Progress Report from NSABB Working Group

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Co-chair, NSABB Working Group

September 28, 2015

Debate About Gain-of-Function (GOF) Studies

What is gain-of-function research?

- "Gain of function" is used to refer to any modification of a biological agent that confers new or enhanced activity

- **A specific subset** of GOF studies have raised biosafety and biosecurity issues:
  - Studies that generate certain pathogens with enhanced pathogenicity or transmissibility (by respiratory droplets) in mammals
  - Ongoing debate about the risks and benefit

USG Deliberative Process for Gain-of-Function Studies

Risk-Benefit Assessment

Gryphon Scientific will conduct risk-benefit assessment of GOF studies

National Academies

Convene public forums to generate broad discussion and receive public and other stakeholder input

NSABB

Serves as the official advisory body for providing advice on oversight of this area of dual use research

The Charge to the NSABB

Task 1

Advise on the design, development, and conduct of risk-benefit assessment of GOF studies

☑ **Deliverable 1**

Framework for the design and conduct of risk and benefit assessments of GOF studies

Task 2

Provide formal recommendations to the USG on the conceptual approach to the evaluation of proposed GOF studies

❑ **Deliverable 2**

Recommendations to the USG informed by the results of the risk and benefit assessments and other input

Progress

- **October 2014:** NSABB tasking and initial discussion; formed working group with broad range of expertise to draft advice on the risk-benefit assessment

- **November:** NSABB issued statement recommending more guidance for the community about the GOF funding pause; USG issued FAQs and worked closely with relevant researchers

- **December:** National Academies hosted two-day meeting; broad discussions of risks, benefits, risk-benefit assessments, risk mitigation, public engagement

- **May:** NSABB approved its framework for guiding the risk-benefit assessment; formed new working group to focus on drafting recommendations on a conceptual approach to considering GOF proposals

NSABB Working Group

After developing the NSABB's Framework for guiding the risk-benefit assessment, the NSABB formed a new working group to:

1. Continue to provide input, as needed, on the conduct of the risk-benefit assessments

2. Develop draft recommendations on a conceptual approach to the evaluation of proposed GOF studies

NSABB Working Group: Roster

NSABB voting members

- Kenneth Berns (Co-chair)
- Joseph Kanabrocki (Co-chair)
- Craig Cameron
- Drew Endy
- Christine M. Grant
- Marie-Louise Hammarskjöld
- Clifford Houston
- Theresa Koehler
- Marcelle Layton
- James LeDuc
- Margie Lee
- Frank Macrina
- Joseph McDade
- Stephen Morse
- Jean Patterson
- Gary Resnick
- Susan Wolf
- David Woodland

Federal Agency Representatives

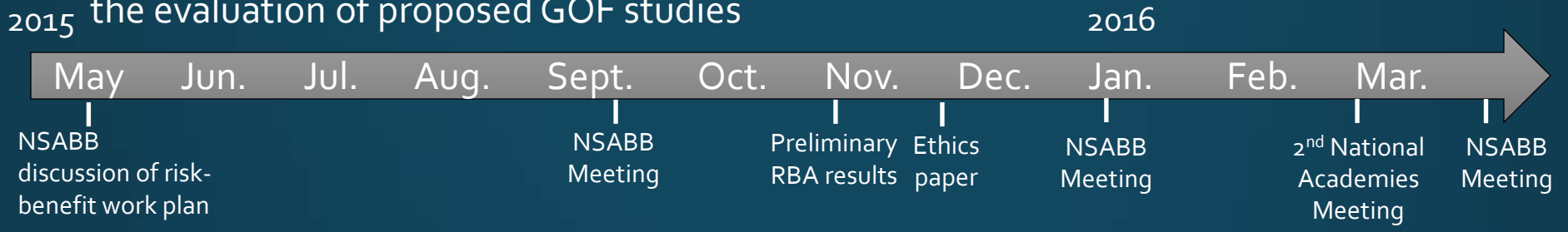
- Todd Anderson (DOE)
- Diane DiEuliis (HHS)
- Dennis Dixon (NIH)
- Gerald Epstein (DHS)
- Meg Flanagan (DOS)
- Wendy Hall (DHS)
- Teresa Hauguel (NIH)
- Betty Lee (DOC)
- Robert Miceli (ODNI)
- Kimberly Orr (DOC)
- Christopher Park (DOS)
- Diane Post (NIH)
- David B. Resnik (NIH)
- Sharlene Weatherwax (DOE)

