United States Senate

Committee on Homeland Security and Government Affairs

Oversight of U.S. Taxpayer Funded High-Risk Virus Research

Prepared Statement of

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Chairman Peters, Ranking Member Paul, and Members of the Committee, I appreciate the chance to provide input on the topic of oversight of publicly funded research on high-risk viruses. My name is Dr. Carrie Wolinetz, and I am currently a senior principal at Lewis-Burke Associates, a small government relations firm specializing in research and higher education policy, as well as chair of the Health and Bioscience Innovation Practice Group at the firm. I have a long history of development and engagement on biosecurity and biosafety policy and research oversight in my previous roles inside and outside of government, and I teach a class on Biotechnology and Security at the School of Foreign Service at Georgetown University. In the federal government, I have served as the Deputy Director for Health and Life Sciences at the White House Office of Science and Technology Policy, Acting Chief of Staff to the Director of the National Institutes of Health (NIH), Associate Director of Science Policy and Director of the Office of Science Policy at NIH, which included relevant experience administering the National Science Advisory Board on Biosecurity, the Recombinant DNA Advisory Committee, leading and participating in multiple interagency policy efforts, and serving as a U.S. delegate in international fora. The opinions expressed herein are my own and do not necessarily reflect the views of Lewis-Burke Associates, their clients, or the other organizations with which I am affiliated.

First, I want to note that the policy conversation around mitigating the risk of research involving high-consequence pathogens is not new. For decades, the United States has been at the forefront of global conversations about how to create a research oversight system that reduces risk while maximizing the benefit of life sciences research, and we have learned a lot about what works and what does not. In thinking about how we might improve our research oversight system, it is important to understand the purpose and context of the policy foundation on which we are building. Central to this is recognizing that the policy landscape represents a mix of laws, regulations, policies, and guidelines based on the interrelated but distinct notion of biosafety – protecting people and the environment from pathogens – and biosecurity – protecting pathogens from people who might use them for harmful purposes.

Collectively, while this policy framework may be imperfect and should continue to evolve with the science and current threat landscape, it arguably represents the most rigorous system of oversight of pathogen research in the world – and in fact the U.S. approach informs the approach of many other governments around the world.

Although each of these policies were developed in reaction to the obvious perceived threat at the time – and their purpose and construction reflect that – none of them were assembled in haste. Each involved years of development and a great deal of stakeholder and expert engagement. This included Congressional actions, multiple interagency committees and activities, independent and commissioned third-party reports and recommendations, input from Federal advisory committees, such as the National Security Advisory Board for Biosecurity (NSABB), and public comment periods and events. It is worth noting that this framework has not remained static but has been subject to re-examination and revision over the past twenty-plus years. For example, in response to a number of high-profile biosafety and biosecurity incidents in 2014, the White House tasked the Federal Experts Security Advisory Panel (FESAP) and Fast Track Action Committee on Select Agent Regulations to evaluate the U.S. biosafety and biosecurity policy system and make recommendations to strengthen it[1]. In 2017, the National Institutes of Health (NIH) led a workshop of stakeholders to evaluate implementation of polices governing dual use research of concern (DURC)[2]. The Select Agent regulations, which first went into effect in 2003, have been both reviewed and revised[3]. Most recently, we have seen new proposals from the Biden Administration to update policies for DNA synthesis screening[4], DURC research, and research involving enhanced pathogens of pandemic potential[5]. While policy processes seldom move as quickly as advances in science and technology, which speaks to the need for flexible, responsive oversight instruments, the U.S. approach to biosecurity and biosafety has clearly been evolving in real-time as new threats emerge.

