Session IV
Discussion of NSABB Preliminary Findings and Draft Recommendations

Ken Berns, M.D., Ph.D.
Joseph Kanabrocki, Ph.D., C.B.S.P.
Co-chairs, NSABB Working Group

GOF Studies of Concern – Draft Recommendations

The WG has formulated draft recommendations regarding GOF studies of concern for consideration:

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.

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.

GOF Studies of Concern – Draft Recommendations

Draft recommendations continued

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

4. The U.S. government 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.

Proposed Conceptual Approach for Funding Potential GOF Studies of Concern

1. Identify proposals anticipated to involve GOF studies of concern, as described by the following attributes:

i. The pathogen generated is highly transmissible in a relevant mammalian model

ii. The pathogen generated is significantly virulent in a relevant mammalian model, and

iii. The pathogen generated is likely resistant to control measures or more capable of being spread among human populations than currently circulating strains of the pathogen.

2. Review proposal to determine whether they meet the following criteria:

i. 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.

ii. 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.

iii. 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.

iv. The investigator and institution proposing the research have the demonstrated capacity to carry it out safely and securely.

v. The research information is anticipated to be broadly and legally shared in order to realize its potential benefits to global health.

vi. 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.

vii. The proposed research is ethically justifiable.

Proposals not meeting these criteria should not be funded.

3. Fund, do not fund, or fund with required additional risk mitigation measures or stipulations.

4. Conduct the research in accordance with applicable oversight policies and employ any additional risk mitigation strategies that were identified at the time of funding or that are deemed necessary during the course of the research.

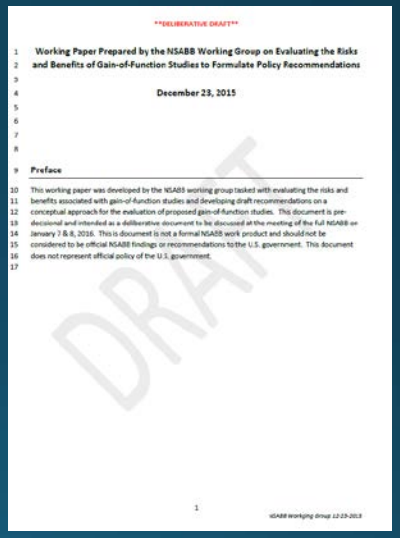
i. Research should be reviewed regularly at the institutional level

ii. Research should be reviewed regularly by the Federal funding agency

Session IV – Discussion of NSABB Preliminary Findings and Draft Recommendations

<u>Discussion Panelists:</u>

- Marc Lipsitch, D. Phil., Harvard School of Public Health
- Jill Taylor, Ph.D., Wadsworth Center, NYS Department of Public Health
- Mark Denison, M.D., Vanderbilt University
- Yoshihiro Kawaoka, D.V.M., Ph.D., University of Wisconsin, Madison
- Philip Potter, Ph.D., St. Judes Children's Research Hospital
- Beth Willis, Frederick Citizens for Bio-lab Safety



DELIBERATIVE DRAFT

Working Paper Prepared by the NSABB Working Group on Evaluating the Risks and Benefits of Gain-of-Function Studies to Formulate Policy Recommendations

December 23, 2015

Preface

This working paper was developed by the NSABB working group tasked with evaluating the risks and benefits associated with gain-of-function studies and developing draft recommendations on a conceptual approach for the evaluation of proposed gain-of-function studies. This document is pre-decisional and intended as a deliberative document to be discussed at the meeting of the full NSABB on January 7 & 8, 2016. This is document is not a formal NSABB work product and should not be considered to be official NSABB findings or recommendations to the U.S. government. This document does not represent official policy of the U.S. government.

DRAFT

1

nSABB Working Group 12-23-2015

Submit questions: nsabb@od.nih.gov

NSABB Preliminary Findings and Draft Recommendations

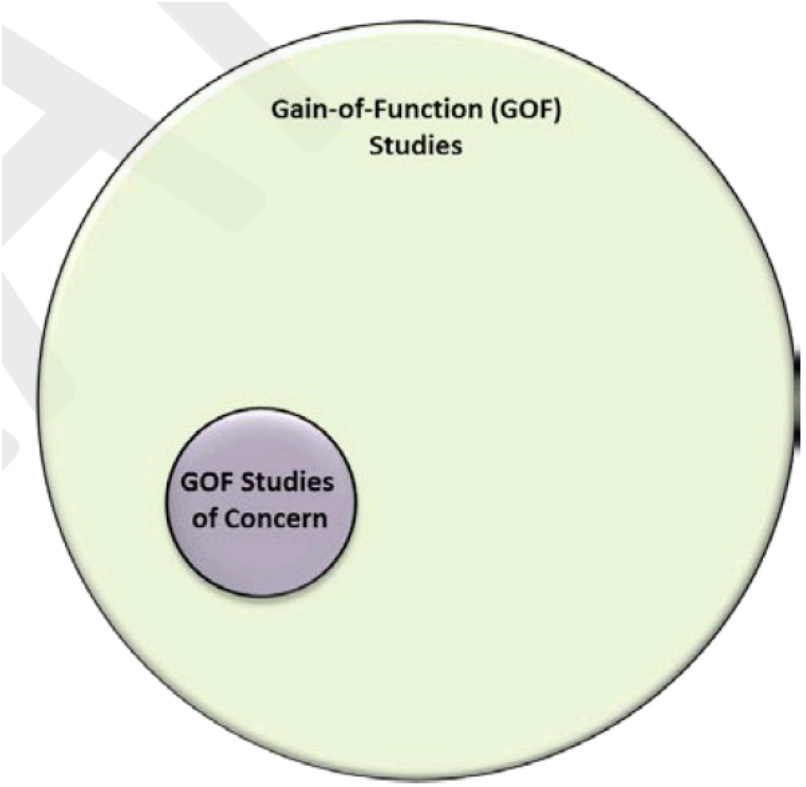
Questions for Discussion

- 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 review of GOF studies of concern 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?

Points

1. NSABB draft's GOF of concern focus is appropriate
2. RBA significantly underestimates risks of GOF of concern
3. GOF of concern risk estimates in Gryphon RBA are nonetheless so high that the experiments should not be performed
4. Gryphon benefit assessment shows major COI and overstates benefits
5. NSABB draft wrongly states that current processes are adequate for regulating GOF of concern
6. US should not perform or fund GOF of concern; other experiments should follow regular processes

Appropriate focus on GOF of concern



Draft NSABB response
Fig. 4

- Reasonably anticipated to produce a pathogen that is highly transmissible and highly virulent in humans
- I would not emphasize escaping countermeasures, because these are uncertain and, in most cases, not globally available (e.g., vaccines)

Gryphon RBA underestimates absolute risk for GOF of concern

- Escape scenarios systematically assume the LAI happens in a high-containment lab – contrary to repeated experience
  - CDC anthrax, Ebola, influenza 2014; DoD anthrax 2015; etc.
- Absolute risk assessment assumes LAI probabilities 10-1000-fold lower than recent data show from BSL3
- Probability of escaping local control is inexplicably low, inconsistent with prior estimates, including by Lloyds-Smith model
  - For coronaviruses because they misread the literature on R0 (3 not 1.5)
  - For influenza viruses, partly because of unsubstantiated assumption of effective community mitigation
- Repeatedly suggests that work with 1918 H1N1 is an acceptable baseline level of risk without justification
  - And uses wrong CFR for 1918, making that arbitrary baseline even higher

GOF of concern is unacceptably risky even with optimistic numbers from Gryphon RBA

Pr(LAI with modified HPAI in BSL3 per labs year) = 3/2000 x 0.1 = 0.015%

Pr(outbreak that escapes local control|LAI) = 0.4%

Pr(outbreak that escapes local control)/BSL3 labs/year = 6×10^5

Attack rate | pandemic = 25%

CFR = 5%

Population = 7×10^9

Expected fatalities | pandemic = 9 x 10

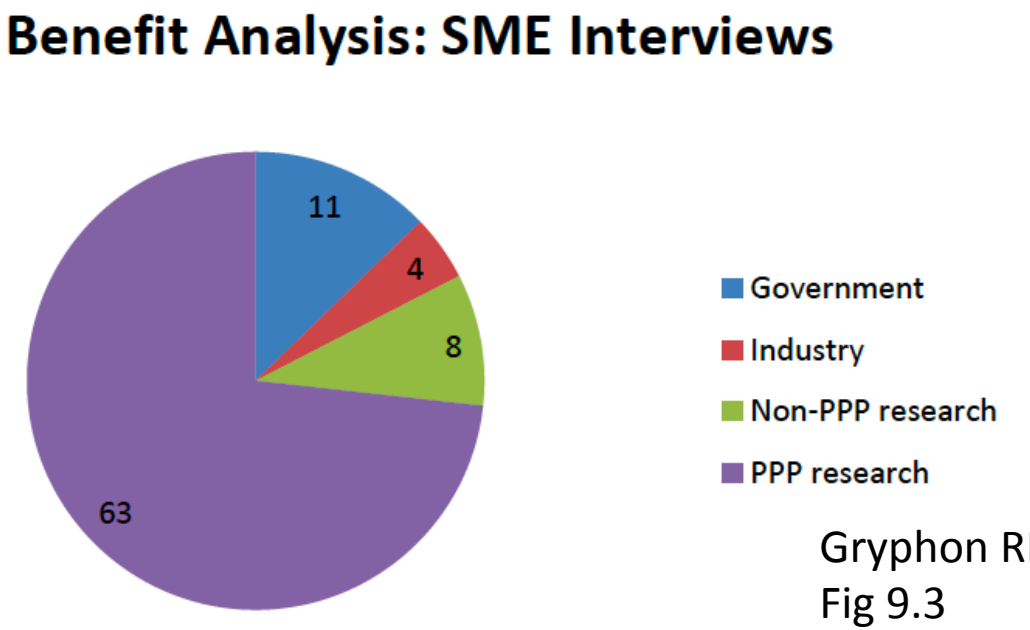
Risk = 54 expected fatalities per lab-year. No IRB would permit a year's worth of research with 54 expected fatalities.