Initial Task: Discuss Risk-Benefit Assessment Work Plan

- WG reviewed Gryphon Scientific's work plan
- NIH working with Gryphon to ensure that the NSABB's Framework continues to guide the assessments
- Risk-benefit assessment will be critical to NSABB's deliberations, providing:
  - Quantitative information about biosafety risks
  - Semi-quantitative information about biosecurity risks
  - Benefits associated with GOF studies
  - Comparison of the relative risks associated with GOF and non-GOF studies, including risks from NOT doing the GOF study
  - Risks and benefits associated with alternative approaches

Work Plan and Timeline

Remaining Task: Develop draft recommendations on a conceptual approach to the evaluation of proposed GOF studies



Phase I
Policy Examination, Research & Information Gathering

- Provide feedback on Gryphon's work plan
- Identification of information and topics to explore
- Examination of relevant domestic and international policies
- Examination of perspectives from funding agencies, journals, and others
- Development of draft principles that might guide deliberations

Phase II
Interpretation, Analysis & Synthesis of Information and Results

- Deliberations to focus on translating information about risk and benefits into recommendations/decisions
- Develop an approach for considering and interpreting the risk-benefit assessment
- Analyze risk-benefit assessment, determine whether there are GOF studies that raise concerns that may not be adequately addressed under current policy
- Begin to outline draft findings and recommendations

Phase III
Development of Recommendations

- Continued analysis of risk-benefit assessment and consideration of other information gathered
- Develop draft findings and recommendations to be discussed at meeting hosted by National Academies
- Develop formal report to the US government containing findings and recommendations

Conduct of risk & benefit assessments

Phase 1: Policy Examination, Research & Information Gathering

Two-day In-person Working Group Meeting

Examining the Policy Landscape for Pathogen Research and Gain-of-Function Studies