Below is a brief synopsis of the current major pieces of biosecurity and biosafety policies that largely make up the U.S. framework for oversight and risk mitigation of research with high-consequence pathogens. While this summary represents the bulk of the framework relevant to the current policy conversation, there are related U.S. laws, regulations, and policies – such as

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[1] Haines and Gronvall (2023 March 6) Improving U.S. Biosafety and Biosecurity: Revisiting Recommendations from the FESAP and FTAC on Select Agent Regulations. *Applied Biosafety,* 28(1). https://www.liebertpub.com/doi/10.1089/apb.2022.0025

[2] Stakeholder Engagement Workshop on Implementation of U.S. Government Policy for Institutional Oversight of Life Science DURC (2017); https://osp.od.nih.gov/wp-content/uploads/DURC_Sep_2017_Policy_Workshop_Agenda.pdf

[3] Federal Select Agent Program History (2020, Sept. 10: https://www.selectagents.gov/overview/history.htm?CDC_AA_refVal=https%3A%2F%2Fwww.selectagents.gov%2Fhistory.html

[4] Framework for Nucleic Acid Synthesis Screening (April 2024): https://www.whitehouse.gov/wp-content/uploads/2024/04/Nucleic-Acid_Synthesis_Screening_Framework.pdf

[5] U.S. government policy for oversight of dual use research of concern and pathogens with enhanced pandemic potential. (May 2024) https://www.whitehouse.gov/wp-content/uploads/2024/05/USG-Policy-for-Oversight-of-DURC-and-PEPP.pdf

export controls, DNA synthesis screening guidance, visa policies, occupational safety and health requirements, and human and animal research participant protections – or local and state requirements which may also play a role in ensuring responsible, safe, and secure conduct of pathogen research.

Summary of the history, purpose, strengths, and weakness of components of the U.S. research oversight framework related to biosafety and biosecurity:

- **Biosafety guidelines:** While practices for working safely with infectious agents in laboratory settings date back to the early days of microbiology research and the era of World War II biological weapons programs, the execution of modern biosafety practices for publicly funded biological research in the U.S. rests primarily on two guidance documents: The *NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules ("NIH Guidelines")* and *Biosafety in Microbiological and Biomedical Laboratories (BMBL)*. Both of these are guidance documents that are highly reliant on being used in concert with professional and expert judgment, so they are neither regulations nor requirements, per se. However, because they are incorporated into the terms and conditions of federal research awards and adopted by institutional practice and professional communities, they are often adhered to by stakeholders and practitioners with the same seriousness of compliance as more rigorous policy approaches.

  The *NIH Guidelines* (1976) date back to the dawn of biotechnology emergence, when it was recognized by the scientific community and the public that the risk of engineering pathogenic microbes in laboratory settings had unknown and potentially high-risk consequences[6]. While frequently pointed to as an example of "self-regulation" by the scientific community, there was a great deal of pressure to create oversight mechanisms or face prohibitions on the use of biotechnologies which provided great incentive for creation and adoption of the *NIH Guidelines.* This biosafety guidance was created, overseen, and updated by an associated Federal Advisory committee, the NIH DNA Recombinant Advisory Committee (RAC), which also provided a public forum for debate over balancing the risks and benefits of this emerging technology. It was the *NIH Guidelines* which created the Institutional Biosafety Committees (IBCs), local expert oversight bodies to "provide local review and oversight of nearly all forms of research utilizing recombinant or synthetic nucleic acid molecules."[7] Over time, IBCs have become involved in review and oversight of research involving other types of biological hazards, including infectious disease research, but this is based in institutional policy and a

[6] Wivel (2014 Jan. 1) Historical perspectives pertaining to the NIH Recombinant DNA Advisory Committee. *Human Gene Therapy*, 25(1): 19-24. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3900000/

[7] FAQs on Institutional Biosafety Committee (IBC) Administration (April 2024): https://osp.od.nih.gov/policies/biosafety-and-biosecurity-policy/faqs-on-institutional-biosafety-committee-ibc-administration-april-2024/

culture of responsible research, rather than required by policy, and is very dependent on institutional resources to support the IBC's work[8].

