equal in weight. Assumptions can vary from precise point values to ranges of values to variations in the shape of distributions to an absence of any assumptions about dependence. When precise, confident assertions are made, there is no opportunity to figure out how the answers depend on those assertions, which leads to uncertainty. By relaxing assumptions at the outset, the answers will be more reliable.

In conclusion, Dr. Ferson said quality assurance checks can be performed on probability models using the imprecise probability approach, and it is more comprehensive than sensitivity analysis. Bounding models work when approximation cannot, and it is useful when it is important to be sure about the results.

Behaviorally Realistic Risk Management
Baruch Fischhoff, Ph.D., Howard Heinz University Professor, and Professor of Social and Decision Sciences / Engineering and Public Policy, Carnegie Mellon University

Dr. Fischhoff explained that behaviorally realistic risk management addresses the roles of

- people in system performance (as sources of vulnerability or resilience),
- expert judgment in analysis (formulation, estimation, and interpretation), and

- communication processes (connecting design with users).

Decision science is an organizing principle of behaviorally realistic risk management. It begins with a formal analysis of systems, followed by empirical studies, interventions, and evaluation.

At least 100 years of research exists on the role of people in system performance, going back to studies of industrial fatigue and efficiency, for example. By combining measurement of various factors (e.g., hourly output throughout the day), it is possible to identify common themes that play out in predictable ways.

In terms of the role of expert judgment in analysis, Dr. Fischhoff said it is possible to assess the weight of expertise. For example, medical experts are much better than educated laypeople at understanding the likelihood of disease transmission or the case-fatality rate. Models can account for level of expertise. Such findings can be used to improve transparency in the risk–benefit assessment used in regulatory decision making about drugs, for example.

Finally, understanding communication processes has led to a focus on improving science communication, specifically communicating uncertainty. The FDA has a strategic plan that offers recommendations on communicating risks during emerging events and suggests the following:

- Have a consistent policy in all domains.
- Provide useful, timely information.
- Address risks and benefits, uncertainty, personal actions, and FDA recommendations.
- Use standard formats and evaluate them routinely.
- Consider the needs of diverse populations.

Accomplishing these applications of the basic science requires the following:

- Constant contact with the user.
- Broad use of behavioral and social science.
- Avoiding simplistic solutions (there is no single answer).
- Empirical evaluation (people often communicate without ever asking anyone whether what they are saying makes sense).

Dr. Fischhoff proposed creation of a dedicated resource center to provide publication-quality research about behaviorally realistic risk management. Such a center would provide quality assurance, economies of scope, a place to pool lessons learned, opportunities to anticipate problems, and access to current science.

Discussion

Dr. Stanley asked each of the speakers to weigh in on Dr. Lipsitch's proposed approach to assessing the risks and consequences of GOF research. Dr. Eubank said Dr. Lipsitch's presentation overlooked the benefits of GOF research, and that he believes the threat of a

natural influenza pandemic over the next 10,000 years is higher than one resulting from GOF research and the consequences the same, which argues in favor of doing such experimentation. Dr. Fischhoff said the logic of the analysis is the same as that underlying behaviorally realistic risk management. The challenges lie in fleshing out the uncertainties and determining the scope of the model. Dr. Fischhoff recommended debating the structure of the analytic approach before deliberating, and he suggested the 1996 NAS report *Understanding Risk* as an informative resource. Dr. Ferson said he did not believe that qualitative assessment would get very far without a quantitative assessment.

Susan M. Wolf, J.D., said that conducting risk assessment within a single laboratory is one thing, but this effort is much broader, potentially international in scope. She asked how the NSABB should establish the scope of the risk assessment and whether it should look only at the risks of GOF experiments in U.S. laboratories that are subject to U.S. oversight. She asked whether the risk assessment should consider that information published by a secure U.S. laboratory will reach unsecure laboratories around the world.

Dr. Eubank replied that the scope is crucial, but that there is no good answer. A starting point may be a grading process that quantifies the problem, should there be an accident in one laboratory and then extend the scope to all U.S. laboratories. Beyond that, the scope should match the regulatory authority, said Dr. Eubank. To impose constraints on laboratories outside of U.S. law and funding, it is necessary to work with international counterparts on risk analysis.

Dr. Eubank reiterated his suggestion that experiments stop when the answer becomes obvious. Research has already determined that H5N1 influenza virus is transmissible between ferrets. If more information is needed, then risk assessment should be revisited. It is not clear why laboratories around the world would repeat such experiments.

Dr. Stanley agreed that scope is important. Risk will be assessed differently, depending on whether the NSABB or the USG focuses only on U.S.-regulated laboratories or includes unregulated laboratories. Also, it is helpful to ask to what extent the risk may be increased by repeating research, and to consider whether some research should be labeled as definitive—that is, indicating there is no reason to repeat it.