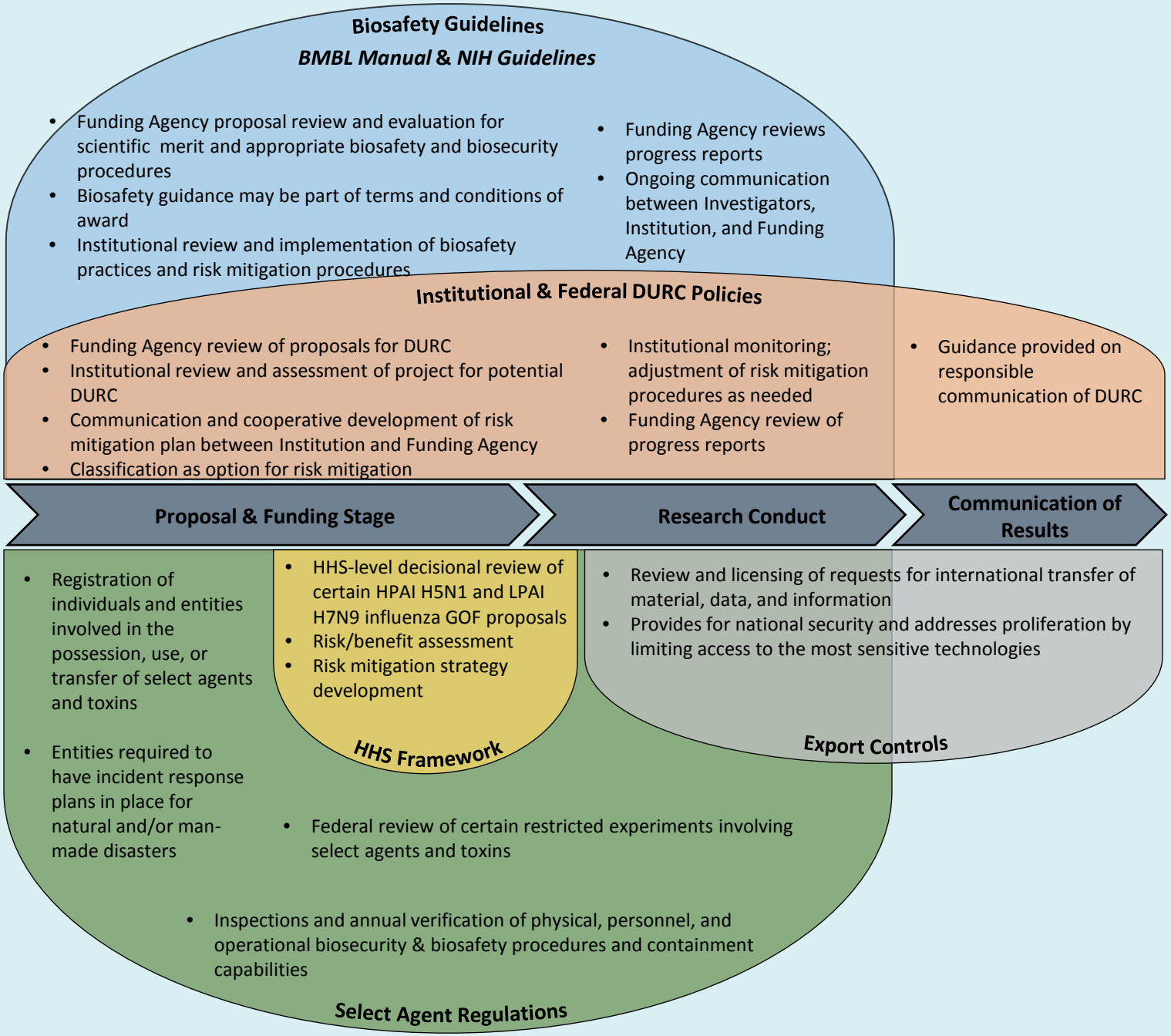
1. Current U.S. Policy Landscape for Research Involving High-Consequence Pathogens
2. Case Studies: Examining How Oversight Policies Apply During the Life Cycle of GOF Studies
3. International Policy Landscape
4. Decision-Making Frameworks and Options for Oversight of GOF Studies

Broad Perspectives on GOF Studies

1. Funding Agency Perspectives
2. Perspectives from Scientific Journals
3. National Security Perspectives

Current U.S. Policy Landscape

- Biosafety oversight
  - *Biosafety in Microbiological and Biomedical Laboratories-5th*
  - NIH *Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules*
- The Federal Select Agent Program
- U.S. Policies for Oversight of Dual Use Research
- HHS Funding Framework for certain avian influenza GOF studies
- Export Controls



BMBL – Federal guidance on biosafety and containment practices for life science research involving biological infectious agents or hazardous material

NIH Guidelines – Federal guidance for oversight of biosafety and containment for research involving recombinant or synthetic nucleic acid molecules

DURC Policies – Federal & Institutional oversight of biosecurity risks, particularly involving the misuse of research information, products, and technologies

