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

January 7–8, 2016
NIH Campus
9000 Rockville Pike
Building 31, Floor 6C, Room 6
Bethesda, MD

MEETING MINUTES

VOTING MEMBERS

Samuel L. Stanley, Jr., M.D. (Chair)
Kenneth I. Berns, M.D., Ph.D.
Craig E. Cameron, Ph.D.
Andrew Endy, Ph.D.
J. Patrick Fitch, Ph.D.
Christine M. Grant, J.D., M.B.A.
Marie-Louise Hammarskjöld, M.D., Ph.D.
Joseph Kanabrocki, Ph.D., CBSP
Theresa M. Koehler, Ph.D.
Jan Leach, 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.
Jeffrey F. Miller, Ph.D.
Stephen S. Morse, Ph.D.
Jean L. Patterson, Ph.D.
I. Gary Resnick, Ph.D.
Susan M. Wolf, J.D.
David L. Woodland, Ph.D.

ABSENT

Clifford W. Houston, Ph.D.

EX OFFICIO MEMBERS/FEDERAL AGENCY REPRESENTATIVES

Brenda A. Cuccherini, Ph.D., M.P.H., Department of Veterans Affairs (*by phone*)
Dennis M. Dixon, Ph.D., NIH, National Institute of Allergy and Infectious Diseases
Gerald Epstein, Ph.D., Department of Homeland Security (DHS)
M. Camille Harris, D.V.M., Ph.D., M.S., Geological Survey
David R. Liskowsky, Ph.D., National Aeronautics and Space Administration

Christopher J. Park, M.S., Department of State
Michael W. Shaw, Ph.D., Centers for Disease Control and Prevention (CDC)
Edward You, Federal Bureau of Investigation (FBI)

DAY 1

WELCOME AND INTRODUCTIONS

Opening Remarks
Samuel L. Stanley, Jr., M.D., NSABB Chair

Dr. Stanley opened the meeting at 8:32 a.m. and welcomed the attendees, including those watching the webcast online. He explained that the NSABB and the National Academies of Sciences, Engineering, and Medicine are charged with gathering input and making recommendations about the evaluation of the risks and benefits of gain-of-function (GOF) research. Federal funding of GOF research involving influenza virus or the coronaviruses that cause SARS and MERS has been paused since October 2014 while the NSABB and U.S. government deliberates the risks, benefits, and policy needs for certain GOF studies.

The NSABB fulfilled the first part of its charge by issuing recommendations for the design and conduct of an independent risk-benefit assessment (RBA) of GOF research. Gryphon Scientific performed the RBA and will present the results at this meeting. Toward its second charge, the NSABB's GOF Working Group (WG) drafted a report to inform the Board's recommendations to the U.S. Government (USG) on how to evaluate proposed GOF studies, and that report will be discussed at this meeting.

Dr. Stanley outlined the agenda for the meeting. The webcast will be archived online. All presenters' slides will be available online. Dr. Stanley emphasized that public comments are welcome during the meeting (in person and via email) and in writing at any time. He stressed the importance of stakeholder input into the NSABB's deliberative process.

Introductions and Review of Conflict-of-Interest Rules
Christopher J. Viggiani, Ph.D., Executive Director, NSABB

Voting and *ex officio* members of the NSABB introduced themselves. Dr. Viggiani explained that members of the NSABB are considered special government employees and are subject to federal rules of ethical conduct. He reviewed the process for assessing and managing potential conflicts of interest.

Approval of NSABB Meeting Minutes
Samuel L. Stanley, Jr., M.D., NSABB Chair

The minutes of the September 2015 meeting were reviewed and unanimously approved by the Board.

THE GOF DELIBERATIVE PROCESS

Carrie Wolinetz, Ph.D., Associate Director for Science Policy, NIH

Dr. Wolinetz said the USG supports a diverse life sciences research portfolio. Gain-of-function research is a common scientific method critical to understanding the basic biology of pathogens, but it also raises concerns about the consequences to public health and national security of accidental releases or deliberate misuse of materials. Therefore, in October 2014, the USG announced a pause in funding for certain GOF research to allow time for a deliberative process to reevaluate the potential risks and benefits associated with GOF research involving pathogens with pandemic potential.

The NSABB is the official advisory body to deliberate this issue and provide recommendations to the USG. NSABB has gathered input from experts in the field and analyzed the RBA. In addition, the National Academies held a large public forum to get additional input from stakeholders and the public, and it will convene another in March. All of these efforts, including public comments, will inform the NSABB's recommendations to the USG, to be finalized in the spring of 2016.

NSABB GOF WORKING GROUP: AN OVERVIEW OF PROGRESS, PRELIMINARY FINDINGS, AND THE NSABB'S DRAFT REPORT

Joseph Kanabrocki, Ph.D., CBSP, Co-Chair, NSABB WG

Dr. Kanabrocki presented the draft report of the NSABB working group (WG). He said the draft report describes: principles for guiding NSABB deliberations, analysis of the RBA, consideration of ethical values, policy analysis, and preliminary findings and recommendations of the NSABB WG. The draft report also describes perspectives of stakeholders, the public, and subject matter experts and draws from domestic and international policy and relevant literature.

The WG generally found the RBA to be thorough and rigorous. It utilized a powerful parametric approach to model how biosafety risk varies under different circumstances as well as an analysis of security risks. The benefits assessment describes unique benefits of and reasonable alternatives to GOF research.

The limitations of the RBA stem from the lack of data on which to base predictions about the likelihood and consequences of potential incidents that would entail risks. To address uncertainties, Gryphon conducted a relative biosafety risk assessment, which is useful but also challenging to interpret. For instance, the analysis of biosafety risks of pandemic influenza GOF research often used the 1918 influenza virus strain as the wild-type strain for comparison. The 1918 strain is highly transmissible and virulent, which sets a high baseline for risks. Finally, risks and benefits are not presented in comparable terms, so they are difficult to compare. (Key findings of the RBA were presented later in the meeting.)

The WG outlined the ethical values that should inform decision making about funding or conducting GOF research, categorizing them as either substantive or procedural values.

(The results of an independent report commissioned by the NSABB to explore the ethical issues will be presented later in the meeting.) The WG's overview of the current policy landscape found multiple relevant, applicable policies in place, but they vary in scope and implementation.

The WG draft report's key findings are summarized here:

> **Finding 1**. Only a small subset of GOF studies—GOF studies of concern—entail risks that are potentially significant enough to warrant additional oversight. GOF studies of concern are those that could generate a pathogen that is highly transmissible, highly virulent, and likely to be resistant to control measures.
>
> **Finding 2**. The USG has effective policy frameworks in place for managing risks associated with life sciences research.
>
> **Finding 3**. Oversight policies vary in scope and applicability; therefore, current oversight is not sufficient for all GOF studies that raise concern.
>
> **Finding 4**. Decisions about whether GOF studies of concern should be permitted will entail an assessment of the potential risks and anticipated benefits. The scientific merit of a study is a central consideration, but other considerations and values are also important.
>
> **Finding 5**. Managing risks associated with all high-containment research requires federal-level oversight, institutional awareness and compliance, and a commitment by all stakeholders to safety and security. Biosafety and biosecurity are international issues requiring global engagement.

The draft report proposes the following preliminary recommendations:

> **Recommendation 1**. Research proposals involving GOF studies of concern entail the greatest risks and should be reviewed carefully for biosafety and biosecurity implications, as well as potential benefits, prior to determining whether they are acceptable for funding. If funded, such projects should be subject to ongoing oversight at the federal and institutional levels.
>
> GOF research of concern was described as research that could be anticipated to generate a pathogen with three attributes: high transmissibility, high virulence, and an ability to spread efficiently among humans.
>
> The WG recommended that following principles be applied and guide the review of and funding decisions about research proposals anticipated to involve GOF studies of concern:
>
> 1. The research proposal has been evaluated by a peer-review process and determined to be scientifically meritorious and has been assessed to be likely to

exert a sustained, powerful influence on the research field(s) involved.
2. An assessment of the overall potential risks and benefits associated with the project determines that the potential risks compared to the potential benefits are justified.
3. There are no feasible, equally efficacious alternative methods to address the same scientific question in a manner that poses less risk than does the proposed approach.
4. The investigator and institution proposing the research have the demonstrated capacity to carry it out safely and securely.
5. The research information is anticipated to be broadly and legally shared in order to realize its potential benefits to global health.
6. The research will be supported through funding mechanisms that include appropriate oversight of a) all aspects of the research including its conduct, b) the sharing of data and materials, and c) the communication of the research.
7. The proposed research is ethically justifiable.

Recommendation 2. In general, oversight mechanisms for GOF studies of concern should be incorporated into existing policy frameworks. The risks associated with some GOF studies of concern can be identified and adequately managed by existing policy frameworks if those policies are implemented properly. However, the level of oversight provided by existing frameworks varies by pathogen. For some pathogens, existing oversight frameworks are robust and additional oversight mechanisms should generally not be required. For other pathogens, existing oversight frameworks are less robust and may require supplementation. All relevant policies should be implemented appropriately and enhanced when necessary to effectively manage risks.

Recommendation 3. The risk-benefit profile for GOF studies of concern may change over time and should be reevaluated periodically to ensure that the risks associated with such research is adequately managed and the benefits are being realized.

Recommendation 4. The USG should continue efforts to strengthen biosafety and biosecurity, which will foster a culture of responsibility that will support not only the safe conduct of GOF studies of concern but of all research involving pathogens.

Finally, the WG draft report outlines additional questions for NSABB consideration, which will be addressed throughout this meeting. The WG plans to refine its report in light of feedback from this meeting and the National Academies meeting and present them for NSABB review and approval. It is anticipated that the USG will consider the Board's recommendations as it formulates GOF research policy.