Lynn Klotz. Sources Table 6.2, Fig. 6.59,

Exaggerated benefit claims

- 14 site visits to speak to GOF/PPP lab PIs, students, postdocs

- >80% of sources were researchers or funders for PPP studies



Gryphon RBA
Fig 9.3

Benefits: General observations

- Almost all GOF of concern benefits will be limited largely to rich countries (BA pp. 438, 442, 444). GOF of concern unjustly imposes risks on whole populations who would be denied the potential benefits.
- Contrary to assertions in BA, nearly all benefits claimed for GOF of concern are not unique to GOF but can be achieved by alternatives. Given that alternative approaches are risk free (for pandemic risk), it would be imprudent and unethical to use GOF approaches instead of alternatives.

Example: PPP studies unncecessary and possibly misleading for prepandemic risk assessment

Mutation claimed to be significant based on GOF by Davis or Schultz-Cherry *mBio* 2014	Prior studies not involving PPP creation that identified these mutations	Counterexamples
H5 H7N9 HA Q222L HA	Chutinimitkul 2010 Jongkon 2009 Yamada 2006 Liu 2009 Stevens 2006 Russell 2006 Tharakaraman 2013	CONTEXT DEPENDENCE: Changes do not quantitatively shift receptor binding in related H5 strains (Tharakaraman 2013)
H5N1 HA S133A S135N S123P S155N	Yamada 2006 Yang 2007	
H7N9 HA T156A Q222L	Stevens 2008 Wang 2011 Gao 2013 NEJM	
PB2 E627K D701N	Subbarao 1993 De Jong 2011	MISLEADING INFERENCE: Both absent in 2009pdm. Would have led to its misclassification as low risk

Existing processes inadequate

- Prior to funding pause, HHS framework inadequate
  - Risk and benefit assessment completely non-quantitative and largely credulously accepting of investigator's claims (Wisconsin IBC)
  - HHS Department-level review done privately, no public input or scrutiny
  - HHS-funded GOF (Richard et al. Nature) on H7N9 was published in same issue as HHS H7N9 Framework: Behind the curve
- Even during pause, SARS GOF paper published without explanation of how it was permitted
- Clear COI placing funders and performers of GOF work, and those supported by its indirect costs, as reviewers of global risk
- No resources provided for IBCs or others to assess GOF risk, benefit

Written comments available at www.cambridgeworkinggroup.org/news

1. NSABB draft's GOF of concern focus is appropriate
2. RBA significantly underestimates risks of GOF of concern
3. GOF of concern risk estimates in Gryphon RBA are nonetheless so high that the experiments should not be performed
4. Gryphon benefit assessment shows major COI and overstates benefits
5. NSABB draft wrongly states that current processes are adequate for regulating GOF of concern
6. US should not perform or fund GOF of concern; other experiments should follow regular processes

EXTRA SLIDES

LAI are likely to occur outside GOF labs

On Dec. 22, a worker at CDC's biosafety level 4 lab in Atlanta — where scientists wear spacesuit-like, full-body protective gear that filters the air they breathe — accidentally confused some specimens and sent an un-killed sample from an Ebola experiment to a lower-level lab with minimal protections. – *USA TODAY* 2/4/2015

…a culture of non-pathogenic avian influenza was unintentionally cross-contaminated at the CDC influenza laboratory with the highly pathogenic H5N1 strain of influenza and shipped to a BSL-3 select-agent laboratory operated by the United States Department of Agriculture (USDA). – CDC press release, 7/11/14

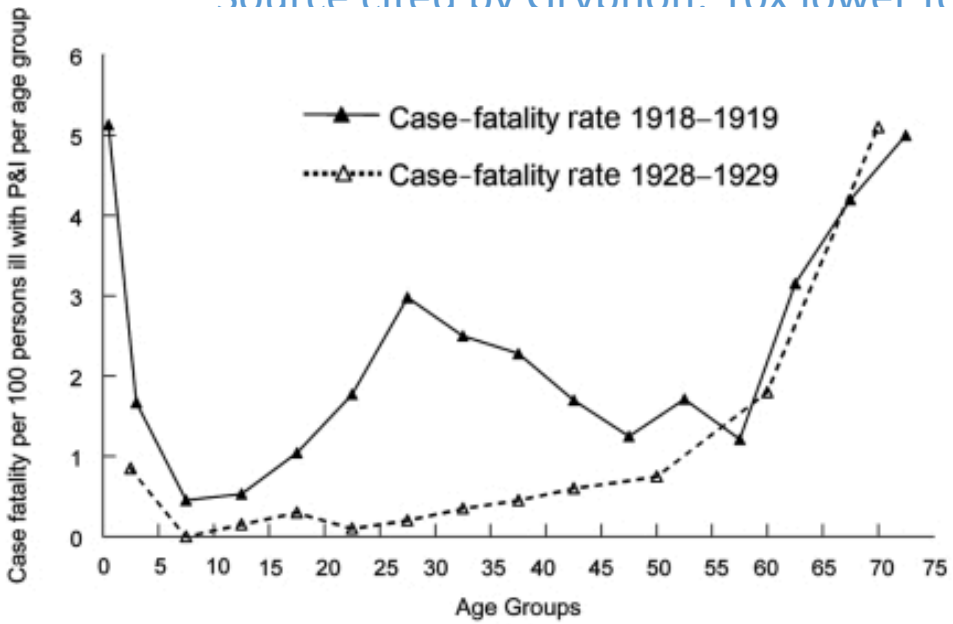
Mr. Work said that live anthrax samples had been sent from Dugway to 86 government and private labs and other facilities in the United States and seven other countries: Australia, Britain, Canada, Germany, Italy, Japan and South Korea. – *NYT* 7/23/15

Errors in CFR

Gryphon report

Table S7. Percentage of Pandemic Influenza Infected Individuals who Die, by Pandemic	
Pandemic	**Percent Mortality of Infected Persons**
1918 Spanish Flu[82]	10% - 20%
2009 H1N1[83]	0.00010% - 0.00043%

Source cited by Gryphon: 10x lower for 1918



2009 systematic review : 10-100 higher: We included 77 estimates of the case fatality risk from 50 published studies, about one-third of which were published within the first 9 months of the pandemic. We identified very substantial heterogeneity in published estimates, ranging from less than 1 to more than 10,000 deaths per 100,000 cases or infections. The choice of case definition in the denominator accounted for substantial heterogeneity, with the higher estimates based on laboratory-confirmed cases (point estimates = 0-13,500 per 100,000 cases) compared with symptomatic cases (point estimates = 0-1,200 per 100,000 cases) or infections (point estimates = 1-10 per 100,000 infections). Risk based on symptomatic cases increased substantially with age. Wong JY, Kelly H, Ip DK, Wu JT, Leung GM, Cowling BJ. Case fatality risk of influenza A (H1N1pdm09): a systematic review. Epidemiology. 2013 Nov;24(6): 830-41. doi: 10.1097/EDE.0b013e3182a67448. Review.

Q1: Are there GOF studies that may be conducted but should require an additional level of review or oversight? If so, what should the oversight entail? Should the oversight occur at the federal or institutional level or both?

A1:

- We support the NSABB definition for “GOF studies of concern” and agree with general requirement for enhanced review and oversight.

- We support a model similar to USG Policy for Institutional Oversight of DURC.
    - Adapt DURC regulations?
    - Already include high path flu; add SARS, MERS, other pathogens with pandemic potential.
    - Expand IRE scope of review to include GOF experiments with potential to create pathogen with pandemic potential.

Jill Taylor, Ph.D.
Director, Wadsworth Center, NYSDOH

Q2: How well does the NSABB's draft working paper identify the GOF studies of greatest concern?

A2:

- We support the approach of identifying the highest risk studies as those resulting in key triad of phenotypes that create pandemic risk → transmissibility + virulence + immune/therapeutic evasion.

- We caution, however, that GOF studies that produce pathogens with only one or two of these phenotypic attributes may still present significant biosafety risks.
    - Need to be sure that GOF regulations do not leave "gap" in safety oversight.

Jill Taylor, Ph.D.
Director, Wadsworth Center, NYSDOH

Q3: Are there GOF studies that should not be conducted? If so which studies and why?

A3:

- Banning studies “a priori” is not a good policy.
- Each individual GOF study should be subject to a thorough risk/ benefit review at both the institutional and federal level, taking into account the current scientific and public health context.
- A “one-size-fits-all” methodology with respect to policy approaches should be avoided. Several of the potential policy approaches discussed may be required to cover all circumstances.

Jill Taylor, Ph.D.
Director, Wadsworth Center, NYSDOH

Q4: How well would the NSABB's draft principles and criteria permit the review of GOF studies that have raised concerns and inform decision about whether to fund such studies?

A4:

- Build on the existing DURC/Guidelines programs to create an appropriate review process.
- Weakness in guidance principle "iv" .
  - Need a mechanism to ensure investigator and institution have the appropriate "culture of safety and responsibility"
  - Who makes this determination?

Q5: Are there specific risk mitigation measures that should be required for certain GOF studies to be conducted?

A5:

- What did we learn from Ebola? For some GOF studies, there will be a need to:
  - Elevate containment requirements.
  - Require a “buddy” system.
  - Elevate occupational health requirements.
- Require on-going internal and external step-wise review of progress.
- Involve local and/or state epidemiology and public health officials in the review process.

➡ Need to strengthen “culture of responsibility” at all institutions.

Gain-of-function studies of Concern

University of Wisconsin-Madison
Yoshihiro Kawaoka, DVM, PhD

Regulations on H5N1 transmission studies

H5N1 transmission studies are highly regulated.

NSABB meeting, October 22, 2014

Working Paper by the NSABB Working Group on

Evaluating the Risks and Benefits of Gain-of-Function Studies to Formulate Policy Recommendations

Recommendation 1

Research proposals involving **GOF studies of concern** entail the greatest risks and should be reviewed carefully…

Example

An experiment that is anticipated to generate **avian influenza** viruses that are **airborne transmissible** in mammals if the starting virus is **pathogenic in humans**.

Recommendation 2

In general, oversight mechanisms for GOF studies of concern should be incorporated into **existing policy frameworks**.