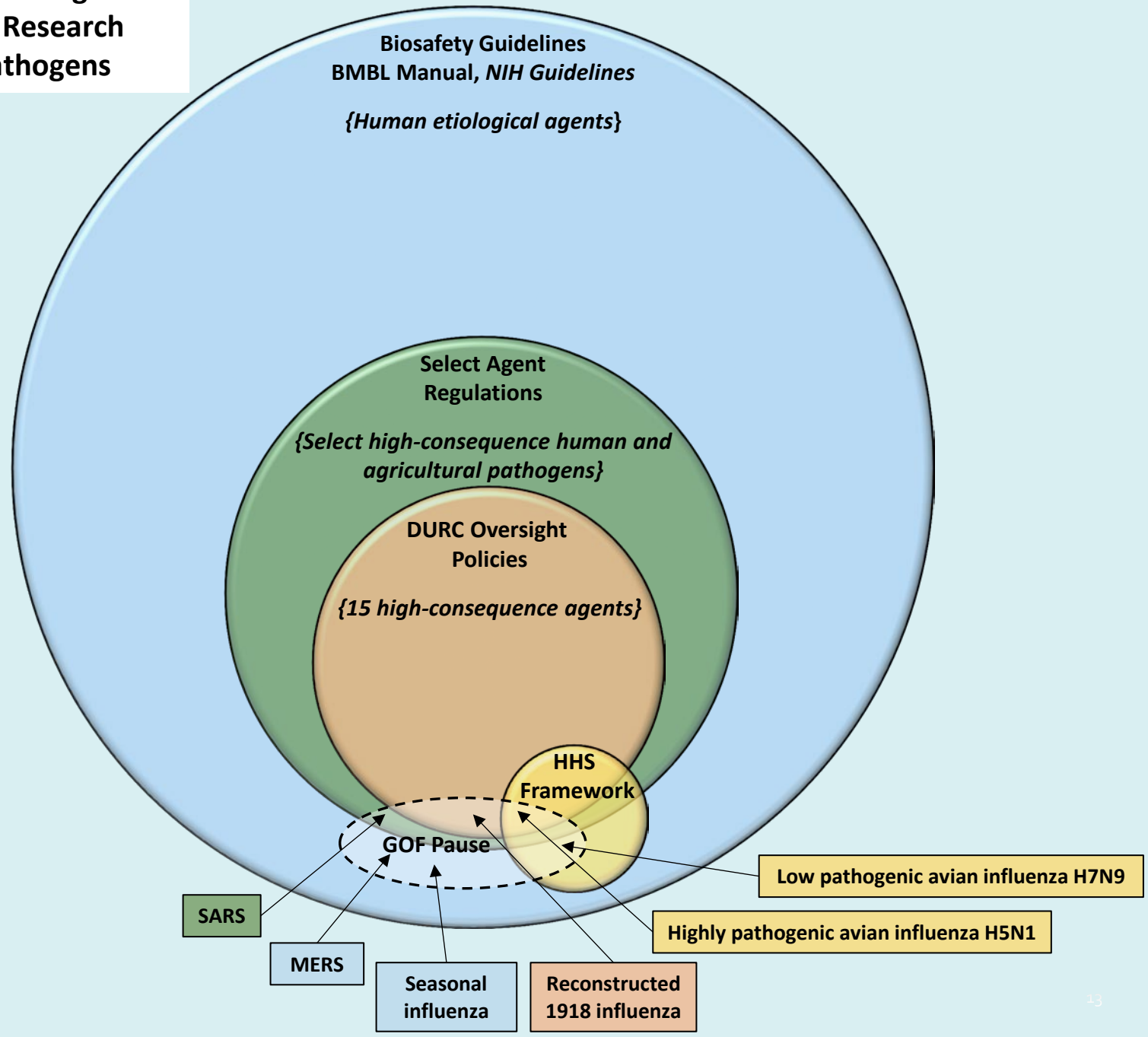
Select Agent Regulations – Federal & Institutional oversight of biosecurity and biosafety risks associated with the use and transfer of high-consequence agents & toxins

HHS Framework – HHS department-level review and approval of proposed gain-of-function experiments involving HPAI H5N1 & LPAI H7N9

Export Controls – Federal oversight to limit access to, and international proliferation of, sensitive material and technologies