NSABB Discussion

J. Patrick Fitch, Ph.D., asked why the WG included in the definition of GOF research of concern the pathogen's resistance to control measures or likelihood of spreading to humans instead of an absolute definition of control. He also asked about the role of workforce protection in preventing or minimizing the consequences of a release. Dr.

Kanabrocki and Kenneth I. Berns, M.D., Ph.D., responded that workforce protection is fundamental. Dr. Fitch pointed out that the draft report does not offer guidance on how to ensure accountability. Dr. Kanabrocki said the WG focused on policy recommendations; the USG will determine how to implement and enforce its policy.

SESSION I: RESULTS OF THE RBA for GOF RESEARCH

James W. LeDuc, Ph.D., and Gary Resnick, Ph.D., NSABB Members, Co-Moderators

Dr. Resnick explained that the USG commissioned an independent, evidence-based analysis of the risks and benefits of certain GOF research to inform the deliberations of the NSABB. Panelists for this session were asked to address the following questions:

- What are the strengths and limitations of the RBA?
- Which GOF studies are of greatest concern, if any? Which are of less concern?
- Are the assumptions, approaches, and findings about risks and benefits associated with GOF studies comprehensive and sound?
- Are there specific risks or benefits that are over- or understated in the RBA?

Summary of the Gryphon Scientific RBA of GOF Research

Rocco Casagrande, Ph.D., Principal Investigator (PI), Managing Director, Gryphon Scientific

Dr. Casagrande summarized the purpose and scope of the RBA, noting that the biosafety risks assessment was designed to be comparative—that is, to determine the change in risk associated with research on GOF pathogens compared with research on wild-type pathogens. The biosecurity component of the assessment was semi-quantitative in nature. The benefits of GOF research were examined qualitatively and compared with alternative approaches. The Executive Summary uses the 1918 influenza virus as a comparator for risks associated with GOF studies involving pandemic influenza, but the full report provides information that allows readers to select any strains for comparison.

Dr. Casagrande offered several cautions on interpreting the results. Specifically, the analysis looks at GOF phenotypes individually, although phenotypes are often linked in the real world, as are risks and benefits. Also, translating empirical studies in animals or cells into epidemiological predictions for humans is impossible.

Biosafety Risk Assessment

Dr. Casagrande emphasized that there is no automatic link between an accident or release involving a dangerous pathogen in a laboratory and a global pandemic. Various barriers and protective factors prevent the spread of a pathogen following exposure or release. The biosafety risk of GOF research was modeled according to three components:

- Probability that an infection occurs
- Probability that an outbreak escapes local control
- Consequences of a global outbreak

Notably, the biosafety risk assessment concluded that a modified strain of influenza virus that is as transmissible as a pandemic strain and causes a disease with a case-fatality rate of 5% or more would pose more risk of a global pandemic than any wild-type strain heretofore identified. Dr. Casagrande pointed out that, for seasonal and pandemic influenza viruses, antiviral resistance increases the consequences of an outbreak, but only in economically developed countries with a significant stockpile of antivirals (the risk is not increased for those who do not have access to antivirals). Manipulating GOF seasonal influenza strains at biosafety level 3 (BSL-3) laboratories may compensate for the increased risk by decreasing the risk of a laboratory-acquired infection (LAI).

For both avian influenza viruses and coronaviruses, wild-type strains are insufficiently transmissible to cause a global outbreak driven by spread among humans. Therefore, increasing transmissibility of either can significantly increase risk.

Dr. Casagrande explained how increasing the transmissibility of a given virus would affect the likelihood that an LAI would lead to infection in the community and the likelihood that the infection would escape local control and become a pandemic. Transmission is influenced by countermeasures, such as social isolation. Dr. Casagrande noted that community mitigation efforts like social isolation would be hard to sustain over months or years, which might be necessary in the case of an outbreak of a coronavirus with a long incubation period, for example.

The RBA also estimated the biosafety risks posed by alternatives to GOF studies. Dr. Casagrande pointed out that many alternative approaches use wild-type strains; therefore, the RBA used the risk associated with wild-type strains as the baseline.

Biosecurity Risk Assessment

To evaluate the risk posed by hostile acts occurring at a laboratory conducting GOF research, Gryphon characterized the threat and defenses against them to determine the plausible threats (a qualitative assessment), then evaluated how GOF research enhances the threat (a quantitative assessment). Among the conclusions, Gryphon found that the source of the initial infection—whether accidental or intentional—is of little consequence once a local outbreak occurs. However, because a breach of biosecurity might involve a covert infection of the public, the infection is much more likely to cause a local outbreak.

Biosecurity breaches include such acts as theft of an infected laboratory research animal or contaminated piece of equipment. Therefore, said Dr. Casagrande, biosecurity breaches pose at least as much risk as biosafety breaches, and the two should be given equal consideration.

Gryphon's analysis of the risk of the misuse of information generated by GOF research considered the availability of information, its capacity for dual use, and the capability and motivation of an actor to use the information to cause harm. The analysis concluded that there is minimal information risk for GOF studies of influenza viruses, because methods to create dual-use strains have already been published. Significant risk remains for GOF studies of coronaviruses, but studies are hampered by the lack of model systems.

Benefits Assessment
Gryphon reviewed the literature and interviewed researchers to understand fully the potential benefits associated with GOF research. Then, Gryphon analyzed the barriers to achieving those benefits. The precise benefits depend on the specific study in question. In some cases, GOF research is critical for countermeasure development; in others, GOF research provides unique benefits for certain types of studies but alternatives may also be used. At present, GOF studies are the only effective strategy for developing sufficient, effective seasonal influenza vaccines and inform pandemic influenza risk assessment and decision making. The RBA also describes alternatives to GOF research.

Discussion

David Relman, M.D., asked whether Gryphon spoke with researchers who avoid GOF research and use alternative approaches instead. Corey Myer, Ph.D., of Gryphon Scientific said all of the interviewees conduct both types of research, and all use alternatives to mitigate risk whenever possible. She said Gryphon did not receive strong responses to requests to interview those who use alternative approaches exclusively.

Panelists
Tom Inglesby, M.D., University of Pittsburgh Medical Center (UPMC) Center for Health Security

Dr. Inglesby challenged some of the RBA findings and conclusions:

- The 1918 influenza virus should not be used as the threshold of acceptable risk. Without extraordinary, unique benefit, experiments in which a release could start a pandemic leading to numerous deaths should not be performed.
- Historic biosecurity incidents may not be relevant for predicting future risks. But Dr. Inglesby noted that Gryphon found that biosecurity risks merit as much consideration as biosafety risks. Dr. Inglesby found this notable, particularly given that biosafety risks have predominated discussions over the past 3 years.
- Better data are needed on laboratory accidents in the United States and globally to determine baseline risk.
- If a pathogen is modified to increase transmissibility, it is not logical to assume it would still be susceptible to existing control measures.
- Evidence does not support the contention that human behavior effectively reduces the transmission of viruses such as influenza, therefore, studies that enhance a pathogen's transmissibility are concerning. It should not be assumed that the spread of a novel pathogen would be controlled.
- With new GOF research, new information risks will arise.
- There are international repercussions of GOF research; a decision to end the pause on funding will set a precedent around the world.
- The benefits are overstated and primarily reflect the opinions of proponents of GOF research. Counterarguments should be included. A public forum that includes vaccine manufacturers and surveillance experts should be held.

- Both the risks and benefits should be assessed without time constraints.

Dr. Inglesby concluded that the benefits of GOF research of concern are not so crucial or singular that they are worth the high risk. Such research should only be funded if a disinterested party can make a highly compelling case for it.

Steve Eubank, Ph.D., Virginia Tech

Dr. Eubank underscored the difficulty of interpreting the evidence when there are so many variables and when outcomes are highly uncertain. Given the scale of a global pandemic, even a "low-consequence" event could result in substantial morbidity and mortality. Assumptions about the independence of an event and the linearity of outcomes should be considered cautiously. The RBA models may over- or understate the magnitude of events by treating related events as independent occurrences.

The balance of risks and benefits could be framed differently. For example, the probability of a laboratory accident involving a highly pathogenic, highly transmissible virus is infinitely higher than it would be for a laboratory that is *not* conducting GOF research. Also, the risk of a global pandemic affects the whole world, while the benefits of GOF research may not necessarily extend to the global population. Dr. Eubank said there is not enough evidence to answer many of the questions raised in the RBA, and the comparisons of risks and benefits are not always weighed on a common scale.

Ron Fouchier, Ph.D., Erasmus Medical Center

Dr. Fouchier pointed out three significant limitations of the biosafety risk assessment:

- The risk is assessed relative to a wild-type pathogen (for which no major outbreaks have occurred).
- The estimate of absolute risk remains hypothetical, as no LAIs with the relevant pathogens have been recorded.
- The assessment explicitly ignores laboratories' biosafety enhancements.

Dr. Fouchier described various occupational health practices and biocontainment features utilized in his laboratory in the Netherlands to prevent losses of containment and prevent LAIs and their possible transmission beyond the laboratory should they occur. He stated that such practices reduce the overall risk from low to very low, influencing the risk-benefit balance. Dr. Fouchier contended that nothing produced by GOF research so far is more dangerous than existing or emerging wild-type pathogens. He suggested the NSABB align its recommendations more closely with existing European laboratory regulations, which focus on minimizing risks.

Dan Jernigan, M.D., M.P.H., CDC

Dr. Jernigan outlined the public health benefits of GOF research, particularly for developing and improving vaccines and therapeutics but also for rapid assessment of the

pandemic potential of emerging viruses. He noted the importance of distinguishing GOF research of concern.