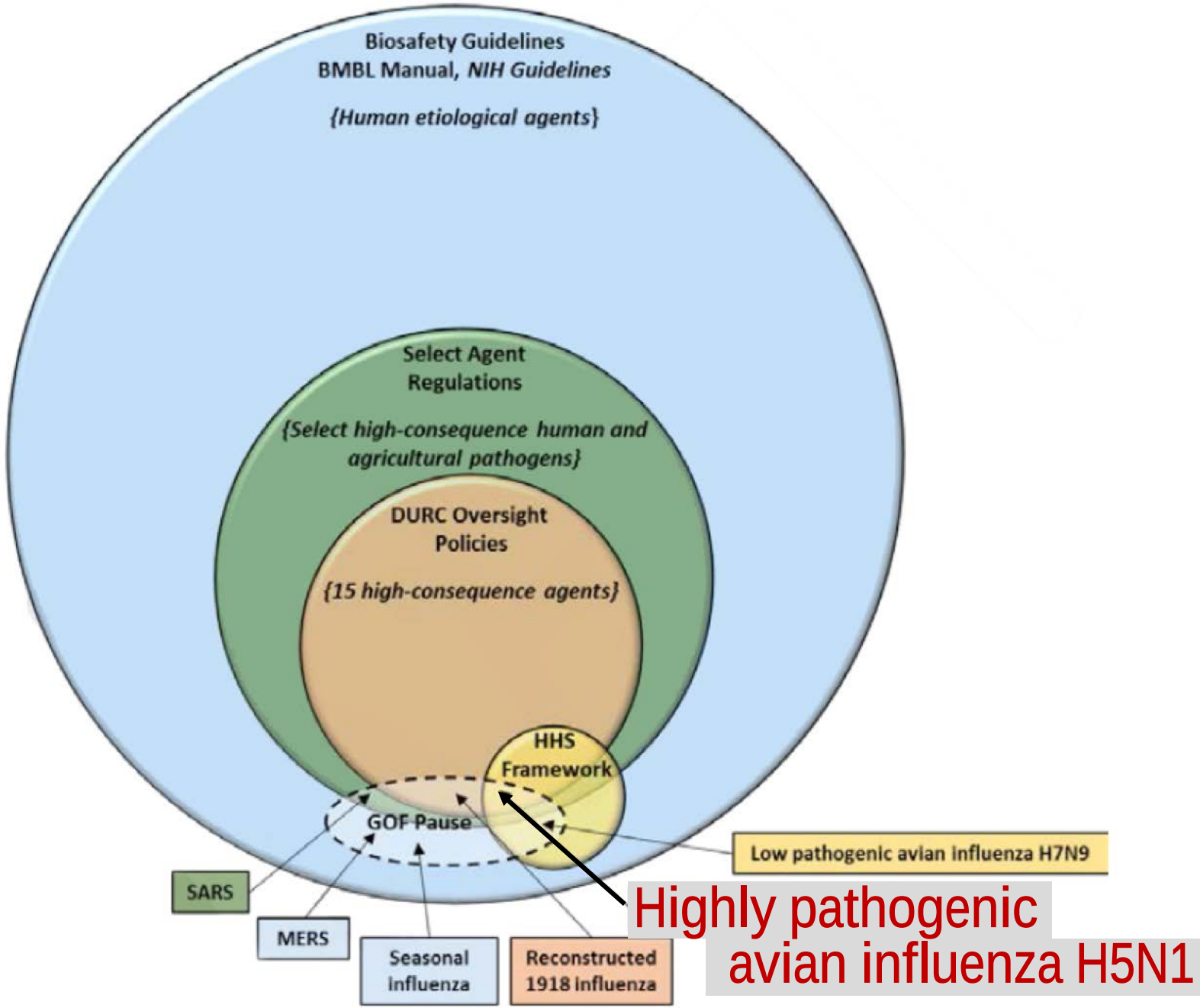
Working Paper by the NSABB Working Group on

Evaluating the Risks and Benefits of Gain-of-Function Studies to Formulate Policy Recommendations

Key Finding 2.

The U.S. government has effective **policy frameworks** in place for managing the risks associated with life sciences research.

- NIH Guidelines
- BMBL (Biosafety in Microbiological and Biomedical Laboratories)
- Policies for the Federal and institutional oversight of DURC
- Select Agent Regulations
- Export control regulations
- International treaties and agreements, and other relevant policies
- Framework for guiding funding decisions for certain GOF studies involving H5N1 and H7N9 influenza viruses


Biosafety Guidelines
BMBL Manual, NIH Guidelines
{Human etiological agents}
Select Agent Regulations
{Select high-consequence human and agricultural pathogens}
DURC Oversight Policies
{15 high-consequence agents}
HHS Framework
GOF Pause
Low pathogenic avian influenza H7N9
SARS
MERS
Seasonal influenza
Reconstructed 1918 influenza
Highly pathogenic avian influenza H5N1

Example

Grant Number: 2R01AI069274-06A1
Principal Investigator(s): Yoshihiro Kawaoka
Project Title: Transmissibility of avian influenza viruses in mammals

Aim 1: To identify the **mechanisms** that control **H5N1 virus transmissibility** in mammals

Aim 2: To characterize the contribution of **viral genes other than HA** to H5N1 virus transmissibility

Key Finding 2.
The U.S. government has effective **policy frameworks** in place for managing risks associated with life sciences research.

- NIH Guidelines
- BMBL (Biosafety in Microbiological and Biomedical Laboratories)
- Policies for the Federal and institutional oversight of DURC
- Select Agent Regulations
- Export control regulations
- International treaties and agreements, and other relevant policies
- Framework for guiding funding decisions for certain GOF studies involving H5N1 and H7N9 influenza viruses

Policy frameworks

- NIH Guidelines
- BMBL (Biosafety in Microbiological and Biomedical Laboratories)
- Policies for the Federal and institutional oversight of DURC
- Select Agent Regulations
- Export control regulations
- International treaties and agreements, and other relevant policies
- Framework for guiding funding decisions for certain GOF studies involving H5N1 and H7N9 influenza viruses

Policy frameworks

- NIH Guidelines
- BMBL (Biosafety in Microbiological and Biomedical Laboratories)

] Reviewed by IBC prior to grant submission

- Policies for the Federal and institutional oversight of DURC
- Select Agent Regulations
- Export control regulations
- International treaties and agreements, and other relevant policies
- Framework for guiding funding decisions for certain GOF studies involving H5N1 and H7N9 influenza viruses

Oversight

Policy frameworks

- NIH Guidelines
- BMBL (Biosafety in Microbiological and Biomedical Laboratories)
- Policies for the Federal and institutional oversight of DURC

UW-Madison DURC Subcommittee:

Members have expertise in microbiology, virology, biosafety, biosecurity, infectious disease, public health, applicable regulations, and risk mitigation.

UW-Madison Biosecurity Task Force:

Regularly reviews the research program and ongoing activities of the laboratory.

The task force comprises individuals with expertise in biosafety, facilities, compliance, security, law, communications, information security, and public health.

Written comments for NSABB meeting Jan 7-8, 2016

Marc Lipsitch, DPhil

Harvard T.H. Chan School of Public Health

Cofounder, Cambridge Working Group

Contains original written comments submitted December 31, 2015 plus additional comments (on benefits) submitted January 3, 2016. Additional comments added to this version concern the Benefit Assessment and are in dark red font.

Dear Chairman Stanley and Members of the NSABB:

Comment I.6. **The suggestion to use existing regulatory approaches for regulating GOF of concern requires that institutional oversight have the capacity to deal with this topic, making fine distinctions that have not yet been defined, much less codified in ways that can be applied at the institutional level.** There is no reason to think that Institutional Biosafety Committees have the requisite expertise to perform risk-benefit evaluations on this scale. As an example, the minutes of the University of Wisconsin IBC obtained by *Nature* for GOF work by Prof. Kawaoka (http://www.nature.com/polopoly_fs/7.18249!/file/WISC_Review.pdf) contain no numerical estimates of risk (that is to say, do not perform risk assessment, although they assert on p. 1 that it includes a risk benefit assessment) and accept uncritically all assertions

- Numerical estimates of risk are not done by the University of Wisconsin-Madison DURC Subcommittee.
- This is precisely why both institutional and federal (the HHS review group) oversite of DURC is needed.

Policy frameworks

- NIH Guidelines
- BMBL (Biosafety in Microbiological and Biomedical Laboratories)
- Policies for the Federal and institutional oversight of DURC
- Select Agent Regulations
- Export control regulations
- International treaties and agreements, and other relevant policies
- Framework for guiding funding decisions for certain GOF studies involving H5N1 and H7N9 influenza viruses

Policy frameworks

- NIH Guidelines
- BMBL (Biosafety in Microbiological and Biomedical Laboratories)
- Policies for the Federal and institutional oversight of DURC
- Select Agent Regulations
- Export control regulations
- International treaties and agreements, and other relevant policies
- Framework for guiding funding decisions for certain GOF studies involving H5N1 and H7N9 influenza viruses

Oversight

Policy frameworks

- NIH Guidelines
- BMBL (Biosafety in Microbiological and Biomedical Laboratories)
- Policies for the Federal and institutional oversight of DURC
- Select Agent Regulations

UW-Madison Registration

- Historically 3 years
- Rigorous inspections by the CDC and APHIS (Both planned and unannounced)
  - Facilities
  - Training
  - SOPs
  - Drills

Policy frameworks

- NIH Guidelines
- BMBL (Biosafety in Microbiological and Biomedical Laboratories)
- Policies for the Federal and institutional oversight of DURC
- Select Agent Regulations
- Export control regulations
- International treaties and agreements, and other relevant policies
- Framework for guiding funding decisions for certain GOF studies involving H5N1 and H7N9 influenza viruses

Policy frameworks

- NIH Guidelines
- BMBL (Biosafety in Microbiological and Biomedical Laboratories)
- Policies for the Federal and institutional oversight of DURC
- Select Agent Regulations
- Export control regulations
- International treaties and agreements, and other relevant policies
- Framework for guiding funding decisions for certain GOF studies involving H5N1 and H7N9 influenza viruses

Oversight

Policy frameworks

- NIH Guidelines
- BMBL (Biosafety in Microbiological and Biomedical Laboratories)
- Policies for the Federal and institutional oversight of DURC
- Select Agent Regulations
- Export control regulations
- International treaties and agreements, and other relevant policies
- Framework for guiding funding decisions for certain GOF studies involving H5N1 and H7N9 influenza viruses

We ensure our research activities are in compliance with these guidelines and regulations.