The *NIH Guidelines* have an advantage of long-history – institutions, researchers, industry, and biosafety practitioners are familiar with this framework and its evolution over time (the guidelines have been amended dozens of times) and have training and institutional processes in place for compliance. While NIH is not a regulatory agency and therefore does not have the statutory authority to enforce these guidelines as regulations (rather than rules, they are self-described "practices" and "principles"), their incorporation at a term and condition of awards (described below) and the potential consequence of institutional loss of federal funding strongly motivates institutions to strictly comply. Moreover, the *NIH Guidelines* demonstrate a "reach through" effect in that they are not applicable just to research funded by NIH but to any applicable research conducted at or sponsored by any institution that receives NIH support for such work as well as research conducted at any host country that does not have its own set of commensurate guidance[9]. This vastly expands the universe of compliance, although because NIH does not have regulatory authority, their ability to enforce violations of the *Guidelines* beyond its own research funding is unclear. More positively, as the frequency of amendments indicates, because this is a guidance document, it is relatively easy to update based on current understanding of science and risk, and it has been suggested that voluntary compliance rates are high[10]. Over time, the *NIH Guidelines* have shifted farther into ensuring the safety of recombinant and synthetic DNA experts involving humans (human gene therapy). The *Guidelines* have retained their historic advantage of an associated Federal Advisory committee (now called the Novel and Exceptional Technology and Research Advisory Committee, NExTRAC) to provide a public setting for discussion and debate over the risks and benefits of emerging biotechnologies, with an emphasis on safety and ethics rather than security in keeping with the biosafety origins of the Committee[11].

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[8]Johnson and Dobos (2019 Dec. 1) The evolving landscape of Institutional Biosafety Committees and biosafety programs: results from a national survey on organizational structure, resources, and practices. *Applied Biosafety*, 24(4): https://www.liebertpub.com/doi/full/10.1177/1535676019886175

[9]*NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules (NIH Guidelines, April 2024):* https://osp.od.nih.gov/wp-content/uploads/NIH_Guidelines.pdf

[10]National Research Council (2004). Biotechnology Research in an Age of Terrorism: https://www.ncbi.nlm.nih.gov/books/NBK222056/

[11] NIH Office of Science Policy, Novel and Exceptional Technology and Research Advisory Committee (June 2024): https://osp.od.nih.gov/policies/novel-and-exceptional-technology-and-research-advisory-committee-nextrac/

Similar to the *NIH Guidelines,* the *BMBL* is not a regulatory document[12] and is not enforceable as such, beyond its use as a term and condition of award. The *BMBL* arose as a collaborative effort between the NIH and Centers for Disease Control and Prevention (CDC) in the 1980s to encourage the research community to develop and promulgate evidence-based practices and methods for ensuring the safety of personnel and the public from the hazards of biological research with pathogens. Now in its 6th edition, *BMBL* represents the collective efforts of hundreds of experts, inside and outside government, and is frequently cited as the gold standard of principles-based guidance for managing the risk of working with hazardous biological agents and toxins in a laboratory or clinical setting. In that sense, the U.S. has set the world's highest guideline for biosafety practice. It is from the BMBL, for instance, that we derive laboratory biosafety levels (BSL 1-4) which are so critical to establishing containment facilities. But as the authors of *BMBL* itself state, "The core principle of this document is protocol-driven risk assessment; it is not possible for a single document to identify all of the possible combinations of risks and mitigations feasible in biomedical and clinical laboratories. The BMBL should be used as a tool in the assessment and proposed mitigations steps…." In other words, use of the BMBL will always require some level of professional judgment and subjectivity, which makes it a weak policy instrument for accountability or codification of standards[13]. More recently, the BMBL has served as one of a number of guidance documents contributing to the development of ISO 350001:2019, Biorisk management for laboratories and other related organisations, which defines "a process to identify, assess, control, and monitor the risks associated with hazardous biological materials[14]", which may be better suited as an instrument of accountability.

- **Biological Select Agents and Toxins:** Notably the only actual regulation (Select Agent Regulations, 7 CFR Part 331, 9 CFR Part 121, and 42 CFR Part 73; effective February 7, 2003)in the U.S. biosecurity oversight framework, the Federal Select Agents Program (FSAP) was created in direct response to the anthrax attacks of 2001, as part of the nation's response to bioterrorism[15]. Codified in the *USA Patriot Act* (2001) *and Public Health Security and Bioterrorism Preparedness and Response Act* (2002), the FSAP is jointly administered by HHS/CDC and the USDA and is, in brief, a series of licensing requirements for both facilities and individuals to oversee the possession, use, or