Dr. Jernigan said the RBA's categorizations of seasonal, avian, and pandemic influenza viruses do not account for differences among the viruses or the effects of population immunity. He questioned the use of the 1918 influenza virus for comparison. The theoretical risks of a laboratory accident appear to have more weight than the demonstrated impact of currently circulating seasonal influenza virus. Dr. Jernigan suggested clarifying the criteria for GOF research of concern and allowing for flexibility in emergencies. How the RBA would be applied in practice is not clear, he concluded.

Kanta Subbarao, M.B., B.S., M.P.H., NIH

Dr. Subbarao delineated several very specific points of concern about the scope and wording of the RBA. She pointed out that while the RBA focuses on highly pathogenic avian influenza viruses, the last four influenza pandemics derived from other sources. The risk assessment fails to take new information into consideration. Some of the risks are overstated, such as susceptibility to the 1918 influenza virus. The RBA understates the risk of not pursuing research related to public health concerns.

Dr. Subbarao called for a more nuanced approach to identifying GOF research by locating it on a spectrum ranging from least to greatest concern. If research of greatest concern is justified on the basis of public health benefits, for example, it should be permitted with greater oversight. Dr. Subbarao suggested expanding the definition of GOF of greatest concern to apply to any highly transmissible, highly virulent virus with a potentially high case-fatality rate and resistance to countermeasures.

The RBA does not address the consequences of the pause on GOF research of concern. It does not speak to research on other pathogens or similar issues, such as antibiotic-resistant bacteria.

David Relman, M.D., Stanford University

Dr. Relman said the WG draft report does not adequately define which GOF research of concern, if any, should *not* be conducted or funded. He argued that if GOF research increases transmissibility of a pathogen then whether it is resistant to existing control measures is irrelevant. Therefore, the third criterion for identifying GOF research of concern should be eliminated.

The finding that current policy frameworks are effective for managing risks is not supported. Dr. Relman pointed to the inherent conflict of interest among institutions that fund and conduct such research and the lack of transparency around decision making.

Dr. Relman challenged the RBA's conclusion that information risk associated with GOF research involving influenza viruses is minimal because most of the information of interest has already been published or other agents of harm are already available. Dr.

Relman noted that the motivations of all actors in all circumstances cannot be known and that new information, or combinations of information, could be misused for harmful purposes. The RBA's analysis of biosafety risks assumes that laboratories around the world apply the same standards for containment as the United States does, which is not true now and unlikely to be true in the future. This compounds the risks associated with information generated by GOF research as experiments may then be replicated in laboratories where safety and security standards may be inadequate. The RBA overstates the uniqueness of the benefits of GOF research and downplays the unique risk.

Discussion

Dr. Casagrande responded to the criticisms of the RBA, noting, for example, that Gryphon attempted to interview researchers on both sides of the issue and reiterating that the RBA allows users to make comparisons with any phenotype, not just the 1918 influenza virus.

Dr. Casagrande cautioned that the RBA's estimates of absolute risk are based on significant uncertainty and, therefore, are the weakest portion of the assessment. Absolute values of risk should not be the basis for policy recommendations. Stakeholders would be better served by determining what level of risk is acceptable. Dr. Casagrande defended the RBA's methods and acknowledged many limitations. He hoped the model underlying the conclusions would be sufficiently flexible to allow for risk-benefit analysis in changing circumstances. Dr. Myer added more details about Gryphon's process. She emphasized that the full report does a better job than the Executive Summary of describing the strengths and limitations of various approaches and conclusions.

Kavita Berger, Ph.D., of Gryphon, added that the security data came primarily from public sources and focused on the United States. Some international issues are also addressed in the RBA.

Dr. Casagrande noted that the vast majority of laboratory accidents are caused by human errors, although the true rate is unknown. The uncertainty of human error is not well addressed by other risk assessments, he said.

Dr. Relman described several scenarios in which actors might use published information to cause harm. Dr. Casagrande agreed that many of the scenarios are possible; however, he argued that there is little benefit (to an actor intent on causing harm) in making highly transmissible strains more transmissible.

Professor Susan Wolf, J.D., asked how Dr. Relman would define GOF research that should not be conducted. Dr. Relman proposed that any effort to generate a novel agent that is highly transmissible, highly virulent, and does not exist in nature should not be pursued. He acknowledged that regulators would have to define "highly" and allow for possible exceptions but recommended his approach as a starting point. Drew Endy, Ph.D., appreciated that a strong recommendation would set a powerful norm, but he had

concerns that certain individuals with malevolent intent might pursue such research, in part because it was designated as "unacceptable." Dr. Relman replied that norms and values should be articulated as a way of raising awareness among those in the field who might not have considered the potential consequences of their work.

Christine M. Grant, J.D., M.B.A., asked CDC to provide a list of GOF research efforts underway in support of public health activities, as well as missed opportunities. She suggested the list look to the future. Dr. Jernigan agreed to provide information on GOF research of benefit to public health efforts.

Joseph E. McDade, Ph.D., pointed out that with prescriptive guidelines, anything not specifically included will be perceived as acceptable. There must be a mechanism for evaluating agents not covered by guidelines. Dr. McDade added that the NSABB should think about how to make the RBA applicable to other agents.

SESSION II: EXAMINATION OF ETHICAL ISSUES ASSOCIATED WITH GOF STUDIES AND DISCUSSION OF POTENTIAL DECISION FRAMEWORKS

Susan Wolf, J.D., and Francis L. Macrina, Ph.D., NSABB Members, Co-Moderators

Professor Wolf said that ethics and values play a key role in the interpretation of the RBA and the consideration of recommendations. Decisions about risk and benefit involve judgment, values, and social context. The NSABB commissioned Michael Selgelid, Ph.D., to review the ethics literature and decisional frameworks around GOF research and propose a potential framework to the NSABB.

Professor Wolf listed the substantive and procedural values described in the WG draft report, noting that scientific freedom and responsible stewardship are newer concepts. She summarized some of the decision-making strategies discussed by the WG and described in Dr. Selgelid's report, including maximax, maximin, expected utility maximization, and precautionary approach. Panelists for this session were asked to address the following questions:

- What ethical values should NSABB consider in moving beyond the risk and benefit assessments in order to formulate policy recommendations on GOF studies involving pathogens with pandemic potential?
- What ethical or other decision-making frameworks should be brought to bear when considering whether to fund and conduct certain GOF studies?
- How can ethical decisions be made in light of the inherent uncertainty associated with potential risks and benefits?
- Is there GOF research that should not be funded or conducted? If so, what are the features of such studies and what considerations should guide the identification of GOF studies that might meet such designation?

GOF Research: Ethical Analysis

Michael Selgelid, Ph.D., Director, Centre for Human Bioethics & World Health Organization (WHO) Collaborating Centre for Bioethics, Monash University,

Melbourne, Australia

Dr. Selgelid prefaced his remarks by saying that his commissioned white paper focuses on policy issues, particularly funding decisions, and that his intent was to provide an objective, neutral analysis of the issue. The proposed ethical framework highlights desired ethical properties, not necessary conditions, and emphasizes the importance of democracy.

Dr. Selgelid pointed out that a decision not to fund research does not necessarily mean that the research should not be conducted. Also, the decision not to fund research because it is anticipated that the results might raise concerns warranting the study not be published is not as weighty a concern as censoring the study. His proposed framework includes eight principles which should be considered:

1. **Research Imperative**: The more important the target research question, the more ethically acceptable the risk is. The riskier the research, the more important the target question must be to justify it.
2. **Proportionality**: The greater the confidence that risky GOF research will yield answers to public health questions and ultimately provide benefits that outweigh the risks, the more acceptable the research is.
3. **Minimization of Risk**: The degree of confidence that no less risky forms of research would be equally beneficial and that reasonable steps have been made to minimize risks inform the ethical acceptability (similar to the least restrictive alternative principle in public health ethics).
4. **Manageability of Risk**: The more manageable the risk, the more ethically acceptable the research. Conversely, the more important or potentially beneficial the research, the more willingness there should be to accept potentially unmanageable risks.
5. **Justice**: The burdens and benefits of GOF research should be shared fairly. Countries conducting or funding GOF research should aim to mitigate risks for those who are especially vulnerable, ensure wide availability of GOF research benefits, and compensate those who suffer harm.
6. **Good Governance and Democracy**: In a democracy, decision making and policy making should reflect the values, risk tolerance, and other concerns of the population, and it should be transparent. Key stakeholders and the public should be engaged.
7. **Evidence**: Policy making should be based on evidence. More evidence will arise from ongoing risk-benefit analyses, social research, and monitoring of GOF research.
8. **International Outlook and Engagement**: Because GOF research affects the global community, decisions and policies should involve consultation, negotiation, cooperation, and engagement with other countries.

Panelists
Alta Charo, J.D., University of Wisconsin Law School

Professor Charo called on decision makers to think hard about who gains and who loses in both the short term and the long term before making assumptions about the risks and benefits. Biosecurity risks are a greater concern for developed countries; the benefits of improving biosafety would be more globally distributed.

Demographic factors and subpopulations should be considered in assessing risk. For example, a pandemic that strikes those of working age would have greater economic consequences than one that targets older people.

In tort law, the concept of reciprocity of risk posits an acceptable range of risk. With GOF research, the risks and benefits do not align neatly, so it is difficult to determine what level of risk is acceptable. Human subjects research seeks to go beyond balancing risks and benefits to optimizing the benefits.

Economic analyses should take into account that the benefits do not always accrue to those who bear the burden of the costs, known as externalization of costs. A legal approach of strict liability internalizes the costs, forcing decision makers to weigh the benefits carefully in light of all costs. Compensation for harm is a common remedy; in the case of GOF research, it may be appropriate to build resources in the field or to create funds for the most vulnerable.