Policy frameworks

- NIH Guidelines
- BMBL (Biosafety in Microbiological and Biomedical Laboratories)
- Policies for the Federal and institutional oversight of DURC
- Select Agent Regulations
- Export control regulations
- International treaties and agreements, and other relevant policies
- Framework for guiding funding decisions for certain GOF studies involving H5N1 and H7N9 influenza viruses

February 21, 2013

Framework for Guiding **Funding Decisions** about Research Proposals with the Potential for Generating **Highly Pathogenic Avian Influenza H5N1 Viruses** that are **Transmissible** among Mammals by Respiratory Droplets

Grant Number: 2R01AI069274-06A1
Principal Investigator(s): Yoshihiro Kawaoka
Project Title: Transmissibility of avian influenza viruses in mammals

After the above grant proposal was peer-reviewed, it was then reviewed by the **HHS review group**, which includes participants from 8 different **agencies** with multidisciplinary expertise, to:

- evaluate the proposed research according to the **7 criteria** outlined in the Framework
- review the funding agency's risk assessment and the risk measures in place.

The 7 criteria

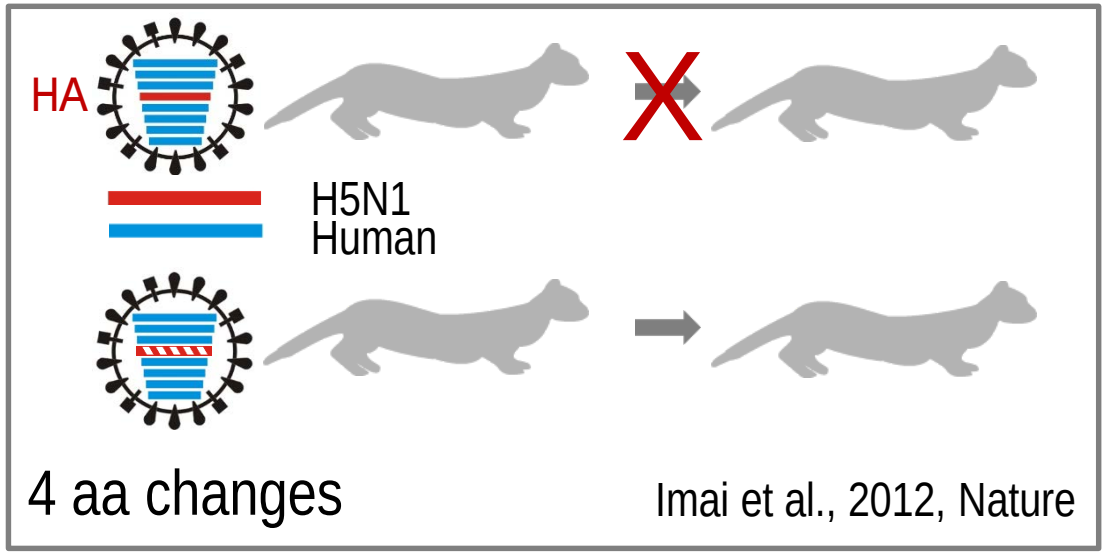
1. The virus anticipated to be generated could be produced through a natural evolutionary process
2. The research addresses a scientific question with high significance to public health
3. There are no feasible alternative methods to address the same scientific question in a manner that poses less risk than does the proposed approach
4. Biosafety risks to laboratory workers and the public can be sufficiently mitigated and managed
5. Biosecurity risks can be sufficiently mitigated and managed
6. The research information is anticipated to be broadly shared in order to realize its potential benefits to global health
7. The research will be supported through funding mechanisms that facilitate appropriate oversight of the conduct and communication of the research

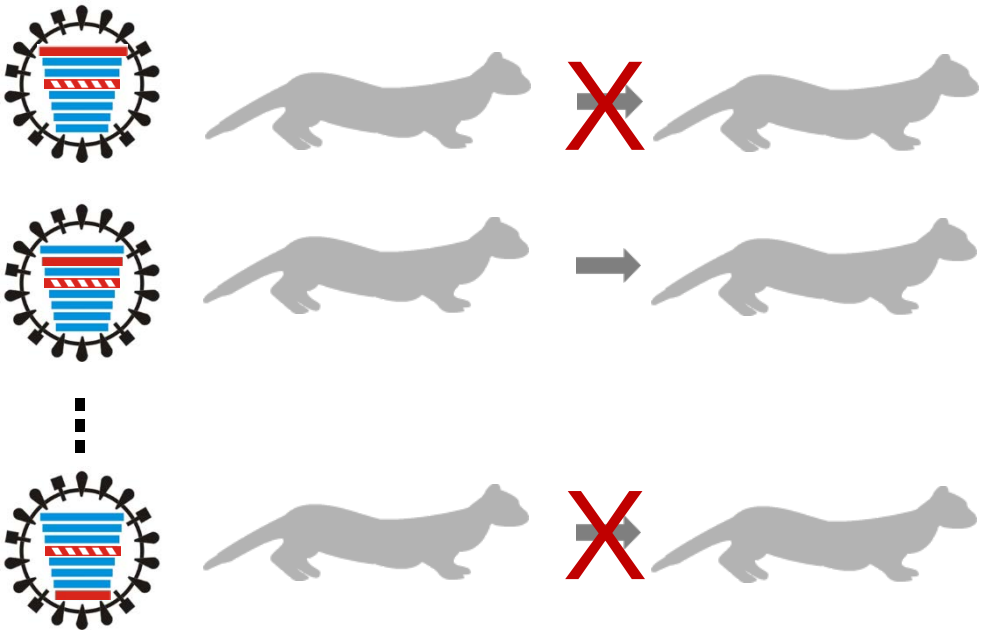
The HHS review group

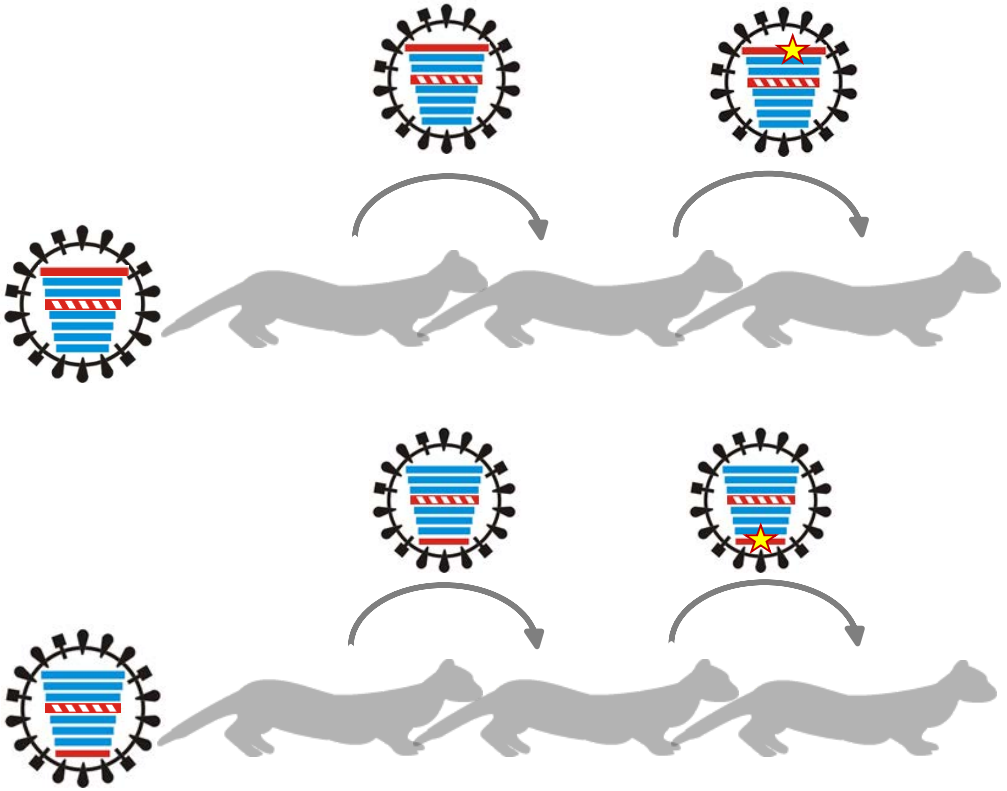
"determined that the proposed research is acceptable for funding with the exception of a set of experiments within Aim 2."

"Specifically, reassortant viruses which lose the ability to transmit among mammals would be serially passaged in the ferret model to select variants that regain transmissibility and these variants would be assessed for genetic changes."

Experimental design







The HHS review group

"The HHS review group felt that the viruses generated in these experiments were unlikely to be produced through a natural evolutionary process (Framework criterion one), and alternative methods with less risk could be used to address the same scientific question (Framework criterion three)."

7 criteria

1. The virus anticipated to be generated could be produced through a natural evolutionary process
2. The research addresses a scientific question with high significance to public health
3. There are no feasible alternative methods to address the same scientific question in a manner that poses less risk than does the proposed approach
4. Biosafety risks to laboratory workers and the public can be sufficiently mitigated and managed
5. Biosecurity risks can be sufficiently mitigated and managed
6. The research information is anticipated to be broadly shared in order to realize its potential benefits to global health
7. The research will be supported through funding mechanisms that facilitate appropriate oversight of the conduct and communication of the research

The HHS review group

"The HHS review group felt that the viruses generated in these experiments were unlikely to be produced through a natural evolutionary process (Framework criterion one), and alternative methods with less risk could be used to address the same scientific question (Framework criterion three)."

"NIAID funding **may not be used** to perform these **serial passaging** experiments."

February 21, 2013

Framework for Guiding Funding Decisions about Research Proposals with the Potential for Generating Highly Pathogenic Avian Influenza H5N1 Viruses that are Transmissible among Mammals by Respiratory Droplets

Grant Number: 2R01AI069274-06A1
Principal Investigator(s): Yoshihiro Kawaoka
Project Title: Transmissibility of avian influenza viruses in mammals

After the above grant proposal was peer-reviewed, it was then reviewed by the HHS review group, which includes participants from 8 different agencies with multidisciplinary expertise, to:

- evaluate the proposed research according to the 7 criteria outlined in the Framework
- review the funding agency's risk assessment and the risk measures in place.