USG Oversight of Life Sciences Research Involving Pathogens

Scope of USG Oversight of Life Sciences Research Involving Pathogens



International Policy

- Biosafety, biosecurity, dual use, and GOF issues are being discussed internationally, though terminology and oversight mechanisms vary
  - In general, biosafety oversight for pathogen research is similar to US (containment and practices based on assessment of risk)
  - In many cases, biosecurity oversight is part of ethical frameworks, codes of conduct, or GMO regulations
- Germany and Canada require certain GOF studies with high path avian influenza be performed at BSL4
- Regulation through funding is not always a feasible option
  - Increasing number of researchers get funding from non-government sources
  - Some countries choose not to have funding entities oversee research, instead placing oversight within the purview of other government agencies

Policy Options and Decision Frameworks

- **A permissive approach:** allow activities unless environment, health, security are clearly compromised
- **A precautionary approach:** limit activities unless environment, health and security are clearly protected
- **Planned adaptation:** a systematic approach to deal with controlling risks in the face of uncertainty

Emerging Technologies Challenge Policy Frameworks

- **Access:** Biological reagents and equipment become less expensive and more readily available

- **Funding:** Projects are being supported by non-governmental and even crowd-sourced funding mechanisms

- **Publishing:** Findings can be self-published online or posted through pre-print servers

The traditional points of oversight may be changing

Funding Agency Perspectives

- Funders support a variety of GOF studies to advance their missions
  - Basic science
  - Public health and preparedness
  - Food and agriculture
  - Innovation
- GOF studies that involve generating pathogens with enhanced pathogenicity or transmissibility are a small fraction of overall research portfolios
- Awareness among domestic and international funders of DURC/GOF is increasing
  - The funding agencies consulted by the WG all had considered the DURC issue and had processes in place for managing DURC
  - U.S. funding agencies, when applicable, had developed processes for identifying projects subject to the U.S. GOF funding pause

Perspectives from Journals

- Awareness of the DURC/GOF issue among journals is increasing
  - Science, Nature, the ASM journals, and others review manuscripts for biosecurity concerns
- Journal editors noted that identifying DURC and trying to manage risks at the publication stage is difficult
  - Redaction or restricted communication make reproducibility and subsequent peer evaluation difficult
  - Some noted the need for a Federal committee to aid journals in risk assessments and DURC determinations
- Pre-print servers, online publication, and data sharing initiatives represent a trend toward open access

Security Perspectives

- Avoid assumptions about terrorist/criminal motives or capacities
- Insider threat
- Communicating dual use information is a security challenge
- Classified intelligence information is important for security professionals but there are limits to its utility
- Security community can assist institutions by raising awareness of the general threats that exist in the biological space

Case Studies

The WG examined several published GOF studies

Aim of this exercise:

- Discuss what existing policies and guidelines for the oversight of research involving pathogens would apply to the studies

- Discuss how risks are identified and managed throughout the research life cycle

Principles for Guiding NSABB Deliberations

The WG has identified a set of draft principles intended to:

- Guide NSABB deliberations
- Outline its approach to interpreting the risk-benefit assessment and developing recommendations

1. **The NSABB deliberations should focus on defining the problem at hand then include broad consideration of possible solutions.**

Principles for Guiding NSABB Deliberations

2. **NSABB will consider the potential risks and benefits of a broad range of GOF studies involving influenza, SARS, and MERS viruses in order to identify those that may raise significant concerns that should be addressed.**
    - NSABB will aim to develop recommendations that are grounded in broadly-applicable concepts and principles that could apply to GOF studies involving other agents that may require evaluation in the future.

3. **NSABB will consider the risks and benefits associated with alternative research approaches to GOF research to understand whether or not these may substitute for or complement GOF studies.**

Principles for Guiding NSABB Deliberations

4. NSABB recommendations will be informed both by data and information about potential risks and benefits as well as values that will guide the evaluation and comparison of these risks and benefits.

5. Uncertainties are inherent in any analyses. NSABB will seek to document important areas of uncertainty in any data or analysis when necessary.

6. NSABB will publicly debate its draft recommendations and describe in its report any dissenting views that may vary substantially from the Board's recommendations.