Policy makers and funders can make decisions about GOF research that affect people who have no say or influence on the decision. Ethically, decision makers should exercise a higher degree of concern for those who cannot participate in the process or at least take extra precautions when there is inequity.

Jonathan Moreno, Ph.D., University of Pennsylvania

Dr. Moreno said national security considerations introduce new dimensions to risk-benefit analysis and ethical assessment. He pointed to the range of opinions already expressed at this meeting about biosecurity risks and suggested the NSABB look at biosafety and biosecurity separately. Confidence in the availability of countermeasures changes depending on biosecurity threats.

People generally have a hard time assessing real risk. Policy makers should take into account that rationality plays only a modest role in an individual's assessment of risks. The scientific community should be alarmed about emerging threats to scientific freedom.

The following documents are applicable to GOF research of concern and should be reviewed:

- *Emerging and Readily Available Technologies and National Security—A Framework for Addressing Ethical, Legal, and Societal Issues*
- Biological Weapons Convention

- *Biotechnology Research in an Age of Terrorism*

David Fidler, J.D., M.Phil., Indiana University, Bloomington

Professor Fidler said the WG draft report and the ethics analysis acknowledge the need for global engagement and the importance of applying ethical principles to decisions about GOF research but only superficially. Both should focus more on the application of ethical principles of risk-benefit analysis of GOF research of concern in the global context.

Ethical aspects of research and their global dimensions have been addressed by other authoritative bodies, such as the WHO, but neither the ethics analysis nor the WG draft report includes findings from previous assessments. The draft report states that international perspectives and experiences are important and refers to well-developed policies on GOF research in other countries but does not describe why or how they are important to crafting U.S. policy. Fidler said a key objective of NSABB deliberation is to translate ethical issues into policy. Therefore, the NSABB should describe lessons learned from global experiences with ethical issues around dual-use research of concern (DURC) and GOF research of concern.

Professor Fidler called on the NSABB to revise the draft report to specifically and explicitly address ethical issues and their global dimensions in the key findings and recommendations and pointed out that there ae credible ways to do so.

John Kadvany, Ph.D., Independent Consultant

Dr. Kadvany explained that decision science aims to break complex topics down into manageable components that inform thinking. He walked through a method of simplifying the components of decision making about GOF research. The top level identifies various outcomes, positive and negative, of the research, which can then be viewed through the lens of demographic factors or geographic regions, for example. The next level describes the sources of knowledge, such as subject matter experts, models, and historical data. The bottom level identifies policy and research options to reach the desired outcomes. Dr. Kadvany stressed that a value-focused approach first pinpoints the desired outcomes, and then works backward to create policy to reach those outcomes.

The benefits of GOF research often take a long time to realize, and it is difficult to attribute the benefit to a single entity or event. Therefore, instead of looking at the long-term, public health benefits of GOF research, it may be easier to consider near-term benefits to science. The WG draft report has good examples of criteria that can be used to assess risk, and the RBA has good examples that could be used to measure benefit. Ultimately, Dr. Kadvany said, decision makers need to construct meaningful models they can use to make good decisions.

The risk model driving understanding of the RBA stems from the criteria described in the draft report for GOF research of concern. But the research enterprise has various risk

management mechanisms in place (e.g., training, education, regulation). Adaptive risk management takes research outcomes, stakeholder views, context, and other factors into account for decision making about GOF research and criteria.

Discussion

Professor Wolf called for suggestions on how to improve oversight, especially if the recommendations addressed international entities. Professor Fidler said the NSABB's recommendations should at least reflect previous efforts to improve oversight, such as those by the WHO, and describe unsuccessful approaches. If the USG aims to create a global norm around GOF research, the NSABB could recommend that the State Department or others promulgate it. The ethics analysis could better describe best practices and failed efforts and identify mechanisms the USG might support.

Dr. Berns acknowledged that NIH funds GOF research and has a vested interest in its continuation; he asked what other body should have definitive oversight of GOF research. Fidler responded that a democratic oversight process should engage multiple stakeholders. Professor Charo said the White House Office of Science and Technology Policy is an ideal source for convening people who could provide insight into decision making before funding determinations are made. They could address perceived fears and discuss methods for mitigating risk.

Dr. Fitch pointed out that ethical acceptability seems to be affected by the fact that GOF research aims to deliberately modify a pathogen. Professor Charo agreed that the concept of agency may influence how research is perceived. She noted that the public often assumes that naturally occurring organisms are better or purer, even when that is not true. Dr. Moreno underscored the importance of listening to public input.

Dr. Endy noted the difficulty of regulating small-scale, amateur GOF research. Dr. Moreno suggested lessons could be learned from those involved in robotics. Professor Charo said the United States tends to address problems that arise from unfettered work, while other countries require permission before embarking on research. The United States can regulate to protect against physical harm, she said; one aspect of the current debate is whether moral outrage is a harm.

George Rudy, and audience member, pointed out that nuclear facilities are subject to strict oversight by the Nuclear Regulatory Commission (NRC) and other entities that ensure a consistent approach across the industry. He suggested determining how to translate best practices from the nuclear field to GOF research. Mr. Rudy also said that effective methods to address GOF research throughout the United States should be in place before an international effort is undertaken. He recommended a single oversight body for GOF research.

SESSION III: ANALYSIS OF THE CURRENT POLICY LANDSCAPE AND POTENTIAL POLICY OPTIONS FOR GOF STUDIES

Joseph McDade, Ph.D., and Marie-Louise Hammarskjöld, M.D., Ph.D., NSABB

Members, Co-Moderators

Dr. McDade described the current policies reviewed by the GOF WG. He noted that all of the policies were developed independently and in response to specific situations. They vary in age, and some have been revised multiple times. Some gaps exist in coverage of certain GOF studies. Only some of the policies address communication of research results. The WG is considering a number of approaches related to decision making and oversight of GOF research, from permissive to precautionary, and several more nuanced approaches in between. Panelists for this session were asked to address the following questions:

- What are the major drivers of risks associated with GOF studies of concern? Are there any deficiencies with current policies in managing those risks?
- If risks are not currently adequately managed, what policy options or oversight might be available to help manage the risks? What should that oversight entail? Should that oversight occur at the federal or institutional level, or both?
- What challenges are associated with managing risks at the stage where research results are being communicated or published? What would journal editors find most helpful upstream to manage risks prior to publication?
- How can oversight measures be developed and employed in ways that would allow the benefits associated with GOF studies of concern to be realized?

Panelists
Gigi Kwik Gronvall, Ph.D., UPMC Center for Health Security

Dr. Gronvall made the case that biosafety, not biosecurity, breaches are the main drivers of risk, so policy should focus on biosafety concerns. An adaptive approach rests on a foundation of earlier work and is not likely to become outdated quickly. The NSABB's actions are likely to be bolstered by other efforts to improve biosafety.

The precautionary approach is short-sighted and damaging to scientific progress, because it paralyzes decision making. Future benefits would go unrealized, which is detrimental to public health.

Dr. Gronvall hoped the NSABB would advise the USG to take an international approach and to lead the way in demonstrating a safe path forward for research. The USG has good guidance and norms for institutions and individuals to practice GOF research safely. There are also initiatives such as the Global Health Security Agenda to improve research around the world. Biosafety is an area of common ground across nations.

Mike Imperiale, Ph.D., University of Michigan Medical School

Dr. Imperiale said federal oversight of GOF research is needed because institutions may not have the expertise to manage the complexities and nuances of assessing such work. However, policies should give clear and consistent guidance on pathogens that pose a real risk. If there are too many barriers to research, good investigators will leave the field.

Despite recent safety lapses, Dr. Imperiale said he believes biosafety can be addressed effectively with a concerted effort.

Journal editors should not bear the responsibility for managing risk when results are submitted for publication. Determining whether work meets the definition of DURC is difficult and may require access to classified information. Dr. Imperiale suggested the NSABB modify the definition of DURC for application to GOF of concern. Journals also lack clear guidance on assessing research of concern that does not involve select agents. The global nature of science and publishing gives rise to conflicts about what constitutes research of concern in different settings.

Publishing redacted results has been considered, but this approach flies in the face of effective science and may not be feasible in the digital age. The suggestion that scientists should self-censor also goes against the nature of scientific exploration. Dr. Imperiale pointed out that the NSABB was created as a review body to consider complex situations. He suggested that some high-risk research could be conducted in a classified setting.

The policy for GOF research should be reviewed regularly and frequently, so misjudgments can be rectified. Decisions about which research should not be pursued or published should occur early in the process, and journal editors should not be the arbiters.

Barbara Jasny, Ph.D., Science Magazine

Dr. Jasny said journals may act as gatekeepers, but research should be subject to appropriate oversight long before results are submitted for publication. She described numerous challenges that complicate journal review of GOF research, including lack of expertise of reviewers, language barriers, interdisciplinary research, information added during the review process, disagreement among experts, and pressures to publish when infections or pandemics are emerging.

Science believes strongly that redaction is not appropriate for journals, because if used there is no mechanism for communicating information to those who need it. In the 21st century, transparency is paramount. Classification of information after the fact is too challenging in an age of electronic submission.

The WG draft report is reactive; it does not anticipate future concerns. Journals have no options other than to publish or reject submissions. Submissions may come from industry or international sources that are not subject to current federal regulations. There is a strong need for responsible communication with the public.