February 21, 2013

Framework for Guiding Funding Decisions about Research Proposals with the Potential for Generating Highly Pathogenic Avian Influenza H5N1 Viruses that are Transmissible among Mammals by Respiratory Droplets

Grant Number: 2R01AI069274-06A1
Principal Investigator(s): Yoshihiro Kawaoka
Project Title: Transmissibility of avian influenza viruses in mammals

After the above grant proposal was peer-reviewed, it was then reviewed by the HHS review group, which includes participants from 8 different **agencies** with multidisciplinary expertise, to:

- evaluate the proposed research according to the 7 **criteria** outlined in the Framework
- **review the funding agency's risk assessment and the risk measures in place.**

In addition, the HHS review group asked about:

- Exposure Protocol
- Quarantine and Isolation Policy
- Animal protocols
- Risk assessments
- Communication strategies

Working Paper by the NSABB Working Group on

Evaluating the Risks and Benefits of Gain-of-Function Studies to Formulate Policy Recommendations

Recommendation 2

In general, oversight mechanisms for GOF studies of concern should be incorporated into **existing policy frameworks**.

on

ction Studies to

Key Finding 2.

The U.S. government has effective **policy frameworks** in place for managing risks associated with life sciences research.

- HHS guidance
- BMBL (Biosafety in Microbiological and Biomedical Laboratories)
- Policies for the federal and institutional oversight of DURC
- Select Agent Regulations
- Export control regulations
- Various other laws and regulations
- Framework for guiding funding decisions for certain GOF studies involving H5N1 and H7N9 influenza viruses

- The US government already has effective policy frameworks in place for managing the risks associated with GOF studies of concern.
- However, GOF experiments have not been performed since the funding pause announcement in October of 2014.

Comments on NSABB Draft Report

Mark R. Denison MD

Vanderbilt University School of Medicine

January 08, 2016

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?

- Draft report adequately describes role and level of oversight review, recommendation and requirement of the BMBL, NIH guidelines, DURC and SATP as well as IBC and program review.
- Recent NIH review of ongoing programs in the GOF pause demonstrates commitment and ability to review in a manner to least hinder research progress.
- Current oversight mechanisms capture all areas of concern for influenza and CoVs

Recommendations:

- Clarification of GOF guidelines will allow for initial identification by PI, at institutional level, and facilitate any additional review of highly meritorious research ***DURING or IMMEDIATELY after*** scientific review process
- Don't add independent new mechanism for GOF
- Possibly harmonize / modify DURC + GOF to "Research of Concern" to allow one-stop guidance and review

How well does the NSABB's draft working paper identify the GOF studies of ~~(greatest)~~ concern?

- Appropriately defines potential concern**: transmissibility + virulence + evasion of MCM.**
- Defines where GOF should ***NOT*** be invoked, including: mechanism of antivirals, vaccine escape, passage for increased replication of attenuated viruses.
- Recognizes that the **circumstances may change**: new pathogen, natural outbreak, vaccine, antiviral or mAb) that may change risk profile
- Organism / proscriptive approach to GOF may fail :
  - Over-represents fading and non-concerns and misses increasing or new concerns.
  - Discourages: High impact, innovative research on critical pathogens and discourages trainees from entering or pursuing research.

Recommend:

- Use of process approach for determination of relative risk throughout experimental design and iterative (e.g. at different experimental stages and outcomes)
- Wildtype viruses or natural strains should not be included in any GOF policy
- **Rationale for inclusion of CoVs has never been well demonstrated**. It should be reconsidered, possibly used as an example of RBA but not included in final Recs

Are there GOF studies that should not be conducted? If so, which studies and why?

- **Possibly, but none should be listed in report**
  - Discourages thoughtful review of high impact science on most important problems
  - Distraction from opportunity to encourage biosafety, biosecurity, and training of new investigators.

Recommendations:

- General Principles + clear guidelines / questions about defined categories of potential concern will capture any clear ethical breach or gratuitous research.
- These should be defined (if any) on project and case basis, not as a goal of the report

How well would the NSABB's draft principles and criteria permit the review GOF studies that have raised concerns and inform decisions about whether to fund such studies?

Recommendations:

- Clear guidelines /questions for investigators and reviewers. **If you can't make it clear, leave it out.**
- Avoid absolutes in risk and benefit: stratify risk and benefit categories and apply on a project basis.

How well would the NSABB's draft principles and criteria permit the review GOF studies that have raised concerns and inform decisions about whether to fund such studies?

Avoid the F-word (funding).

- This should not be a threat that looms over research proposals.
- For NIH mechanisms (R, K, U), this should be post merit review for *highly meritorious peer-reviewed research,* that should **NOT affect funding, but should allow for modification of** aims, scope, approaches, mitigation, alternatives.
- Any combination of above under almost all circumstances should allow work to proceed.
- Encourage policy that allows funding and support to be used for this process of testing mitigation and alternatives.
- Don't incorporate up-regulation in security, safety or mechanism (EG BSL4, classification).

Proposed Conceptual Approach for *Funding* Potential GOF Studies of Concern

Identify proposals anticipated to involve GOF studies of concern, as described by the following attributes:

i. Highly transmissible

ii. Increased virulence, and

iii. Resistant to control measures.

Review proposal to determine whether they meet the following criteria:

i. Reviewed and scientifically meritorious

ii. Potential risks compared to the potential benefits are justified.

iii. No feasible, equally efficacious alternative approaches to same scientific question with less risk

iv. Capacity to carry out research safely and securely.

Proposals not meeting these criteria should not be funded.

3. Fund, do not fund, or fund with required additional risk mitigation measures or stipulations.

4. Conduct the research in accordance with applicable oversight policies.

i. Research should be reviewed regularly at the institutional level

ii. Research should be reviewed regularly by the Federal funding agency

Proposed Conceptual Approach for *Review*

Identify proposals anticipated to involve GOF studies of concern, as described by the following attributes:

i. Highly transmissible

ii. Increased virulence, and

iii. Resistant to control measures.

Review proposal to determine whether they meet the following criteria:

i. Reviewed and scientifically meritorious

ii. Potential risks compared to the potential benefits are justified.

iii. No feasible, equally efficacious alternative approaches to same scientific question with less risk

iv. Capacity to carry out research safely and securely.

Proposals not meeting these criteria would be considered on a case basis for possible modification, risk mitigation, alternatives, or alteration in scope

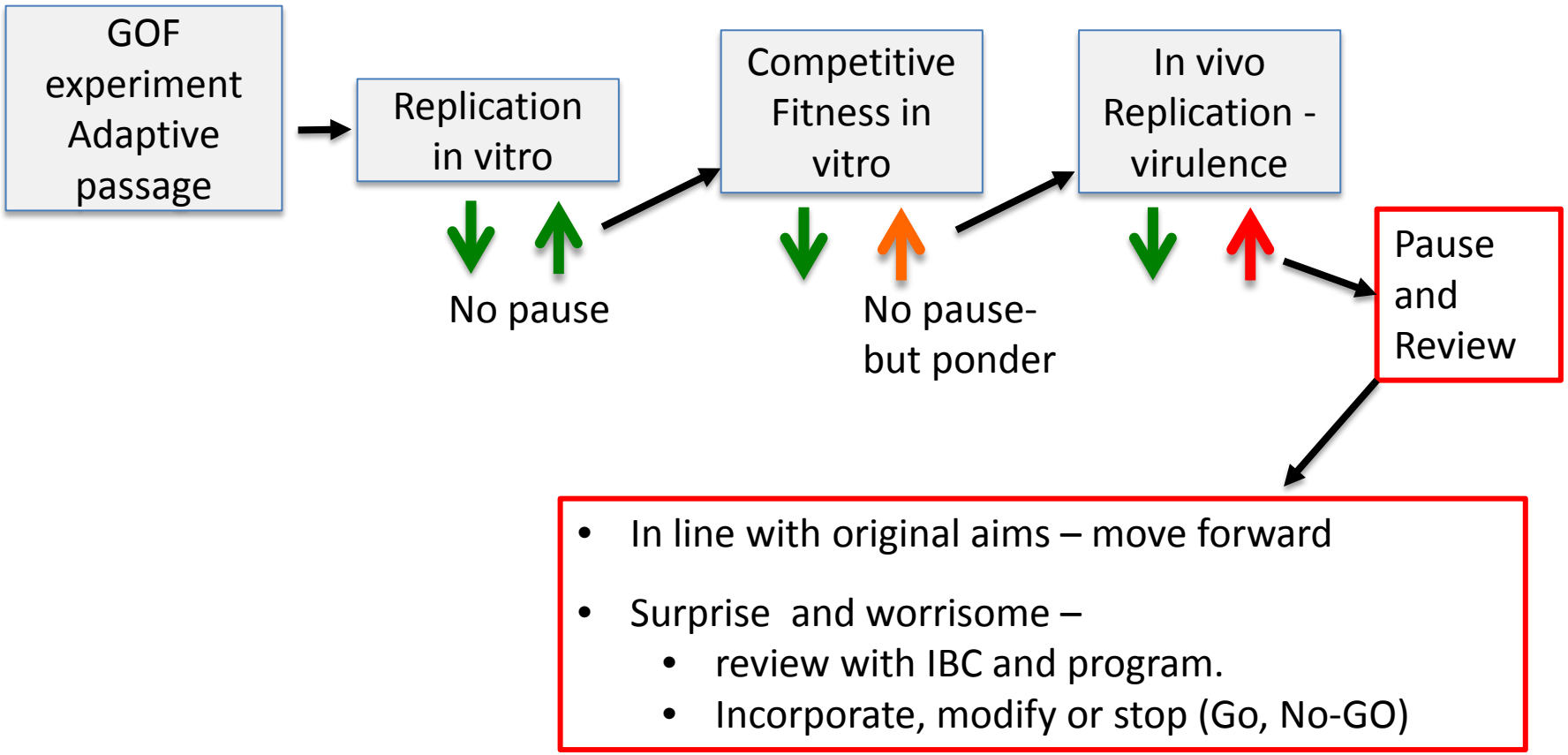
4. Conduct the research in accordance with applicable oversight policies.

i. Research should be reviewed regularly at the institutional level

ii. Research should be reviewed regularly by the Federal funding agency

Design and Process Model for GOF management

Design – Initiate -- Milestones and Review Criteria -- Pause and Review – Go / No Go



Any other comments comments about the report?

- Additional risks not incorporated in report
  - Current approach encourages distrust of scientists and their motivations – by other scientists and the public
  - Broad statement to young investigators that these fields are dangerous -- to pursue as careers
  - Institutions may stop supporting emerging pathogen research
  - Significant potential for loss of research trajectory, investigators, complete research programs,
  - Potential loss of fields of research
- Outcomes and implications feel mostly proscriptive and punitive
  - Encourage open recognition and reporting of possible risk
  - Reward novel approaches and best practices to use new methodologies, approaches, and biosafety practices to achieve research goals.