Principles for Guiding NSABB Deliberations

7. NSABB will consider current USG policies and guidelines, determine whether they adequately address risks associated with GOF research, and make recommendations that are consistent with that determination.

8. NSABB will be mindful that the Board's recommendations and U.S. policy decisions will also influence non-USG funders of life sciences research.

9. NSABB will consider whether there are certain studies that should not be conducted under any circumstances, and if so, articulate the critical characteristics of such studies.

10. Maintaining the public's confidence and trust in life sciences research is critical and must be taken into account as recommendations are formulated.

Preliminary Observations and Findings

1. **As with all life sciences research involving pathogens, GOF studies entail inherent risks.**
   - The greatest concern associated with GOF studies involving generation of pathogens with pandemic potential would be the intentional or accidental release of a highly transmissible, highly dangerous pathogen to which a significant proportion of the global human population is susceptible.

2. **In considering the value of GOF studies, it is essential to consider both the risks and the benefits of the study.**

3. **There are many types of GOF studies and not all of them have the same levels of risks**.

Preliminary Observations and Findings

4. **The U.S. government has a robust policy framework in place for managing risks associated with life sciences research.**
   - It will be important to determine whether these policies adequately manage risks associated with GOF studies involving pathogens with pandemic potential.

5. **There are several points throughout the research life cycle where risks can be managed and oversight can be applied.**
   - Policies and oversight alone will likely not be sufficient to fully address the associated risks.
   - Seek a culture of "citizenship" whereby all participants in the research enterprise have a sense of shared responsibility for its continued beneficial contribution.

Preliminary Observations and Findings

6. An adaptive policy approach is a desirable way to ensure that oversight and risk mitigation measures remain commensurate with the risks associated with the research.

7. While information associated with scientific research could be misused to cause harm, managing information risks at the publication stage is difficult.

8. Biosafety and biosecurity are international issues requiring global engagement.

Next Steps

WG to continue its deliberations

November: WG to review results of risk-benefit assessment

January 7 & 8: Full NSABB meeting to discuss WG draft recommendations

March: Meeting hosted by National Academies, to discuss NSABB draft recommendations and related issues

Reference Slides

Policy References

- Occupational Health and Safety Administration standards for chemical hazards, biological hazards, other hazards, and personal protective equipment.
- Biosafety in Microbiological and Biomedical Laboratories, 5th edition
- NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules
- USG Policy for Oversight of Life Sciences Dual Use Research of Concern, March 2012
- USG Policy for Institutional Oversight of Life Sciences Dual Use Research of Concern, September 2014
- Select agent regulations, 7 CFR Part 331, 9 CFR Part 121, 42 CFR Part 73
- Export administration regulations
- International Traffic in Arms Regulations

NATIONAL SCIENCE ADVISORY BOARD FOR BIOSECURITY

Working Group on Evaluating Risks and Benefits of GOF Studies
July 23 - 24, 2015

Bethesda North Marriott Hotel and Conference Center
Salon H
5701 Marinelli Road, Bethesda, MD

MEETING AGENDA

Day 1: Examining the policy landscape for pathogen research and gain-of-function studies

8:30 am – 8:50 am	**Welcome and Introductions**

Introduction of NSABB Working Group Members
Christopher J. Viggiani, Ph.D.
Executive Director, NSABB

Opening Remarks
Kenneth I. Berns, M.D., Ph.D.
Joseph Kanabrocki, Ph.D., C.B.S.P.
NSABB Working Group Co-Chairs

Review of the Working Group Tasks and Goals for the Meeting
Christopher J. Viggiani, Ph.D.

8:50 am – 9:00 am	**The HHS Biosafety and Biosecurity Framework**

Nicole Lurie, M.D., M.S.P.H.
Assistant Secretary for Preparedness and Response
Department of Health and Human Services

9:00 am – 10:30 am	**Current U.S. Policy Landscape for Research Involving High-Consequence Pathogens**

Questions to address:

- How do the laws, regulations, policies, and guidelines apply to studies involving pathogens?
- Do these apply to the agents or types of GOF studies under consideration? If so, how?
- How do these help to identify and mitigate potential risks associated with pathogen research and/or GOF studies?