Dr. Jasny recommended the following:

- Consistent federal oversight
- Documentation that oversight of federally funded research continued up to submission for publication (to avoid the late appearance of unanticipated results)
- Mandatory training for researchers and institution and government representatives

in communicating with the public
- Creation of an independent agency to set standards and advise journals
- Harmonization of international standards

Regine Aalders, M.Sc., Embassy of the Kingdom of the Netherlands

Ms. Aalders explained that numerous ministries are involved in biovigilance (a term which encompasses biosafety and biosecurity) in the Netherlands, each with its own approach. Since research support comes from a variety of sources, controlling research through funding decisions is not an option. The country has many safety regulations, but they are not all linked, and each has different notification requirements.

To address the situation, the Netherlands is creating a biosecurity office, linked to the National Institute of Public Health and the Environment. The biosecurity office will bring together the country's 25 safety regions under one law, although it is still not clear which ministry will ultimately be responsible for the law. The biosecurity office will work on making the existing code of conduct for scientific research more pragmatic. It will promote the process for obtaining export licenses, which is still voluntary. In the future, export licenses and other factors will be better linked. The ultimate goal is to improve cooperation across ministries.

Discussion

Dr. LeDuc asked why all GOF research of concern is not performed in BSL-4 laboratories, given the concerns about the global pandemic potential. Yoshihiro Kawaoka, D.V.M., Ph.D., said BSL-4 laboratories are almost identical to BSL-3-Agricultural (BSL-3-Ag) laboratories, and there is no difference between the two when it comes to influenza research. Dr. Fouchier concurred; he added that his laboratory meets the standards of a BSL-4 laboratory.

Dr. Kanabrocki said that confining GOF research to BSL-4 laboratories would limit the number of people involved in research, and he suggested that the NSABB should further discuss the need for strong containment policies, training, competency assessment, and occupational medicine components. Dr. McDade agreed that the NSABB's recommendations should address these issues in the context of answering whether existing policies cover current work. Ms. Grant said she wanted to learn more about how the U.S. Department of Health and Human Services (HHS) committee that addresses very concerning GOF research functions before weighing in on the effectiveness of existing polices.

In response to Jan Leach, Ph.D., Dr. Jasny said journal editors communicate with their international colleagues and there are some efforts to harmonize standards across journals. Dr. Imperiale said authors rejected by one journal can seek publication in another domestically, internationally, or online.

Responding to Professor Wolf, Dr. Imperiale said he did not know the mechanics of

conducting GOF research of concern in a classified setting, and he acknowledged it would not be an ideal approach. Dr. Fouchier said classification of research would not remove biosafety risks; in fact, without knowledge of ongoing work, more states might attempt GOF research to answer the same questions, increasing the overall risk.

Jeffrey F. Miller, Ph.D., proposed that a researcher doing GOF research of concern could be required to use any available options to make working with the pathogen safer. Dr. Fouchier cautioned that there will always be experiments that require the use of unmodified pathogens, which is why he and others have invested so heavily in high-containment laboratories.

Edward You said that by focusing on specific pathogens, rather than the intent behind the research, the NSABB risks coming back to the table whenever a new pathogen of concern arises. He asked how the core tenets of the RBA could translate to policy and implementation. The message for institutions is to focus on improving oversight at the local level. Effectively implemented, a policy can create a web of detection in which everyone understands how to spot concerns so they are flagged early in the process. Mr. You encouraged NSABB to provide good examples and clear suggestions for implementation. A culture of responsibility requires a culture of awareness.

Gerald Epstein, Ph.D., advised the NSABB to avoid getting bogged down in defining GOF research of concern. He pointed out that the only reason to define DURC is to inform actions. Some means for screening for and identifying research of concern is needed, but only as a first step in identifying what is needed to prevent or mitigate risk.

PUBLIC COMMENT PERIOD

John Steel, Ph.D. of Emory University said the RBA does not compare the risk of conducting GOF research with the risk of not doing such research. He hoped the NSABB recommendations would focus on GOF research of concern for viruses that are highly transmissible and work toward a quantitative definition of "highly transmissible."

Marc Lipsitch, D. Phil., Harvard School of Public Health, noted that despite the RBA's conclusions, discussion at this meeting seems to suggest that biosecurity is not as much of a concern as is biosafety. Also, biosecurity risks should not be assessed on the basis of rational considerations about the most efficient or effective agent. The NSABB should revisit the notion that some experiments cannot be done more safely. Also, many decisions about acceptable research methods are made on the basis of concerns other than risk to human life which he feels is paramount.

Dr. Casagrande responded that Gryphon's assessment of the relative risks of biosecurity and biosafety breaches aligns with the findings of other studies. He added that the RBA narrowly defines biosecurity; a lot of events categorized as biosecurity attacks are crimes that happen to involve a contagious agent.

George Rudy of the Frederick County & City Containment Laboratory Community

Advisory Committee said the RBA is an excellent generic starting point, but risk assessments need to be done on a laboratory by laboratory basis. In one laboratory he assessed, the PI said it was difficult to choose between safety and productivity. Mr. Rudy said that in the world of nuclear science, safety trumps everything.

Andy Kilianski said the WG draft report should be made available for public comment and should address implementation of recommendations. He hoped the paper would be fleshed out in time for the upcoming National Academies meeting in March so the public can provide input.

Dr. Fouchier said he is more concerned about many naturally-occurring viruses than those on which his laboratory is conducting GOF research. He noted that whatever the NSABB recommends will probably have a huge impact on all future infectious disease research. He suggested the NSABB consider whether its findings and recommendations are specific enough to GOF research of concern or applicable to all high-containment research.

Nicholas Evans, Ph.D. of the University of Pennsylvania pointed out that scientific freedom is an admirable principle, but in practice, it is limited by funding, and funding favors successful investigators. Likewise, the principle of justice is influenced by practical considerations. Finally, in nuclear science, classifying research enabled significant violations of ethical principles to take place for a long time.

Wendy Hall, Ph.D. of the U.S. Department of Homeland Security asked Dr. Fouchier about 1) the Dutch approach to public engagement and 2) whether GOF research should be limited to laboratories with specialized capabilities. **Dr. Fouchier** stated that he believes GOF research should be limited to laboratories capable of conducting them under the appropriate conditions. He described his laboratory's response to the public after the NSABB determined in 2011 that publishing his research was too dangerous. He noted that his laboratory has never been secretive about its work and invites the media in periodically.

Dr. Selgelid reiterated the idea that research should not be divided into two categories—research of concern or not of concern—but rather located on a spectrum ranging from most to least concern. Similarly, the reaction to concerns should not be identified as either doing something or doing nothing; the policy responses can be defined to address a range of concerns depending on the risk.

Dr. Eubank noted that classification might enhance biosecurity but not biosafety. In fact, the results may be worse when research is done outside of the public eye and there are no forums for discussion. Decision making about GOF research is an asymmetric exercise; only research that is not approved is likely to come up for discussion again in the future. With classified research, the default position for surprising results is not to publish them. In some research domains, investigators do not expect to have the freedom to publish all their findings, and it is surprising that restrictions on publishing are seen as censorship.

Christopher Park of the U.S. Department of State cautioned that attempts to refine definitions (e.g., of DURC) can contribute to ambiguity. Decision makers have to bound the universe somehow. Seeking to distinguish "GOF research of concern" can lead to arbitrary binary distinctions. A more productive question that decision makers can ask is whether the research poses risks and, if so, whether the risks can be mitigated. When there is a threshold of concern that involves strongly subjective elements, there will inevitably be imbalances. Also, if one local entity decides to fund a project, others will see that as a stamp of approval.

Megan Palmer, Ph.D., of Stanford University referred the NSABB to a paper she published with Dr. Relman ("A More Systematic Approach to Biological Risk," *Science*, 2015, 350:1471–3). The Gryphon report again highlighted the lack of data on which to base predictions, particularly the lack of information about laboratory accidents. The absence of such data undermines public confidence, so the NSABB should keep exploring and encouraging ways to improve processes and collect data that will contribute to substantive, critical review. The NSABB's recommendations should describe mechanisms to facilitate assessment of the implementation of its recommendations and ensure accountability. Consideration is needed of whether the NSABB is well positioned to make recommendations that will be implemented and whether it has capacity to shape policy at various scales and resolve inherent conflicts of interest that may be present.

DAY 1 CLOSING REMARKS
Samuel L. Stanley, Jr., M.D., NSABB Chair

Dr. Stanley thanked all those attending for providing helpful input on critical issues. He adjourned the meeting for the day at approximately 5:30 p.m.

DAY 2

OPENING REMARKS
Samuel L. Stanley, Jr., M.D., NSABB Chair

Dr. Stanley pointed out that the previous day's discussions on risk-benefit analysis, ethics, and policy brought forth other questions for further exploration:

- Whether some GOF research of concern should not be conducted and, if so, how to define that work?
- How to describe the application of ethical principles more explicitly and embed ethics into guidelines?
- How to craft USG guidelines so they have international impact?
- What oversight and implementation should consist of and how they should be put into place?

More topics will likely come from the National Academies meeting. Dr. Stanley indicated the NSABB will wait until after that meeting to make substantive changes to its

draft report.

SESSION IV: DISCUSSION OF NSABB PRELIMINARY FINDINGS AND DRAFT RECOMMENDATIONS

Kenneth Berns, M.D., Ph.D., and Joseph Kanabrocki, Ph.D., CBSP, Co-Chairs, NSABB WG on evaluating the risks and benefits of GOF

Dr. Berns reviewed the key findings and draft recommendations in the NSABB WG draft report before the panelists for the session were asked to address the following questions:

- Are there GOF studies that may be conducted but should require an additional level of review or oversight? If so, what should that oversight entail? Should that oversight occur at the federal or institutional level, or both?
- How well does the NSABB's draft working paper identify the GOF studies of greatest concern?
- Are there GOF studies that should not be conducted? If so, which studies and why?
- How well would the NSABB's draft principles and criteria permit the review of GOF studies that have raised concerns and inform decisions about whether to fund such studies?
- Are there specific risk mitigation measures that should be required in order for certain GOF studies to be safely conducted?