[12] The website for the BMBL emphasizes this point, stating "We wish to emphasize that the sixth edition of BMBL remains an advisory document recommending best practices for the safe conduct of work in biomedical and clinical laboratories from a biosafety perspective. The BMBL is not intended to be a regulatory document…" (https://www.cdc.gov/labs/bmbl/index.html)

[13] Biosafety in Microbiological and Biomedical Laboratories, *6th Edition:* https://www.cdc.gov/labs/bmbl/index.html

[14] ISO 350001-2019 (Edition 1, 2019): https://www.iso.org/standard/71293.html

[15] *Ibid*, https://www.selectagents.gov/overview/history.htm

transfer of pathogens and toxins that pose a direct threat to human public, animal, or plant health. While there is overlap in FSAP requirements and biosafety containment practices, FSAP is a ***biosecurity*** policy, designed to keep dangerous agents and toxins out of the hands of actors who wished to use them for harmful purposes. The relevant agents and toxins are based on a list, developed through regulatory process, comprising nearly 70 regulated agents[16]. Those that pose the greatest threat are deemed 'Tier 1' agents and have an even higher bar of requirements for possession or use.

The FSAP has significant strengths and weaknesses as a mechanism of research oversight. Its strength lies in its power and conceptual simplicity. Although the requirements of the FSAP are detailed and complex, the fundamentals are not: a researcher can only conduct research with Select Agents in a registered, approved facility if they themselves are screened, approved, and licensed[17]. Anyone else is excluded from this work and consequences for noncompliance are significant in terms of fines and criminal penalties. However, a list-based system is itself a weakness, both in creating a barrier for regulating new and emerging threats or in reducing high-barriers to entry for research on agents that may pose a global health risk but are not likely agents for bioterrorism. Through years of biosecurity policy discussions, there have been questions raised about expanding the FSAP scope for oversight of emerging biosecurity or biosafety concerns, ranging from dual use research to proliferation of high-containment labs. However, because the ability to work with Select Agents is extremely limited due to the security controls, this would present a significant barrier to research that may not pose an immediate threat of bioterrorism or misuse.

- **Dual Use Research:** In the wake of the 2001 anthrax attacks, when the U.S. was understandably sensitized to the threat of bioterrorism, concerns were raised about a number of biological science publications, produced in the process of legitimate scientific inquiry, that could be misused as a "blueprint" for nefarious purposes. The focus on "dual use research" – which could be used for benefit or harm – was primarily on responsible communication of the research methodology and findings and the role of the scientific community (i.e. – funders, scientists, publishers, and institutions) to reduce the risk of those communications. The National Academies published a landmark study, *Biotechnology Research in the Age of Terrorism (*2004), commonly referred to as the Fink report, which for the first time called for additional oversight of dual use research, including laying out a list of pathogen experiments which might qualify as posing risk[18]. The Fink report also called for a Federal advisory group to help advise funding agencies on oversight, and the National Advisory Board for Biosecurity (NSABB) was established in

[16] Select Agents and Toxins List (2024, May 17): https://www.selectagents.gov/sat/list.htm
[17] *Ibid*, https://www.liebertpub.com/doi/10.1089/apb.2022.0025
[18] *Ibid*, https://nap.nationalacademies.org/catalog/10827/biotechnology-research-in-an-age-of-terrorism

2005, comprising science and security experts external to government and a USG wide representation of *ex officio* representatives.

The NSABB's *Proposed Framework for the Oversight of Dual Use Life Sciences Research* was released in 2007[19] and largely served as the basis for the federal policies for dual use research of concern (DURC), which emerged in 2012 and 2014 (and have been recently updated in a new policy released by OSTP described below). In reviewing the work of the NSABB through release of the USG policy in 2012, it remains clear that the greatest challenge in DURC oversight was agreeing on a definition of what constituted DURC. Despite of years of discussion and analysis, experts consistently disagreed on a definition that easily leant itself to a practical oversight system that didn't either capture too many low risk studies – which would hamper research progress – or missed studies that potentially posed risks. The compromise ultimately adopted by the federal agencies was to define the scope of DURC policy by a matrix of 15 Select Agents and 7 experimental approaches (similar to those identified by the Fink report and NSABB)[20]. The original DURC policy established review and risk-mitigation steps at both the federal agency and institutional level, including mandating the use of an Institutional Review Entity (most institutions repurposed their IBC). Institutions were encouraged to consult with federal agencies if they identified research that was outside the scope of the policy but still raised concerns, and a 2017 stakeholder consultation held by NIH to evaluate the DURC policy suggested that some institutions were reviewing and considering the risks of DURC beyond the list of agents listed in the policy. The government developed a companion guide to help investigators and institutions comply with the policy, which remains to this day an excellent benefit and risk assessment tool[21]. In addition to the public work of the NSABB and the many related reports, workshops, and meetings, the DURC policy was the result of an extensive interagency process run by the National Security Council and the Office of Science and Technology Policy (OSTP).