Biosafety Oversight
Joseph Kanabrocki, Ph.D., C.B.S.P.
Associate Vice President for Research Safety
Professor of Microbiology
University of Chicago

The CDC Select Agent Program
Robbin Weyant, Ph.D., RBP (ABSA)
Director, Division of Select Agents and Toxins
Center for Disease Control and Prevention

Oversight of Dual Use Research
Susan Coller-Monarez, Ph.D.
Assistant Director, National Health Security and International Affairs
Office of Science and Technology Policy
Executive Office of the President

Export Controls and Dual Use Research
Kimberly Orr, Ph.D.
Chemical and Biological Controls Division
Bureau of Industry and Security
Department of Commerce

10:30 am – 10:45 am	**Break**
10:45 am – 12:00 pm	**Case Studies: Examining How Oversight Policies Apply During the Life Cycle of GOF Studies**

Session aims:

- To examine three case studies based on published gain-of-function (GOF) work
- To discuss what existing U.S. Government (USG) policies and guidelines for the oversight of research involving high-consequence pathogens would apply were the studies to be proposed and conducted in the U.S. today
- To discuss how risks are identified and managed throughout the research life cycle

Christopher J. Viggiani, Ph.D.

12:00 pm – 1:00 pm	**Lunch**
1:00 pm – 2:30 pm	**International Policy Landscape**

Questions to address:

- What laws, regulations, policies and guidelines issued by foreign governments or international organizations apply to dual use research?
- Do these apply to the GOF studies under consideration?
- How do these laws, regulations, policies, and guidelines help identify and manage potential risks associated with pathogen research, DURC, and/or GOF studies?
- What lessons can be learned from how other countries and international organizations approach the DURC and GOF issues?

Christopher Park
Director, Biological Policy Staff
Bureau of International Security and Nonproliferation
Department of State

Jo Husbands, Ph.D.
Scholar/Senior Project Director
Board on Life Sciences of the US National Academy of Sciences

Marianne Donker, Ph.D.
Director of Public Health, Ministry of Health
The Netherlands

David Franz, D.V.M., Ph.D.
Consultant
Former Commander, United States Army Medical Research Institute for Infectious Diseases

2:30 pm – 4:00 pm	Decision-Making Frameworks and Options for Oversight of GOF Studies

Questions to address:

- What decision-making frameworks exist that involve making risk and benefit determinations?
- Can any of these be applied to decisions about GOF oversight?
- What lessons can be learned from the oversight of emerging technologies or research in other scientific disciplines that might inform the development of policy options for GOF studies?
- What key considerations and principles should be brought to bear when identifying options for the oversight of GOF studies?

Kenneth Oye, Ph.D.
Associate Professor of Political Science and Engineering Systems
Massachusetts Institute of Technology

Robert Temple, M.D.
Deputy Director for Clinical Science
Center for Drug Evaluation and Research
Food and Drug Administration

Todd Kuiken, Ph.D.
Senior Program Associate
Science and Technology Program
Wilson Center

Arturo Casadevall, M.D., Ph.D.
Alfred and Jill Sommer Professor and Chair
Bloomberg Distinguished Professor
Johns Hopkins University

4:00 pm - 4:30 pm	Working Group Discussion

Kenneth I. Berns, M.D., Ph.D.
Joseph Kanabrocki, Ph.D., C.B.S.P.

4:30 pm	Adjourn

Day 2: Examining broad perspectives on GOF studies

8:30 am – 8:45 am	Review of Day 1

Kenneth I. Berns, M.D., Ph.D.
Joseph Kanabrocki, Ph.D., C.B.S.P.
NSABB Working Group Co-Chairs

8:45 am – 9:45 am	Funding Agency Perspectives

Questions to address:

- Are DURC and/or GOF studies currently or previously funded by your agency/organization?
- If so, are such projects subject to additional review or oversight?
- How do such studies fit into your agency's broader portfolio and/or contribute to its overall mission?
- How are the risks and benefits associated with such studies identified and addressed?