Panelists
Marc Lipsitch, D. Phil., Harvard School of Public Health

Dr. Lipsitch said the NSABB's focus on GOF research of concern is appropriate but its definition of such research is unduly narrow since, due to limited availability and distribution, the existence of medical countermeasures do not sufficiently mitigate global risk.

Dr. Lipsitch voiced concerns that the RBA significantly understates the risks; yet the risk estimates in the RBA are still so high as to indicate that GOF research of concern should not be conducted. He believes the risks are even higher than estimated and the probabilities of LAIs and of an infection escaping local control are inexplicably low in the RBA, noting that the RBA does not justify its contention that the risk of working with the 1918 influenza virus is an acceptable baseline level of risk.

Dr. Lipsitch said Gryphon's benefits assessment reveals major conflicts of interest and dramatically overstates the benefits. The claims of unique benefits are exaggerated because they come from people who are already doing GOF research. The benefits largely accrue to rich countries while imposing risks on whole populations. Effective research alternatives exist, making it unethical to conduct such dangerous experiments.

He thought the NSABB was wrong in stating that current processes are adequate to

regulate GOF research of concern. He noted that even during the funding pause, a paper describing SARS GOF research was published. Placing funders and researchers in charge of decision making is a clear conflict of interest. There are no resources to help institutional biosafety committees (IBCs) or others assess the risks and benefits of GOF research. For these reasons, Dr. Lipsitch said, the United States should not perform or fund GOF research of concern.

Jill Taylor, Ph.D., Wadsworth Center, New York State Department of Public Health

Dr. Taylor offered her perspective as leader of a public health authority that conducts research. She and her colleagues requested more clarity regarding review and oversight and favored that DURC policies be adapted for GOF research of concern rather than establishing another level of oversight.

Dr. Taylor agreed that risk should be considered on a spectrum. Proposed studies should be evaluated individually, not banned *a priori*. The planned adaptation and risk-based approach to oversight and review is preferable to a one-size-fits-all policy.

The proposed criteria for review of GOF research of concern requires that investigators and institutions have a culture of safety and responsibility, but it is not clear how to verify such a culture. A checklist is not enough, as every institution and every IBC is different.

Dr. Taylor and her colleagues agree there are certain risk mitigation measures that should be required for certain studies. When Ebola virus became an immediate threat, organizations committed to increasing safety procedures and employees accepted them. With GOF research of concern, such approaches should be standard. Ongoing internal and external research progress reports, reviewed by federal entities, should be required so that risks are identified and better understood.

Institutional review processes should involve local and state epidemiological and public health representatives who will be part of incident response. Dr. Taylor also emphasized the need to strengthen the culture of responsibility and awareness in all institutions.

Yoshihiro Kawaoka, D.V.M., Ph.D., University of Wisconsin, Madison

Dr. Kawaoka made the case that GOF research of concern on H5N1 influenza virus is already highly regulated and effective oversight policy frameworks are in place. Such research is covered by *all* the policies summarized in the draft report; it is also reviewed before grant submission by an IBC applying federal policy guidelines and its conduct subject to federal and institutional oversight. Furthermore, it falls under select agent and export control regulations.

Dr. Kawaoka described how his grant proposal to study the transmissibility of avian influenza viruses in mammals included review by his institution's IBC for adherence to the NIH Guidelines and the BMBL prior to submission, as well as a DURC subcommittee. He noted that H5N1 is a select agent so the university is registered under

the Select Agent Program and subject to rigorous Federal inspections. He explained that after NIH peer review, the grant was additionally reviewed as required by a multidisciplinary group according to the *HHS Framework.* The review group assessed the proposed research he proposed and found it acceptable for funding consideration with the exception of certain experiments involving reassortant viruses. Dr. Kawaoka said the review process provides further proof that effective policies are in place to identify research of concern, and GOF research of concern can be worked into existing policies. Dr. Kawaoka explained that the HHS review group evaluated the proposed experiments, the risk mitigation measures and other procedures in place, including communication strategies and questioned how such a review could be conducted publicly, as it would expose sensitive research information.

Mark Denison, M.D., Vanderbilt University

Dr. Denison stressed the risks not pursuing GOF research might pose to the careers of young investigators and the future of research. He agreed that adequate mechanisms for review and oversight are in place. Clarifying guidelines will facilitate identification of research of concern at the institutional level and enable review of meritorious research. Dr. Denison also advocated for modifying DURC or other guidelines to include GOF research of concern rather than establishing independent review mechanisms. Policies should be flexible so they do not discourage pursuit of high-impact, innovative research. An approach that determines relative risk throughout the research life cycle and allows for iterative design is preferable. He added that wild-type virus and coronaviruses should not be included in the GOF policy.

Dr. Denison believed that some GOF research should not be conducted, but that listing examples only discourages thoughtful review and does not improve biosafety or biosecurity. Describing general principles and giving clear guidelines about research of concern will capture ethical breaches or gratuitous research. He suggested that if a topic cannot be addressed in clear language, it should be left out to avoid muddying the waters. Guidelines should avoid absolutes and instead characterize risks and benefits in a way that can be applied to individual cases.

Dr. Denison thought the NSABB should not address funding, because researchers will avoid work that threatens their funding. Mechanisms should allow for review of highly meritorious research, encourage novel approaches, and support relevant modifications of scope or mitigation of risk. Policies should avoid overregulation of security, safety, or other limiting mechanisms (e.g., requiring all GOF research of concern to be conducted in BSL-4 laboratories) and instead should encourage support for testing risk mitigation approaches and experimental alternatives.

He encouraged that the process for review and decision making be transparent and open to scrutiny, but said investigators need a confidential peer-review mechanism so their work can be vetted. Dr. Denison proposed a model for reviewing research design and processes on a case-by-case basis that incorporates periodic opportunities for reconsideration.

He indicated that the WG draft report does not address several real risks: encouraging distrust of scientists and their motivations, discouraging young investigators from pursuing GOF research, and convincing institutions to stop supporting some research. All of these risks could jeopardize the field. The likely outcomes and implications of the draft recommendations seem proscriptive and punitive. The NSABB is not required to propose new oversight mechanisms or policies if existing ones are sufficient.

In conclusion, Dr. Denison said the draft report gives a high-level, 40,000 foot perspective and encouraged the NSABB to "land the plane" by providing guidance and modeling the implications of its recommendations.

Philip Potter, Ph.D., St. Jude Children's Research Hospital

Dr. Potter described his institution's experience evaluating potential DURC and GOF research of concern. St. Jude has a well-constructed DURC review group with broad representation (including senior scientists), but even that group found the *HHS Framework* difficult to interpret so they leaned toward over interpretation. Any recommendations or guidelines around GOF research should be so clear that even a novice to the field can understand them, said Dr. Potter. Interpretation of terms such as "highly," "significant," and "likely" vary, and institutions may not know how to address the subjectivity.

Dr. Potter expressed confidence in the quality and makeup of his institution's IBC and DURC review group but did not know how they compare with those of other organizations. Some entity must be able to assess whether institutional review bodies are good enough he said.

The NSABB's recommendations should be definitive, obvious, transparent, and clear. If they are, institutional evaluation of the science will be easier to do, more valid, and easier to communicate. However, from a scientist's point of view, establishing generic regulations prohibiting certain types of experiments interferes with good science and provides no benefits. Guidelines must be flexible so they can be applied to emerging viruses. Multiple bodies should review GOF research of concern and consideration should be given to institutions that do not receive federal funds and whether investigators rejected in this country will pursue their work elsewhere.

Beth Willis, Frederick Citizens for Bio-Lab Safety

Ms. Willis said that community advocates for biosafety have seen their concerns play out in real life with recent safety lapses around the country. She was struck by the lack of scientific consensus on how to proceed with GOF research of concern. Funding and conducting such research without consensus about safety gets the attention of the public, as do concerns raised about conflicts of interest among decision makers.

Ms. Willis called for developing and implementing specific, robust, transparent, and

replicable decision making and oversight processes in which the public can have confidence. Reordering the balance of power and including ethical and public health values in decision-making criteria would protect against some of the risks posed by human hubris. Recommendations should be specific and actionable; they should also acknowledge the need for funding (much more than currently provided) to implement good oversight, public communication, and public engagement.

Ensuring public safety makes GOF research of concern more costly. Such research should be evaluated at the funding phase in the context of overall research priorities. If an entity cannot afford the necessary protections, the research should not be funded.

The WG draft report identifies the principles of public engagement and communication as key, and efforts should be made to ensure that transparency is real. Achieving meaningful transparency will take significant, additional commitment from the USG. The public needs more information about funding decisions, such as who approves research and what risks are identified. The draft report does not describe who determines an acceptable level of risk or how mitigation efforts are evaluated.

Ms. Willis appreciated the acknowledgment that risk analysis is uncertain and has limitations, because that allows room for the application of wisdom and common sense. She suggested that public engagement throughout the research lifecycle should be required and facilitated by, for example, a clearinghouse of information and technical assistance for laboratories and communities to develop locally effective goals and approaches. The scope should expand beyond the NIH; communities need assurance that safety mechanisms are in place for all research of concern, including research conducted by private entities with no federal oversight.

If risky research is conducted, it must fall under an independent oversight mechanism that is adequately funded. Perceived inadequacies in the safety culture at Federal laboratories should be high on the list of concerns. Decisions to conduct GOF research of concern must address the tension between safety and competitive pressures. The public seeks a clear authority empowered to make health and safety decisions for the public good—a core function of government—but no such structure exists.