Any other comments comments about the report?

- **Land the Plane -** View from 40,000 feet seems clear, but provides no guidance or ability to test / model implications of recommendations
- One practical example is worth a thousand theoretical discussions
- Use a Case Based Approach and incorporate these in your final recommendations. Consider these in followup NAS meeting

St. Jude Children's Research Hospital
ALSAC • Danny Thomas, Founder

Response to NSABB Working Group

Phil Potter, Ph.D.
DURC Sub-Committee Chairman
St. Jude Children's Research Hospital

Why does DURC/GOF affect St. Jude?

- NIAID Centers of Excellence for Influenza Research and Surveillance; WHO Collaborating Center for Studies on the Ecology of Influenza in Animals (PIs Drs. Webby and Schultz-Cherry)
- Influenza-positive samples (of unknown genotype) submitted to St. Jude from all around the world
- Highly pathogenic avian influenza virus is one of the organisms regulated by DURC
- Sequencing, biochemical and in vivo studies are performed on derived virus
- Swapping of viral segments into low risk category virus is frequently undertaken to assess role of identified mutations
- We have encountered potential GOF studies (pause and HHS) – St. Jude determined GOF, NIH no GOF

St. Jude Children's Research Hospital
ALSAC • Danny Thomas, Founder

DURC/GOF assessments

- DURC committee consists of both scientists and non-scientist with PI responsible for espousing the risks/benefits of the proposed studies

- Areas of concern
  - No GOF in virus resistant to antiviral agents
  - Availability of vaccine
  - Difficulty in evaluating ‘gray’ areas (‘altering host range and/or tropism’)
  - Ferret as gold standard for biological testing

- St. Jude DURC committee has categorized H7N9 studies as ‘durc’

St. Jude Children's Research Hospital
ALSAC • Danny Thomas, Founder

NSABB WG working paper

- Good initial draft that provides guidance to PIs and Institutional officials
- Multiple layers of oversight are required
- Criteria for assessing GOF research are reasonable, but are not specific (terms ‘highly’, ‘significant’ and ‘likely’ are used)
- For example, point iii ‘pathogen generated is likely resistant to control measures…’. St. Jude DURC committee would ensure parental influenza virus is sensitive to oseltamivir prior to approval

Other concerns

- Generic regulations prohibiting select types experiments may be counterproductive
- If PI can justify risk/benefit to local DURC/IBC committees, and to USG, should such studies be prohibited?
- For example, would knowing the amino acid residues responsible for enhanced mammalian transmission of influenza virus, that might only be identified via GOF studies, be beneficial?

St. Jude Children's Research Hospital
ALSAC • Danny Thomas, Founder

Summary

- Lack of definitive descriptions of GOF studies that are, are not, acceptable
- As an individual who will be tasked to interpret GOF guidelines, clarity and defined criteria will make evaluation much more informed/complete
- Guidelines should be flexible to address emerging/future virus
- 'GOFoC' should be reviewed by multiple bodies (local, independent, Federal)
- Do guidelines only refer to USG funded studies? (What about institutes that do not receive Federal funds, companies, etc?)
- Prohibiting specific experiments may be counterproductive, especially if such studies can occur in Europe

Session IV: Discussion of NSABB Preliminary Findings and Draft Recommendations

Panelist remarks: Beth Willis mcbeth@mac.com

Good morning. I am Beth Willis, with Frederick Citizens for Bio-lab Safety, Frederick MD. I am here to speak to some of the perspectives of communities in these proceedings and to say something about many members of the general public who are deeply engaged in the issues we are discussing here.

Since 2004, I have worked with the Frederick Community and with a nation-wide coalition of communities living in proximity to BSL-3 and 4 laboratories. We have worked to bring a public perspective and concerns about health and safety and containment laboratories to policy makers and to Congress. Until a few months ago I served as Chair of the Containment Laboratory Community Advisory Committee (CLCAC) in Frederick MD, which is home to the National Interagency Biodefense Campus. The CLCAC is joint committee appointed by the elected officials of both Frederick City and the County.
(http://www.cityoffrederick.com/index.aspx?NID=127)

It is new, and important for a member of the public to be included on a panel such as this.

In my experience, community advocates who have engaged with these issues have worked hard to overcome significant technical barriers in order to understand the health and safety implications for their communities of all types of biological research of concern. Some of us are scientists; some are just highly motivated. We have to work through the technical detail to discern the bottom line safety impact for our communities. We have seen a great many of the specific safety concerns we have raised over the years play out in reports of safety and oversight lapses.

We submitted detailed comments to the Office of Science and Technology Policy on Dual Use Research of Concern policy and Gain of Function research in 2013, and in 2015 on Select Agent Regulation. We have recommended a structure of independent oversight, based upon other existing federal programs. These documents are germane to the issues under discussion at this meeting, and are available. What we say in these papers is not so very different from what others in this room have been speaking about.

All of us here have spent two days discussing complex matters with no easy answers.

There does not yet appear to be scientific consensus on how to proceed. That is striking when considering the potential consequences of conducting GOF research of concern. Funding risky GOF research in the absence of scientific consensus about safety does get the public's attention. As does the repeated references at this meeting to conflict of interest within the system.

So, I am here to speak for the application of common sense and wisdom as you grapple with all of this. I'm here to speak for putting your money where your words are and building out from where you are today by developing and implementing specific, robust, transparent and replicable decision-making and oversight processes that the public can have confidence in.

At this meeting, I heard the beginning of a reordering of the historically unbalanced balance of power between large institutions and public concerns. I saw some reordering of the balance of decision-making criteria from the strictly scientific and technical to what I hope will be the application of an equal measure of ethical and public health values.

I would propose that doing so will provide us all with some measure of protection from the risks of technical hubris. Human history is littered with the unintended consequences of technical hubris committed in the name of progress and national security.

There are a few bottom line points that jump out for this member of the public, points that also apply to DURC, select agent, and other research of concern. I hope these points will inform whatever final recommendations comes from the NSABB:

1. Getting specific and actionable. The report speaks broadly to many concerns raised by the public over the years. The task is to now move from the principles in this paper to that, which is actionable, funded and consistently required. From a community perspective, the usefulness of these ideas is in the detail and in funding.

It costs money to implement the good oversight, public communication and engagement and other concepts contained in the report, funding well beyond what is currently occurring. Implementing the recommendations that enhance public safety needs to be as much a part of doing business as any other aspect of the research. Otherwise all that we are discussing will be empty words and unfunded mandates. GOF research of concern projects that can't afford to implement such requirements should not be funded. I don't know why we are here unless this is a guiding principle.

Additionally, this "total cost of doing business" for GOF of concern makes such research more costly than less risky research. That should also be a factor when deciding what to fund in the context of the country's overall research priorities in an era of limited research funding.

2. Making the transparency objectives real. The working paper includes a greater and welcome emphasis upon transparency and principles of public communication and engagement than community advocates have seen in the past.

Last October, the White House issued a memo with numerous recommendations about BSAT research, emphasizing specific aspects of transparency, inventory control, accident and mishap reporting and other important matters, including evaluating the amount of such research that should be conducted. I would think these recommendations should explicitly inform the NSABB GOF effort.

I also note that initial efforts by media outlets to obtain information based upon the White House Memo have not been highly successful. This is to observe that achieving the transparency we all speak of will take significant additional commitment by the US Government.

With regard to making funding decisions, the public should also be informed of the decision-making process, and, among other things:

- Who approved the research.

- The identified risks and for whom.
  By that I mean questions of environmental justice, not just globally but within specific minority and disadvantaged populations in this country. Others discussed this extensively at this meeting.

- The criteria for deciding if the risk is too great.
  That criteria has not been defined. What constitutes too great a risk has not been defined.

- Who decided that the risk analysis was sufficient.

- And, of course, what has been done to mitigate the risks.

- The independent oversight that gives the public evidence that all of this has been properly conducted

3. This report is candid about challenges and the limitations of risk benefit analyses and the importance of a good balance of public health and ethical factors in making funding decisions. This idea is also new and welcome in the experience of communities living in proximity to containment laboratories. Acknowledging the reality that risk analyses have their limitations and uncertainties allows for that application of wisdom and common sense.

The report also suggests a number of ways to engage the public in meaningful ways throughout the life cycle of projects, some of it pre-decisional. Those who are at-risk need to be a part of the decision-making process. Engaging with the public should be required and assistance provided to make it so. Assistance might include a clearinghouse of ways this is being done, or could be done paired with technical assistance to laboratories and communities so they can develop locally effective goals and approaches.

4. The scope needs to expand beyond NIH funded research. Yes I understand the scope of the NSABB. But communities expect the US Government to be responsible for ensuring that safety mechanisms are in place. We are not so concerned with the details of Departmental scope. Research of concern in proximity to our communities comes from a great many more DOD, other federal, and private funding sources than NIH, some of which currently have no federal oversight. It is time to finally address this issue, which has been under discussion for years now.

5. Long-term independent oversight is the lynchpin of these recommendations. If risky research is to be funded, an adequately funded independent oversight system that covers the current oversight gaps also needs to be funded.

Laboratory safety and oversight failures have been in the news regularly in 2015, and for many years prior. Congressional testimony has not been reassuring. We've heard in some detail about the ways in which the system does not appear to be working well, with systemic institutional safety failures and inadequate safety cultures in more than a few federal and other laboratories. How can this overall situation with high containment laboratory safety in the nation not be high on the list of concerns when considering GOF research of concern?

It would be fair to conclude that the science we are discussing and the associated containment laboratory industry is young. There are a vast number of new laboratories and new researchers. Competition for money and career advancement is fierce. There is tension among these pressures and safety. Decisions to conduct risky research must acknowledge and find ways to address this reality. Time and

again we see that financial, mission and institutional pressures can negatively impact safety.

6. The public is looking for a clear authority structure that governs the full scope of risky research. We need an authority structure empowered to make health and safety decisions for the public good. Acting on behalf of public health and safety is a core function of government. That clear authority structure does not now exist, and the diffuse and overlapping authorities currently in place don't seem to adequately serve either science or the public.

Of course there is research that should not be conducted. Yes, we need both federal and institutional oversight. The public is looking for evidence of an effective and well functioning process that engenders confidence in both decision-making and the conduct of this work.

I am available to discuss approaches to engaging the public.

The following documents were mentioned during the panel discussion and are appended here as reference.