Linda Lambert, Ph.D.
Chief, Respiratory Disease Branch
Division of Microbiology and Infectious Diseases
NIAID, NIH

Eileen Thacker, D.V.M., Ph.D., DACVM
National Program Leader
Animal Health and Food Safety
U.S. Department of Agriculture

Ruxandra Draghia-Akli, M.D., Ph.D.
Director of the Health Directorate
Research DG of the European Commission

Michael Shaw, Ph.D.
Senior Advisor for Laboratory Science
Office of Infectious Diseases
Centers for Disease Control and Prevention

9:45 am – 10:45 am	Perspectives from Scientific Journals

Questions to address:

- Does your publication have an existing review policy for manuscripts that raise dual use issues?
- If so, what does that policy or review entail? Would GOF studies fall within that policy and receive any additional review?
- Given your perspective as an editor or publisher of scientific research, how do GOF studies fit within the broader scientific context of research that you would publish?
- How do GOF studies contribute to the scientific knowledge base?
- How do you think GOF studies are viewed by the scientific community and the general public?

Arturo Casadevall, M.D., Ph.D.
Bloomberg Distinguished Professor
Johns Hopkins University
Founding Editor in Chief, mBio

Kalyani Narasimhan, Ph.D.
Executive Editor
Nature Publishing Group

Barbara Jasny, Ph.D.
Deputy Editor of Insights
Science

Richard Sever, Ph.D.
Assistant Director
Cold Spring Harbor Laboratories Press
bioRxiv ("bio-archive")

10:45 am – 11:00 am	Break
11:00 am – 12:00 pm	A National Security Perspective

Questions to address:

- What types of biological threats and malicious actors are of concern to the national security communities?
- How are the risks associated with GOF studies evaluated by the national security communities and how do the risks fit into the broader national security context?
- Do GOF studies generate information or describe methodologies that present unique national security concerns?
- What are the strengths, limitations, and uncertainties associated with classified information? Is such information necessary to make judgments about the risks associated with GOF studies? What level of classification would be needed?
- If classified information is needed, how can such information be accessed and used to support the assessment of risks associated with GOF studies within the security and intelligence community, and those without security clearances?

Jerry Epstein, Ph.D.
Deputy Assistant Secretary for Chemical, Biological,
Nuclear, and Radiological Policy
Department of Homeland Security

Patricia Long, J.D., LL.M.
Deputy Assistant Secretary for Security, Intelligence and Counterintelligence
Office of Security and Strategic Information
Department of Health and Human Services

12:00 pm – 12:15 pm	Concluding Remarks

Kenneth I. Berns, M.D., Ph.D.
Joseph Kanabrocki, Ph.D., C.B.S.P.
NSABB Working Group Co-Chairs

12:15 pm	Adjourn

Case Studies

The following studies were discussed by the NSABB WG:

H5N1 hybrid viruses bearing 2009/H1N1 virus genes transmit in guinea pigs by respiratory droplet (Zhang et. al., Science, 2013)

A Mouse-Adapted SARS-Coronavirus Causes Disease and Mortality in BALB/c Mice (Roberts et. al., PLoS Pathogens, 2007)

Airborne Transmission of Influenza A/H5N1 Virus between Ferrets (Herfst et. al. Science, 2012)

Identification, Characterization, and Natural Selection of Mutations Driving Airborne Transmission of A/H5N1 Virus (Linster et. al. Cell, 2014)

Effect of receptor binding domain mutations on receptor binding and transmissibility of avian influenza H5N1 viruses (Maines et. al., Virology, 2011)

Virulence and transmissibility of H1N2 influenza virus in ferrets imply the continuing threat of triple-reassortant swine viruses (Pascua et. al., PNAS, 2012)