The limitation of the scope to a short list of already highly regulated Select Agents seemed to undercut the idea that nearly any research involving human pathogens and one of the experiments of concern could possibly pose dual use risks. It also created an opportunity for "checkbox compliance" because anyone not working with the 15 agents could ignore the policy and its intent. And yet the codification of the policy seemed to accomplish what decades of policy debate had not: a heightened awareness in the community of institutions and investigators working with high-risk pathogens that they

[19] National Science Advisory Board for Biosecurity. (https://osp.od.nih.gov/wp-content/uploads/Proposed-Oversight-Framework-for-Dual-Use-Research.pdf

[20] United States Government Policy for Institutional Oversight of Life Sciences Dual Use Research of Concern (2014, Sept. 24): https://www.phe.gov/s3/dualuse/Documents/durc-policy.pdf

[21] A companion guide to the USG policies for oversight of life sciences dual use research of concern (Sept. 2014): https://www.phe.gov/s3/dualuse/Documents/durc-companion-guide.pdf

had to pay attention not just to the biosafety risk of working with the agents and the biosecurity risks related to potential loss of the agents, but also the information and experimental hazards related to laboratory manipulation of these pathogens. The DURC policy was never designed to stop experiments – because the very term "dual use" suggests inherent benefit – but having to comply with it forced agencies, investigators and institutions, just by virtue of the evaluation process, to pause for a moment and think about the relative risks of the proposed experiments and how they might be mitigated.

Another major theme that has persisted through the NSABB's nearly two decade existence is the challenge of controlling information in an open science environment. Most of the policy debate around DURC was not about the experiments themselves – there was overwhelming sentiment that the work was important and could yield benefits to advances in human health – but whether it was appropriate to share all of the methodology for how to, for example, enhance the virulence of a mousepox virus, for fear of that technique being misused. Discussions at NSABB meetings, in policy discussions worldwide, in reports published by thinktanks and experts generally reached the conclusion that while it was important to frame the work appropriately in terms of justifying how the potential benefits outweigh the risks, there were a host of practical and philosophical obstacles to limiting research publications. These obstacles ranged from scientific integrity and reproducibility to open records laws to the removal of the fundamental research exemption of export control policies. However, the policy discussion itself resulted in publishers of pathogen research results to put in place policies and procedures to review manuscripts for dual use concerns and work with authors to communicate their findings responsibly.

- **Oversight of Enhanced Pathogens of Pandemic Potential:** In addition to their work on DURC policy, the NSABB was at the center of the policy discussion in 2012 over laboratory experiments that increased transmissibility of influenza, raising public concern over research that could enhance the pandemic potential of existing pathogens. When two proposed publications on avian influenza, funded by NIH and conducted in labs at the University of Wisconsin-Madison and Erasmus University in the Netherlands, were reviewed by NSABB prior to publication, the Board made an unprecedented recommendation that the articles not be published (later it reversed that decision). Although this led to global policy discussion and Congressional oversight hearings, it is important to recognize that the initial policy debate was really an extension of the dual use research conversation: to publish or not to publish? As Senator Joe Lieberman, then HSGAC Chair summed up the issue during oversight hearings, "[G]iven the lethality of the virus, publishing the results could create huge security risks by offering a blueprint

for a deadly biological weapon.[22]" Which isn't to say that the question of appropriate biosafety and biosecurity policies and review of research were not being raised – for example in a 2012 *New York Times* opinion piece[23]- but the policy discussion shifted significantly in the direction of asking whether such research should be done at all and did it merit oversight above and beyond existing mechanisms in 2014, when a series of biosafety lapses in federal labs occurred, launching a major investigation of the adequacy of U.S. biosafety and biosecurity policies.[24]