- Statement to the OSTP Listening Session on Select Agent Regulations on Science, Technology and National Security
- Comments on 2013 Office of Science and Technology Policy Proposed Policy on Dual Use Research of Concern
- Proposal for Establishing a Bio-Safety Facilities Safety Board

Statement to the OSTP Listening Session on Select Agent Regulations on Science, Technology and National Security

February 17, 2015

From: Beth Willis, Chair, Containment Laboratory Community Advisory Committee (CLCAC), Frederick, MD http://www.cityoffrederick.com/index.aspx?NID=127

and representing the National Coalition of Concerned Communities

To my knowledge this is the first time that members of the public who represent community concerns have been included in such a meeting. Communities are a vital part of this conversation and of the safety strategy.

The concerns of communities regarding high containment BSAT research conducted in our neighborhoods do not fit neatly into the topical structure of today's meeting or within the box of Select Agent Regulation. I invite everyone to think outside of the box, and the walls and fences of the laboratories when considering the public. There are many actions that need to be taken at a federal level in order to start including the public in the safety plan.

Supporting information and earlier submissions to OSTP and other federal decision-makers are attached.

The broad themes are: reduce the number of labs, greatly improve transparency and accountability, and guarantee community rights. We need to be able to reconcile the concerns of both researchers and communities.

1. Communities support proposed actions discussed in the August 16, 2014 memo Enhancing Biosafety and Biosecurity in the United States and the 12/16/14 FACT Sheet: Biosafety and Biosecurity in the United States. Making specific improvements to inventory control, training, culture of safety etc. are very important. But we highlight the following: taking a step back to evaluate the size, scope, purpose, risks and benefits of the entire BSAT program.

    a. <u>Formally addressing the number of BSL-3 and 4 laboratories now operating and planned.</u> This is of central importance and has been spoken of by many, including Dr. Frieden of the CDC.

    Our communities have been subjected to decisions about risk made by others, and at the same time our voices have been excluded. This has been done for what has been a significant growth industry since the anthrax letters of 2001, and in the absence of a rigorous national assessment of need and capacity to manage oversight effectively. (see attached open letters)

Open, formal, timely action on this, independent of vested interests, is long overdue and needs to occur on the near horizon. Yes, what is the minimal number of labs required? And even more to the point what are the requirements goals and objectives that need to be met, and how to they reconcile with available resources when considering other vital public health research needs?

We agree with the July 2014 editorial in the *Annals of Internal Medicine* which states "…greatly limiting the number of BSL-3 and BSL-4 laboratories would probably better enable us to ensure their safety. We must contain the terror within."

b. Confusion of authorities. Communities are well aware of the confusing and labyrinthine regulatory system that disperses executive, congressional and academic/corporate interests and authorities. The public also lives with that every day as we struggle to obtain safety information and work with the many players who operate and regulate labs in our neighborhoods. In particular, we are concerned by the apparent lack of federal authority to compel safety review actions in private and academic BSAT labs. We are deeply concerned about the lack of federal authority with regard to decisions about the efficacy and safety of some experiments. (see attached comments on DURC policy which largely applies to all BSAT research)

2. Why does the public matter? While this question may appear self evident, we do not find evidence of the public's important role reflected in policies or procedures. Here are a few reasons why the public is important in this conversation:

    a. Protection of the public's welfare is a core government function
    a. Lack of public trust can and has derailed projects
    b. Lack of public trust can negatively impact science over the long-term
    c. It can also harm reputations of both institutions and individuals
    d. Public engagement is a key part of the safety plan
    e. Scientific and government debates about the public's welfare won't work without the public's voice
    f. That public voice needs to be independent of the financial and professional interests of researchers and research institutions
    g. We live in a democracy

3. Transparency

    a. Public transparency about safety and safety performance is essential.

b. Lack of transparency results in profound public distrust, whether or not it is warranted.

c. Public transparency about safety throughout a facility's life cycle is important, from planning through decommissioning. The NEPA process is a limited and inadequate communication tool and clearly does not apply to every BSAT lab.

d. Fact-based safety performance information is most important. People most want to know how well equipment, lab designs, policies, procedures and training are actually working. People consistently state that they want fact-based evidence of safe performance.

e. Current federal law and regulation makes it very difficult to impossible for the public to obtain fact-based safety performance information. The public's right to know about safety is not guaranteed by law or public policy. It is impossible to obtain information about safety performance at academic and private BSAT labs. The public is not allowed to even know of their existence in our communities.

f. Currently federal policy consistently invokes national security in order to deny public access to a very wide swath of information. This effectively trumps public health and safety concerns making them subservient to anything labeled national security.

g. Each of the many government entities conducting or funding BSAT research has different cultures, rules, and chains of authority and transparency policies. This creates an extreme and highly tangled burden on communities seeking information.

h. This industry and federal regulators have not yet adopted standards for what safety information should be made publicly available, despite numerous recommendations about this made by the ABSA, the 2009 Transfederal Task Force, the journal *Nature* last July, those who testified before the House Energy and Commerce Committee last summer, and many others.

   The CLCAC, whose membership includes biosafety experts and safety metrics experts have also made numerous recommendations. (see attached) The public is in a no-win situation in the absence of federal policy. There are solutions that respect security and safety culture, but no action has been taken.

   We agree with the July 2014 editorial in *Nature* that authorities should require reporting of all serious accidents and near misses in

biocontainment labs. They go on to say "Timely incident reports should also be made available on public websites—as many nuclear regulators require of power plants—perhaps with an option for sharing details more-sensitive information confidentially."

i. Other industries with national security concerns have figured out ways to communicate safety performance to the public, even in situations involving highly technical information. The safety status of nuclear power plants is available online. Airline safety and accident records are available online. Citizens do not have to individually negotiate with each power plant or airline.

   But citizens DO have to individually negotiate with, make lengthy FOIA requests to or bring lawsuits to obtain safety information from any of the federal or 1500+ private/academic BSAT laboratories. These requests are all too often denied. This is an unacceptable situation for communities.

4. The impact of money on health and safety. Community concerns include:

   a. Sufficient money to keep safety, maintenance, adequate oversight and public engagement a first priority in an age of limited federal funding and competitive and profit-driven research. In the past year, safety and oversight failures have brought home this issue. Conversations with laboratory safety professionals, particularly in the smaller private labs have not been reassuring and reveal resource limitations, i.e. lack of money for adequate biosafety programs.

   b. There is particular concern about budgets for safety and maintenance over time, over the full life cycle of a facility.

   c. There is particular concern about the financial and professional drivers for research decisions trumping public interest. There is concern about inadequate legal authority and budgetary resources to conduct oversight of decision-making for risky experiments and the risk of unintended consequences stemming from technical and scientific hubris in the name of progress. (see attached)

   d. Engagement with the public costs time and money. It is not currently part of the cost of doing business and needs to be.

   e. It is important to distinguish among PR activities with local civic and business organizations, the terrific work some labs perform with schools etc., and the fraught efforts of communities to obtain factual information.

f. Laboratories impose financial burdens on communities, which are often dismissed. These include stretching medical resources, which may be entirely inadequate to address a laboratory-acquired infection, intentional malevolent release or more extensive public health event. There are financial burdens on hospitals, medical personnel, police, fire, first responder, public health and emergency management systems within communities. None of these public services are adequately compensated for the additional burden. Some communities are in financial distress and are already experiencing cuts to services. Some communities are not confident in the monitoring conducted by laboratories and feel obligated to invest in their own costly independent monitoring. Some communities have no medical personnel qualified to deal with the relevant pathogens, thus requiring a ramp up in training they are in no position to provide.

g. What is the federal responsibility to address these financial issues as a cost of building and operating or funding laboratories? This is also part of the cost of doing business that has not been addressed.

5. Community Roles and Rights. A short list of needed foundational actions:

a. Specific community concerns need to be included in industry standards for oversight and transparency. (see attached)

b. Legal and policy guarantees for community rights are essential. These rights include the right to information and the right to participation in decision-making that impacts the community. (see attached)

c. Accountability to the public on safety matters must be an embedded part of the cost of doing business.

d. Institutional structures that include public representation need to be the norm at every level, including mechanisms to ensure that information flows back to the public. Each community is unique with its own specific safety, geographical, demographic, and economic issues and concerns.

e. Barriers to community participation must be addressed and solutions institutionalized with commitment and resources. Barriers are technical, communication and a balance of power. Many members of the public are very well informed. But that takes more work than should be generally expected. The technical nature of this research creates a barrier for the public at large, which take time and effort to address.

f. The imbalance of power between research institutions and public interest needs to be reordered. In many locations there has been an adversarial relationship between large powerful institutions and communities that hold almost no power. This benefits no one.

g. There needs to be priority on public health, which includes actually addressing specific public concerns in communities.

6. Other

a. Communities have concerns about the adequacy of risk assessments in this industry. The National Research Council and others have verified these concerns.

b. There is concern that current biosecurity risks are not adequately communicated to all of the laboratories, particularly to the large number of private and academic labs sited throughout the country.

c. There are concerns about reports of extreme difficulty in diagnosing LAI's, when researchers are unaware they have been exposed and particularly with researchers in private and academic BSAT laboratories. How can this be addressed? This is a first line public health issue.

Attachment 1. Examples of Safety Performance Information suggested/sought by the CLCAC and others:

1. Executive summaries of regulatory and oversight reviews, such as from the CDC, USDA….

2. Listings posted of what external entities do oversight on what schedule.

3. Metrics related to 1) employee biosafety operational performance; 2) facility biosafety system maintenance and performance; and 3) biosecurity performance. Metrics should include both lagging indicators (e.g. performance outcomes), as well as leading indicators (e.g. precursor events, near-misses etc.).

4. For reported incidents:

    - Indicate threshold for an incident to be reportable to CDC and other agencies.

    - Indicate how many incidents were reportable to CDC and other agencies in specific time period.

5. Provide sample incident reports, so that community can better understand those evaluations. Better yet, provide the incident reports on all accidents and mishaps.

6. Post information on required corrective actions from oversight reports, and their closeout. Include issues of some consequence, not long lists of minor / administrative matters.

7. Provide information from Institutional Biosafety Committees, including

    - IBC rosters
    - Committee composition
    - Qualifications of all members
    - Agendas
    - Decisional documents
    - Electronic communication concerning the INC or its activities
    - Rules/Procedures under which the IBC operates
    - Written records
    - Processes
    - Meeting information
    - Minutes

Attachment 2: Letter from Members of the Public to Congress on High Containment Laboratories, July 2014

Attachment 3: Comments on 2013 OSTP proposed policy on DURC, April 2013. Comments are largely applicable to all BSAT research

Attachment 4: Open Letter to Biodefense Decision-makers, from National Coalition of Concerned Communities, April 2012.