Discussion

Dr. Kawaoka outlined some of his laboratory's procedures for responding to an accident or release of a pathogen from containment and emphasized that local public health authorities are involved in mitigation planning. Regarding public engagement, Dr. Kawaoka said the IBC has a public representative, and the laboratory hosts an annual open house.

Dr. Fitch asked whether St. Jude specifically communicates its appetite for risk to its review committees. Dr. Potter said St. Jude is exceptionally conservative because it relies heavily on its brand for fundraising. Dr. Taylor said understanding an institution's tolerance for risk requires incredible personal involvement and constant communication.

Projects are reviewed on a case-by-case basis, and the capacity to manage risks is discussed. Dr. Taylor suggested moving away from a focus on definitions of research of concern and toward a process that identifies the risks and how they can be addressed.

Ms. Grant said the NSABB has heard repeated, stellar examples of conscientious researchers following guidelines in good institutions, but all institutions vary. The question remains of how to avoid penalizing the best and most conscientious researchers. Dr. Lipsitch pointed out that it is not reasonable to focus on what happens in superb, high-containment laboratories, because pathogens are getting into other settings through mistakes and safety lapses—even during times of intense scrutiny. What happens outside of containment areas is of most importance, he said.

Ms. Grant suggested, and Dr. Taylor agreed, that public health representatives should be engaged in the review of GOF research proposals. Dr. Potter noted that the county public health officer who serves on St. Jude's IBC and DURC review group is very helpful; she is also the main contact for response coordination. Marcelle C. Layton, M.D., said, in contrast, that public health officers in New York City are not aware of what is going on in laboratories; they have proposed that laboratories be required to notify public health authorities about research of concern. She suggested the NSABB include such a recommendation.

Dr. Layton noted that the draft report has been criticized for being too general, and she called for direction on how to change it. Dr. Denison requested enough specificity to identify risks but enough flexibility to review and respond to risks. Guidelines should not be so specific that they limit research or, alternatively, inadvertently encourage risky research because it is not explicitly prohibited.

Dennis M. Dixon, Ph.D., said that conventional peer review is not the place to factor into scoring of DURC and GOF research of concern. At NIH, such issues require additional review by the HHS Framework review group, which is impartial. Dr. Dixon described the reach-through concept: any proposal involving recombinant DNA research must be reviewed by NIH's Recombinant DNA Advisory Committee (RAC). The RAC guidelines have tremendous influence on behavior and practice in the United States. For the DURC guidelines, in addition to reviewing federally funded research, all non-federally funded research conducted at the same institutions must be reviewed. Dr. Denison said funding should not be seen as a viable carrot or stick in driving GOF research. Meritorious, highly scored research should be supported.

Dr. McDade asked Dr. Dixon for input on combining GOF research with the DURC review process. Dr. Dixon said he would assess whether there is way to create a crosswalk between the two topics; the two issues should not be considered in isolation. Dr. Stanley said the NSABB would be happy to weigh any NIH suggestions.

Michael W. Shaw, Ph.D., described some of the international aspects of data and material sharing. He reminded the NSABB that other countries may decide they do not like the limitations imposed and refuse to share biological samples for research which could have

potential side effects on international disease surveillance. Such a situation is a current problem with MERS samples.

Dr. Resnick asked whether stakeholders agree that the lack of a single entity for review adversely affects the situation. Dr. Denison said current strategies in place could accommodate questions about GOF research, and existing definitions and guidelines could be harmonized. Dr. Potter said institutions and investigators need to know whom to contact when confusion arises. Ms. Willis said there is no authority or oversight of private companies that may be working with certain concerning agents, and BSL-3 laboratories could be conducting risky research in her community without the public's knowledge. From a public health perspective, communities would like to be assured that some effective oversight is in place, said Ms. Willis.

Dr. Epstein said other federal bodies are addressing whether there should be a regulatory process around biosafety and biosecurity beyond select agents and toxins. Proposed rules and opportunities for public input are announced in the *Federal Register*.

PUBLIC COMMENT PERIOD

Dr. Casagrande said he initially thought that Gryphon's analysis would support Dr. Lipsitch's contention that most of the risk is related to events outside containment areas. Instead, it found that reports often conflated incidents with LAIs. Many of the incidents were bad events that have degraded public trust but have not caused infection. Dr. Casagrande also defended the inclusion of coronaviruses in the category of GOF research of concern and reiterated that comparators other than the 1918 influenza virus can be used to model the probability of potential negative events.

Dr. Meyer emphasized that the RBA concluded that GOF research is uniquely critical for strengthening the predictive utility of models and advancing science. She pointed to the CDC's use of GOF research findings along with epidemiological, environmental, and other data to identify new viruses as they emerge. Dr. Meyer said that in interviews, investigators identified a strong need for support of research to determine whether alternative approaches to GOF research are valid and meaningful. She also said that the field takes definitions very seriously, and investigators tend to err on the side of caution in determining when to halt GOF research.

Mr. Rudy said his county and state health departments seem to want to avoid the issues under discussion today, and efforts to get information from government entities, including public health authorities, are usually shut down. He was impressed by the call for qualified, independent reviewers. He noted that the NRC assigns an independent, on-site inspector to all nuclear facilities. The Fukushima nuclear reactor disaster shows what happens when owners and inspectors are "in bed together," said Mr. Rudy. He added that in the nuclear field, federal regulations require communities to have a first-responder program.

In response to a question raised earlier by Professor Wolf about whether insurance was a

consideration in conducting GOF research of concern in a BSL-3 laboratory, **Dr. Fouchier** said the considerations are the same as for research on wild-type viruses. Professor Wolf acknowledged that the insurance question goes beyond GOF research. Dr. Fouchier pointed out that many NSABB discussions about GOF research are not specific to GOF research, which complicates matters. He said the NSABB cannot resolve all the issues around dangerous pathogens in infectious disease research at the same time.

Dr. Lipsitch said insurance companies are certainly calculating the risks and thinking about consequences and probability. Most infectious agents studied in laboratories are not transmissible or countermeasures exist to protect against their spread. However, the magnitude of the consequences of an accident or release involving GOF research of concern is significantly higher.

Dr. Jasny said it would be helpful for journal editors to see annual progress reports submitted by investigators to federal funders. Such information would help minimize unanticipated events.

Dr. Palmer asked whether there should be more scrutiny of the overall structure of oversight. She encouraged the NSABB to identify issues that fall outside its mandate that require more investigation, more resources, or different authority and capacity.

Dr. Taylor said that when there is more community engagement and understanding, communities are proud to host laboratories. One step in that process is for individuals like Mr. Rudy to ask the public health commissioner for information. Individuals can also request information from IBCs under the *Freedom of Information Act*. Most public health laboratories would be delighted to have community members involved, said Dr. Taylor, because community awareness is particularly important when an incident occurs.

Mr. Park asked for suggestions from the research community on how to reduce reliance on GOF research, such as funding for research on the predictive value of other markers. **Dr. Denison** expressed skepticism about obtaining funding to assess alternatives. He gave an example that illustrated the lack of enthusiasm for funding foundational work in mouse hepatitis virus because it is not immediately relevant to SARS or MERS. He added that researchers try to do as much groundwork as possible using a safe surrogate, but that is not always an effective substitute for using an emerging human pathogen.

DISCUSSION OF UPCOMING NATIONAL ACADEMIES MEETING

Jo Husbands, Ph.D., Scholar/Senior Project Director, National Academies of Sciences

Dr. Husbands said the National Academies will take into account all of the input from this meeting for its March 10–11, 2016 gathering in Washington, D.C., at the National Academies' main building. Details are available at the project website.

The National Academies meeting will not seek to build consensus or make recommendations but rather provide a forum for discussion. It will be webcast, and the webcast will be archived. A transcript and meeting summary will be produced.

Individuals are encouraged to contact the planning committee with comments and suggestions for the agenda.

Following this NSABB meeting, the National Academies' planning committee will identify key issues to address, particularly those that will help the NSABB to move its process forward. The March National Academies meeting will allot time for discussion of the RBA. Dr. Husbands encouraged those interested to contact her by email (GOF@nas.edu) or sign up for the listserv via the project website.

NSABB DISCUSSION
Samuel L. Stanley, Jr., M.D., NSABB Chair

Dr. Stanley asked Board members what issues should be fleshed out in light of the tremendous input received on the draft recommendations, RBA, ethics paper, and policy landscape review. He called on each Board member for comments.

Dr. Miller suggested more discussion of the criteria for GOF research of concern, specifically resistance to control measures. Regarding ethical principles, he advocated for adopting a risk-based, adaptive, iterative approach and articulating it in the recommendations. He requested that Gryphon revise the RBA Executive Summary to include comparators other than the 1918 influenza virus, ideally before the National Academies meeting.

Theresa M. Koehler, Ph.D., said the NSABB should look at the degree to which social distancing should be considered as a countermeasure. The NSABB should home in on a mechanism for oversight and try to determine what will work and be acceptable.

Margie D. Lee, D.V.M., Ph.D., said she was troubled by the gaps between what the community and public health departments know about biosafety in local laboratories and what is happening. She expressed surprise that a major funder of GOF research does not require involvement of community public health systems.

Dr. Fitch raised concerns about accountability. If an event occurs, he asked, how will the public perceive the appropriateness of the review preceding the event? There should be consideration at each level—investigator, institution, government, and funder—of what might illuminate the criteria for review and where final approval should fall.

Ms. Grant called for synthesizing or coordinating policies and procedures around DURC and GOF. Instead of making detailed recommendations, the NSABB should guide the USG in pulling these issues together from the request for proposals through continuous monitoring.