Dr. Ferson said it is up to the NSABB to determine the scope. He noted that part of the risk lies in what happens once knowledge is disseminated, and that is beyond any regulations. Dr. Fischhoff said the ambiguity of the White House document is a result of agencies with different foci coming together to solve a problem, because they are all solving different problems.

Dr. Endy asked what the USG hopes to learn from modeling the risk, adding that, in his experience, models are mostly heuristic tools and questions, such as what should be included in or excluded from a model, need to be confronted. He noted that research creates benefits that lead to more research but also sometimes to negative outcomes and negative feedback that stops research. Dr. Eubank noted that the Board has an

opportunity to prevent the type of oscillations between rapidly-increasing research and research stoppages that were described by Dr. Endy. He added that efforts could have been under way to address some of the concerns in the period between the moratorium that was enacted two years ago and now.

Dr. Fischhoff stressed that structuring the problem will help the scientific community avoid being blindsided. Poor communication has not served the community well. The NSABB should take the time to identify the problem and develop a structure, not just focus on the intuitive problems that people are studying.

Dr. Stanley noted that the NSABB has a specific charge and can try to make that work for the scientific community and the country. In the discussion of scope, the NSABB members should think about appropriate tools for risk assessment that inspire the most confidence. People should know that risk assessment was designed and carried out in ways that acknowledge a variety of opinions and have some analytic basis. For that reason, Dr. Stanley said some quantitative component should be included, because it will be easier to discuss. However, such analysis could also dampen results.

Jan Leach, Ph.D., asked how much weight should be given to comparing natural release against laboratory release in a risk assessment and whether mutation rates are known. Dr. Eubank said that at a single site, mutation rates may be known, but the length of time required for a wild virus to develop capacity for human transmission is not known. He agreed that it is important to compare risk associated with laboratory escape against that of natural evolution. Dr. Kawaoka added that the ability to assess the risk of mutation depends on environments and conditions.

Dr. Perez pointed out that a pandemic is a possible consequence of doing nothing. With the 2009 H1N1 virus, which was a naturally occurring virus, little was known about its potential to cause a pandemic. Until 2009, there was a dogma that pandemic influenza required an antigenic shift, which has since been refuted. Influenza, like other viruses, is full of surprises. If it is possible to quantify the risk of laboratory release, the risk of doing nothing should also be quantified.

Dr. Lipsitch clarified that no one has proposed doing nothing. Rather, the question is whether doing things other than GOF experiments would better reduce the risk of a pandemic overall. Dr. Eubank agreed with Dr. Lipsitch, but wondered whether the risk of performing GOF research significantly affects the risk that is already there. That is, if we expect to see an influenza pandemic every 30 years, does adding the risk [resulting from GOF research] of a pandemic once every 10,000 years significantly change that calculation? Dr. Lipsitch responded that we do not expect to see an influenza pandemic every 30 years, but the question touches on the kinds of details that should be explored.

Dr. Fitch said there appears to be some shared risk managed among institutions, international organizations, PIs, the public, and others. It may be helpful to consider who is accountable for the risk. Clearly, the USG is accountable because its resources sponsor the research, but companies have some accountability (beyond compliance and training).

Dr. Fitch asked how a risk assessment model can address the various risk owners. Completing the process within a year sounds like a massive undertaking, he added.

Dr. Fischhoff said the boundedness of the system is very important—that is, determining which perspectives are key. He also said that modeling the structure of the different arguments would help clarify what is needed. For example, if the role of international regimes is important, but we do not know how to accommodate that into the risk assessment, then perhaps the portfolio is incomplete.

Dr. Eubank cautioned that the perception of risk is important. In communicating about risk, be aware that risk is perceived differently by different people, particularly people who are not involved in this discussion.

Dr. Fitch asked how many projects under way are affected by the moratorium. If thousands of projects are affected, the current approach makes sense, but if only two or three are affected, a case study approach may be better. Dr. Stanley said the NIH estimates about 20 projects are affected, but the number is not certain.

Public Comment

Mr. You of the FBI again recommended getting a baseline understanding of the risk, particularly in terms of security concerns. A supplement to Dr. Kawaoka's publication about the 1918 influenza virus addressed the role of biosafety review and the local biosecurity task force. It demonstrated that risk assessment procedures were in place, including mitigation efforts, and that all those involved assumed some accountability and buy-in. It may be helpful to determine what systems already in place are addressing the same questions and how they determine the scope of their efforts. It is a shame that the approach to biosecurity was only described in the supplemental information, because people in laboratories want to know how these things are done for their own personal safety and for the safety of their institutions.