Attachment 5: Proposal for establishing a Bio-Safety Facilities Safety Board to address independent oversight issues. First submitted to Members of Congress, by communities, in 2008

Comments on

2013 Office of Science and Technology Policy Proposed Policy on

Dual Use Research of Concern

The Office of Science and Technology Policy (OSTP) has requested public comment for its policy on Dual Use Research of Concern (DURC). The following comments reflect concerns from members of the public who live in proximity to laboratories across the U.S. where DURC is conducted.

We have particular concern about the adequacy of the DURC policy, given the March 2013 Government Accountability Office (GAO) report that cites lack of adequate federal oversight of high containment laboratories and the need for a comprehensive national assessment of research needs:
http://www.gao.gov/products/GAO-13-466R

This is coupled with the call for a moratorium on Gain of Function (GOF) research of all types, as published in Nature on March 27th: http://www.nature.com/news/h5n1-viral-engineering-dangers-will-not-go-away-1.12677

And the related concerns expressed by the Foundation for Vaccine Research (FVR), as further reported by the Center for Infectious Disease Research and Policy (CIDRAP):
http://www.cidrap.umn.edu/cidrap/content/influenza/avianflu/news/mar2913ethics.html

These recent reports and statement make clear the need for a DURC policy that ensures the engagement of communities, elected officials and a much broader scientific consensus when considering risk, and the appropriateness of DURC. While we understand that DURC and GOF research are not identical, they overlap and are interconnected issues.

We join the FVR in calling for a moratorium on such research until the safety and ethical issues are resolved.

This research occurs in laboratories in our communities. We were not consulted when decisions were made to conduct this research in our neighborhoods.

- **Overall concern:**

We represent citizen groups from many localities throughout the U.S. who have specific health, safety and environmental concerns about the presence of advanced biodefense laboratory research in our neighborhoods and cities**.** In each of our communities, we have found that environmental impacts and hazards associated

with these labs have not been analyzed with thoroughness, clarity and scientific rigor. Additionally, there has been inadequate community input to the planning and design of risk assessments, resulting in assessments that do not reflect community concerns. That concern is much greater as we consider risk assessments associated with DURC.

Transparency is a prerequisite for effective oversight, for establishing trust with communities and with others who may not trust the intentions of the United States. It is important in relation to Biological Weapons Convention. Yet the work conducted in U.S. biodefense labs is not transparent, and nothing in the proposed DURC policy suggests increasing transparency, even for unclassified research.

Despite great effort, community groups have been unable to obtain vital information about what is actually happening or planned for laboratories in our communities. Security concerns are used as an excuse to inappropriately restrict citizen access to reports of ongoing or planned studies. Freedom of Information Act requests about accidents and the minutes of Institutional Biosafety Committee meetings are routinely denied. We are concerned that nothing in the proposed DURC policy addresses these issues.

- **Defining acceptable risks.**

  "Low-probability" but "high-consequence" accidents that could result in a public health disaster in our communities are of great concern. Who decides what is an acceptable level of risk? Should an academic institution, a corporation, or a federal agency decide what is acceptable risk for the at-risk citizens?

  These high consequence, low probability events have a high probability of fatal outcome and require more isolation than what can be obtained in residential areas. Just because an event 'hasn't happened before' is not scientific reason for assuming that it is safe to proceed.

- **Poor research agenda oversight.**

  The research agenda of U.S. biodefense programs has also expanded greatly in the wake of the 2001 anthrax letters. Nothing in the proposed DURC policy addresses the question of who sets priorities for risky biodefense research.

  Oversight of Research Proposals. The 2012 policy and the 2013 proposed DURC policy update, speak to detailed procedures for submitting research plans, risk assessments and risk mitigation plans. Decision-making authority is alluded to but not made explicit.

  Given the extreme difficulty and confusion of authority and process in evidence from the international debate about ongoing H5N1 and other Gain

of Function (GOF) research, the undersigned members of the public believe it is imperative that there be a clear and open process by which decisions are made regarding the safety and appropriateness of proposed DURC. Important questions include:

a. Who exactly is authorized to decide if DURC is too risky?
b. By what criteria?
c. What is the scope of that authority?
d. Who is authorized to decide if the risk assessment and risk mitigation plan is adequate?
e. Who determines if the safety record of the researchers / institution warrants approval?

Scope- Does this policy extend to private labs? It needs to. That is not clear.

- **Transparency.**

Transparency is the key component to compliance with the Biological Weapons Convention, and is cited as critical by the GAO, the 2009 Report of the Trans-Federal Task Force on Optimizing Biosafety and Biocontainment Oversight, and others.

Yet transparency with communities is missing from this policy.
Communities have the right to know about risk and risk mitigation for research being conducted in their midst. It is not acceptable to say that no information can be made public because public release of all information may not be appropriate from a security perspective. Increased secrecy breeds increased mistrust locally and abroad. Yes, the public should be told, for example, if H5N1 research or GOF research is being conducted locally.

The public should be told:

a. Who approved the research,
b. What, the risks are,
c. Who decided the risk analysis was sufficient,
d. What has been done to mitigate the risks,
e. How to provide input in a timely manner and how to track the ways in which their participation has been considered and influenced decisions.

This can all certainly be accomplished at an appropriate level of specificity to ensure that security concerns are not compromised.

- **Classified research**.

The policy appears to say that the remedy for research risks that are not adequately mitigated is to make the research classified. Making the research

classified makes it a secret; it does nothing to protect from accidental release, LAI's or malevolent intent. This approach decreases transparency. We find this solution to risks that cannot be mitigated appallingly inappropriate. Such research should be banned. The federal government should exert authority in ensuring it is banned.

- **Biological Weapons Convention (BWC)**

  How does this policy address BWC requirements? That is not clear.

- **Institutional Procedures for DURC.**

  We fully support making procedures for reviewing DURC accessible to the public.

- **Role of a coherent federal oversight mechanism and decision-making process.**

  The fragmented federal approach to oversight and decision-making on matters of critical health and safety is apparent in this policy. In addition, this fragmented approach disenfranchises communities with concerns about the research being conducted in its midst. The recommendations in the 2013 GAO report are relevant here, and we specifically ask that the report be considered as part of our comment, along with the Nature article and the statement by the FVR cited earlier. Moreover, OSTP's assertion that oversight and needs assessments for research have been adequately addressed are not supported by this policy, even accounting for DURC being a subset of what the GAO was addressing.

Submitted by:

Beth Willis (contact)
Frederick Citizens for Bio-lab Safety, for
The National Coalition of Concerned Communities
mcbeth@mac.com
301-694-9410

Proposal for Establishing
a Bio-Safety Facilities Safety Board (BFSB)

A Bio-Safety Facilities Safety Board (BFSB) would be authorized to assist Congress in public health and safety oversight of bio-safety facilities that work with select agents and other pathogens such as SARS, that represent a risk to public health. This board would be independent of agencies currently planning for and/or operating bio-safety facilities. The board would have access to all documentation dealing with safety and would conduct on site reviews as necessary to assure that there is no undue risk to the health and safety of the work force and the public. Findings and recommendations resulting from these reviews would be provided to Congress and the applicable executive branch agencies for appropriate action. BFSB reviews would seek public input and all findings and recommendations and the corrective plans would be available to the public.

Members of the board would be approved by Congress. The current National Science Advisory Board for Bio-security (NSABB) is not affected by this action and there is no intended overlap in responsibilities between these two entities. The BFSB would perform the same functions for Congress on oversight of bio-safety facilities as the Defense Nuclear Facility Safety Board established in 1988 does for the defense nuclear facilities.

Background: The Defense Nuclear Facility Safety Board (DNFSB) (http://www.dnfsb.gov/) was created by Congress rather swiftly in 1988, at the height of the Rocky Flats crisis. While circumstances are not identical to the bio-defense labs, there are a number of lessons to be learned from the nuclear weapons complex environmental and safety crises. It should also be noted that the Department of Homeland Security has endeavored to model the bio-defense lab system on the DOE National Laboratory system.

An important point in parallel: The safety and environmental disasters associated with the nuclear weapons complex came about at least in part because of a cold war political climate that valued swift progress in service of weapons production over safety. The resulting history of devastating environmental and human health consequences is well known, at Rocky Flats, Hanford, Paducah and many other locations around the country. Some of these sites are shockingly close to major population centers such as Denver and San Francisco.

The past thirteen years has found the nation in a similar political climate, with a similar safety culture with regard to the proliferation of laboratories conducting research and development (R & D) with bio-warfare pathogens. This culture is further complicated by the extraordinary private sector economic stakes involved in bio-defense R & D programs. Clearly a Bio- Safety Facilities Safety Board would need to provide oversight of academic and private sector facilities as well.

How does the Defense Nuclear Facilities Safety Board function? The DNFSB created a methodology for safety programs and safety reviews. It is empowered to make safety

recommendations that both Federal and contractor entities are required to respond to; corrective action is taken, including operational stand-down, if warranted.

The DNFSB reports to Congress quarterly. While no one mechanism can make the nuclear weapons facilities perfectly safe, the DNFSB has by all accounts significantly improved safety and oversight within the nuclear weapons complex. The DNFSB has also been used as the operating model for a number of other powerful boards providing oversight for other DOE programs and labs. The DNFSB includes scientists who also often work with the National Academy of Sciences.

Relationship of a Bio-Safety Facilities Safety Board to the NSABB. The National Science Advisory Board on Biosecurity (NSABB) has been in place for several years, but has a different charter from what is being proposed here. (http://www.biosecurityboard.gov/) The NSABB makes recommendations re: dual use research for all life science research. This does not appear to be an overlap. NSABB recommendations would presumably be used by the Bio-Defense Facilities Safety Board in conducting its reviews.

In summary, the new Bio-Safety Facilities Safety Board would focus on:

- evaluating and improving actual safety performance across all funding sources from all Federal agencies, and

- reporting to Congress and to the public.

- independent, transparent, safety oriented accountability by researchers, laboratories and funding agencies.

Submitted by:

Beth Willis, Frederick Citizens for Bio-lab Safety, on behalf of the national coalition of concerned communities.

mcbeth@mac.com