Dr. Leach suggested addressing the possibility that investigators might move their research or publish their findings abroad to circumvent U.S. guidelines. She said NSABB recommendations should be general, not pathogen-specific, or the same issues would arise again in a year.

Dr. Hammarskjöld said the NSABB still needs to ensure that its recommendation are clear and that it lands the plane. The recommendations should not be subject to individual interpretation and must recognize that risk is not bimodal but falls on a spectrum.

Dr. McDade agreed that the NSABB's recommendations should be prescriptive enough to land the plane but not overly prescriptive. He asked whether NIH and others announce research awards to affected communities and public health entities. Dr. Wolinetz said all awards are public, but NIH defers to the awardees to do public outreach. She added that awardees should have, for example, emergency response plans involving public health entities. Dr. McDade suggested that organizations had systems in place to identify anything of interest in the *Federal Register,* and the same could be done for awards.

Dr. McDade was concerned that the ethical principles were not well integrated into the draft report. He asked for consideration on how current USG oversight of life sciences research involving pathogens might be improved, if members deemed current oversight inadequate. He also said the NSABB should keep in mind the difficulty of getting funding to attenuate strains and assess alternatives to GOF research and consider how important that is to consider as recommendations are developed.

Dr. Layton said she was struck by acknowledgement that there is some GOF research that makes everyone uncomfortable but it is hard to define it in way that anticipates future research. She suggested reviewing the criteria for GOF research of concern to determine whether all three conditions must be present. Regarding the proposed conceptual approach, she asked for input on how to ensure that no feasible alternative methods are available and how to verify that investigators have fully considered alternatives. Dr. Layton said there should be some assurance that state and local public health authorities are involved in discussions about GOF research at the proposal stage.

Dr. Berns said he looked forward to input from the National Academies meeting on several issues:

- The extent to which knowledgeable people think there are holes in the decision-making process and what is missing from the existing oversight frameworks
- The notion that it does not matter how a pathogen is produced but rather what was produced and how dangerous it is perceived to be
- A substantive approach to addressing GOF research internationally

Dr. Kanabrocki sought more clarification about experiments that should not be done. Many of the examples given describe experiments that lack scientific merit, which may be the only ones that fall into this category. He said international issues must be part of NSABB deliberations even if the recommendations only apply to U.S. policy, and he hoped the National Academies meeting would give insight on how to strike a balance.

Dr. LeDuc said the NSABB should discuss whether all GOF research of concern should be conducted at BSL-4 laboratories. The NSABB should organize thoughts about what

the risks of GOF research are and what mitigation strategies should be in place. It should provide an organizational framework that takes into account different capabilities and study designs and allows some flexibility. Dr. LeDuc said the NSABB should articulate that data on LAIs should not be equated with the number of incidents or spills, because there have been few infections, and the risk should not be overstated. Many good examples exist around influenza that demonstrate good safety procedures are in place to prevent the spread of disease. Dr. LeDuc added that recommendations should not be limited to influenza, but the NSABB should consider whether coronaviruses should be included as GOF research of concern because of the potential negative impact on the field.

Dr. Resnick said he is concerned that existing regulations may not be robust enough to support the NSABB's recommendations. The recommendations should be actionable, practical, and clear, and they must be expressed in the context of existing policy and regulations. Dr. Resnick questioned whether it is possible to execute the NSABB's recommendations in an effective way.

Jean L. Patterson, Ph.D., wondered why the numbers of laboratory accidents and infections vary so widely depending on the source. She said the field is more likely to overreport than underreport, and she would like to see the data to understand why opponents of GOF research of concern believe there are so many more accidents and infections than reported. Dr. Patterson said there should be more communication with the public so that they do not only hear inaccurate information. She asked whether someone could identify the accurate data and address the sources of the alternative numbers that have been presented.

Stephen S. Morse, Ph.D., agreed that the NSABB should not create a list of pathogens but rather describe criteria for GOF research of concern. Emerging viruses will always pose challenges, and recommendations should be useful for addressing future problems. While it may be too late to change the terms used, there are problems with definitions, and the NSABB should be concerned about different interpretations of what constitutes a security threat, a public health threat, or a biosafety threat. Dr. Morse said there is an opportunity to raise awareness about biosafety and laboratory safety. He said it is hard to find data on LAIs, but the data should be more available for the sake of transparency.

Dr. Morse said GOF research is intended to benefit public health but apparently public health entities are left out of discussion. Much is still being learned about how to ensure effective public engagement; it is essential that the public know what is happening in its communities and have an opportunity to give input and shape processes. Dr. Morse hoped the NSABB's deliberative process could be a model for public engagement, but he noted that the private sector is only tangentially affected by this effort, and international partners still need to be engaged.

Dr. Endy urged the National Academies meeting to explore the agreements and legislation that led to the formation of the National Transportation Safety Board. He said guidelines are needed that will help the field be proactive and stay ahead of potential

threats. The NSABB should respond to the demand for oversight and accountability. While there are lots of reasons not to farm out the task of oversight, there seems to be a call for a broader charge (beyond HHS and NIH).

David L. Woodland, Ph.D., indicated that the draft recommendations seem to be close to the mark, and that he thinks they are reasonable. He called for more discussion, probably at the National Academies meeting, about whether to include resistance to control measures in the definition of GOF research of concern. Also, the NSABB must provide clear recommendations to those who have to develop the new regulations and guidelines.

Professor Wolf said it would be helpful at the National Academies meeting to dig into the specifics about oversight design so that the NSABB recommendations are clear. The lack of data and conflicting data are a concern. Good governance requires built-in data collection. Professor Wolf hoped to hear more about existing data sources, how to combine them, and how to reconcile divergent data. She suggested the NSABB strengthen its claim that current oversight mechanisms, if effectively implemented, cover most of the issues at hand by providing supporting evidence and outlining areas that are not adequately addressed. The NSABB report should also better address international collaboration, harmonization, coordination, and other issues.

Professor Wolf suggested Gryphon model probabilities using a different comparator, such as the 2009 H1N1 virus, and better demonstrate what moves an item from one risk category into another. The NSABB should capture some of the documents mentioned by presenters, such as reports by the NRC and the National Academies, the Biological Weapons Convention, and work on biosecurity frameworks, international GOF research, and oversight design. The NSABB should also provide a visual description of the proposed oversight framework.

Dr. Macrina said the NSABB's report should address international issues in more depth, and those should be raised at the National Academies meeting. For the sake of balance, it should also include the risks to the next generation of researchers of curtailing GOF research of concern.

Dr. Stanley appreciated all the helpful input. He was pleased that the principles outlined in the draft were generally accepted, and he agreed that more attention should be given to how recommendations would be implemented. Dr. Stanley also agreed with suggestions to draw more insights from outside the field of biological science.

Dr. Stanley said the NSABB has laid out a framework, and while he believes the wording could be improved in some areas, he would rather not tinker with it until input is gathered from the National Academies meeting. He invited ex officio members to give input.

Dr. Epstein said frustration with the ambiguity of definitions and recommendations has been continuous. He suggested more consideration of whether scientific merit alone is sufficient to justify GOF research of concern. Should such research be limited to instances in which there is a public health rationale? Dr. Epstein also asked for deeper

assessment of whether biosecurity risks significantly add to the consequences that biosafety risks may entail.

Dr. Hall said it is not sufficient to trust that GOF research of concern will be conducted by well-known investigators working in high-containment laboratories and asked – what if the influenza research by Dr. Fouchier had taken place in a non-democratic country that is not as friendly to the United States as the Netherlands? Three questions should be posed about research anywhere in the world: Who is doing the work? What is the motivation? Is the laboratory safe? The acceptability of the recommendations may depend on whether they could serve as a model for the rest of the world.

Mr. Park pointed out that this issue came to light through the funding process, which is just one vehicle for review and action. The NSABB should take into account the different policy options available to respond to concerns about biosafety versus biosecurity versus information security. Data collection is difficult; requiring reporting can discourage reporting, so anonymization and other tactics must be discussed in order to address the lack of quality data on incidents.

Mr. Park continued that discussion about international issues to date have been limited to raising awareness about U.S. policies and eliciting information from other governments. The NSABB should address whether there are drivers that the United States wants to affect or whether minimum biosafety standards should be developed.

Dr. Kanabrocki noted that incident reporting is already required under the Select Agent Program. In the past, codes of conduct and reporting have been a key part of biosafety, and the GOF WG should further discuss these matters. Dr. Stanley agreed that PIs should understand the potential risk and take responsibility. There is a need for educational tools to help guide the application of codes of conduct.

Dr. Macrina said when the issue of DURC arose 10 years ago, there was discussion about an oath of responsible conduct. Dr. Berns said the American Society for Microbiology and other professional societies have well-articulated codes of conduct. Dr. Hammarskjöld said education is key; particularly for IBCs. Dr. Stanley noted that education efforts could be part of implementation. Professor Wolf said including case studies could help bolster implementation. She suggested revisiting the impressive suite of materials developed regarding DURC as a starting point; Dr. Stanley agreed.

Dr. McDade said that previous discussions about the culture of responsibility and current focus on education point to a leadership problem. Evaluation of what works in well-run laboratories could reveal helpful information.

CLOSING REMARKS AND ADJOURNMENT
Samuel L. Stanley, Jr., M.D., NSABB Chair

Dr. Stanley thanked all the participants, especially the public, panelists, and experts who listened and contributed. He thanked the *ex officio* members for their helpful

contributions and extended special thanks to the Board members and the WG members in particular. Dr. Stanley said the WG would reconvene to discuss the input from this meeting and prepare for the National Academies meeting in March, when the NSABB would hear more from colleagues across country and the world on these important issues. The meeting was adjourned at approximately 1 p.m.