Gerald Epstein of the U.S. Department of Homeland Security said the real challenge is making one general assessment, given that the stakeholders all have different tools, techniques, and information sources they use to assess risk. Also, Dr. Ferson described incertitude, in which some factors are unknown but knowable, and the stochastic approach, in which some factors cannot be known but their distribution can be identified. Dr. Epstein said the risk assessment of research is especially challenging because it will have to blend both natural risk and the risk of terrorism. The risk of terrorism can fall into either category (incertitude or variability). The level of uncertainty is even more complicated than what has already been discussed. In addition, some speakers have said the worst-case scenario should not be used, while others have said the issue hinges on the worst-case scenario. For all these reasons, distinctions will have to be drawn.

Dr. Kawaoka suggested getting more information about the number of projects affected by the policy. He said a good figure can be determined by comparing the amount that the NIH spends on this kind of research with the amount spent on vaccine production.

Path Forward to Address the NSABB Charge
Samuel L. Stanley, M.D., NSABB Chair

Dr. Stanley called for a discussion about how the NSABB should proceed—focusing more on structuring their deliberations than on the scope of the charge. He proposed that the NSABB break into working groups that meet via teleconferences and report back to the NSABB at specific intervals or milestones. The working groups can draft recommendations for the NSABB to consider. The NIH staff will reach out to members to determine the makeup of the working groups. Working groups can bring in outside experts to discuss specific issues or to inform the discussion.

Dr. Stanley reminded the Board of the charge and its components. Among the first steps is to advise on the design and development of risk assessment and benefit assessment studies that will be conducted by an external group. The first NAS forum will inform the working group's efforts to advise the risk and benefit assessments. The second NAS forum will take place after the NSABB drafts preliminary recommendations to be discussed among the broader scientific community.

Dr. Stanley suggested looking at the timeline according to four phases:

1. Advise on the design of risk and benefit assessment studies.
2. Perform risk and benefit assessment studies (carried out by a private firm with specialized expertise), likely followed by the NSABB's consideration of the product.
3. Develop recommendations based on working group proposals and other input.
4. Submit recommendations to the USG.

Dr. Stanley reiterated the description in the charge about what the NSABB should consider in making its recommendations on the design and conduct of risk and benefit assessments. He added that the Board can also consider other steps, such as the following:

- Advise on which pathogens should be included in a policy on GOF research (e.g., whether SARS or MERS should be included).
- What types of GOF studies should be addressed.
- The critical role of biosafety.
- Models and other methods for evaluating risks.

In addition, the NSABB should keep in mind that the outcomes of life sciences research are unpredictable, benefits are not always realized or recognized immediately, and that the moratorium may have an adverse effect on research.

Discussion
In response to Dr. Leach, Dr. Stanley said that the moratorium will be in place while the NSABB deliberates. However, the NSABB will communicate its opinion about the moratorium to the White House.

Theresa M. Koehler, Ph.D., reiterated the importance of defining what is meant by GOF studies and proposed the term "GOF research of concern." In response to Dr. Layton, Dr. Stanley suggested that the NSABB discuss whether to focus on influenza, MERS, and SARS or whether to address other pathogens as well.

Jean L. Patterson, Ph.D., emphasized the importance of addressing the moratorium on surveillance. Dr. Stanley agreed, saying that despite Dr. Dixon's assurances that surveillance is exempt, there appears to some ambiguity that should be addressed.

In response to Dr. Macrina's question about the role of the Board in the NAS conferences, Amy P. Patterson, M.D., of the Office of the Director of the National Institutes of Health, said some NSABB members may be asked to speak or serve as panelists. The conferences will be summarized in writing; they will also be webcast, and webcasts will be archived for future viewing.

Gardiner Lapham, R.N., M.P.H., asked how the NSABB communicates to the public. Dr. Amy Patterson responded that the NSABB meetings are webcast and archived, minutes and transcripts are available, and all Board meetings are public. As the NSABB develops draft recommendations and concepts about study designs emerge, the public will have opportunities to learn about the Board's progress, ask questions, and give comments.

Follow-Up Item
The NIH staff will review the transcript from this meeting as a basis for proposing what types of working groups should be formed and their potential members. Board members should communicate to Dr. Groesch or Dr. Amy Patterson their ideas about the working groups. The Board will finalize its advice on the risk and benefit assessment study design, where after the USG will select the firms to carry out the studies.

Follow-Up Item
The Board will communicate the concerns expressed about the moratorium during the meeting to the White House.

Adjournment
In closing, Dr. Stanley said the Board has a great responsibility but also a great opportunity to serve the scientific community and the world. He adjourned the meeting at 3:53 p.m.