Shortly thereafter (October 16, 2014), NIH announced a moratorium on what was called "gain of function" (GOF) experiments involving influenza and two coronaviruses, SARS and MERS[25] while awaiting the results of a deliberative policy process led by the White House OSTP[26] "to assess the potential risks and benefits associated with a subset of life sciences research…" The pause included an exemption process for studies that addressed urgent public health need, which included early studies to develop animal models for MERS[27]. This deliberative process, which ultimately took three years, concluded with the NSABB issuing a report and recommendations for oversight of what it called "gain of function research of concern" (GOFROC)[28] which was then used by the NSC/OSTP interagency to develop "Recommended Policy Guidance for Departmental Development of Review Mechanisms for Potential Pandemic Pathogen Care and Oversight (P3CO)", released on January 9, 2017[29]. There was an extraordinary amount of input into this 3 year policy process, including six public NSABB meetings, two open

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[22] "Committee plumbs policies for publishing high risk scientific research: (2012, April 26): https://www.hsgac.senate.gov/media/reps/committee-plumbs-policies-for-publishing-high-risk-scientific-research/

[23] New York Times editorial (2012, March 3) "The truth about the doomsday virus?" https://www.nytimes.com/2012/03/04/opinion/sunday/the-truth-about-the-doomsday-virus.html

[24] Owens (2014, July 26) Anthrax and smallpoz errors highlight gaps in U.S. biosafety. *Lancet,* 283(9940) :294. https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(14)61246-0/fulltext

[25] NIH Director's Statement on Funding Pause on Certain Types of Gain-of-Function Research (2014, Oct. 16): https://www.nih.gov/about-nih/who-we-are/nih-director/statements/statement-funding-pause-certain-types-gain-function-research

[2626]Doing diligence to assess the risks and benefits of life science gain-of-function research (2014, Oct. 17) https://obamawhitehouse.archives.gov/blog/2014/10/17/doing-diligence-assess-risks-and-benefits-life-sciences-gain-function-researcH

[27] Kaiser (2014, Dec. 18) « Moratorium on risky experiments lifted for MERS mouse studies. *Science* news. https://www.science.org/content/article/moratorium-risky-experiments-lifted-mers-mouse-studies?adobe_mc=MCMID%3D55904419230330112713971932519358154690%7CMCORGID%3D242B6472541199F70A4C98A6%2540AdobeOrg%7CTS%3D1720211814

[28] NSABB (May 2016) Recommendations for the Evaluation and Oversight of Proposed Gain of Function Research: https://osp.od.nih.gov/wp-content/uploads/2016/06/NSABB_Final_Report_Recommendations_Evaluation_Oversight_Proposed_Gain_of_Function_Research.pdf

[29] Recommended Policy Guidance for Potential Pandemic Pathogen Care and Oversight (2017, Jan. 9): https://obamawhitehouse.archives.gov/blog/2017/01/09/recommended-policy-guidance-potential-pandemic-pathogen-care-and-oversight

National Academies symposia, an 1100 page independent risk-benefit analysis by Gryphon Scientific, an ethical analysis, and external stakeholder feedback.

The deliberative process brought forth a number of issues, some of which remain relevant to today's policy debate. First, the term "gain of function" was a source of much controversy. From the outset, virologists objected to the use of the term in the context of discussions about a very specific area of research (namely laboratory manipulations that increased the risk of viruses by enhancing virulence and/or transmissibility)[30]. They argued that "gain of function" was a broad term of art in microbiology research and that it was an inartful term for the influenza studies at the heart of the debate. While NSABB continue to use the term GOF in its final report, OSTP's policy guidance deliberately moved away from the term, replacing it with "enhanced pandemic potential pathogen" experiments and HHS's resulting review policy (described below) does not use the GOF terminology, at all.

A second observation of the enhanced pathogen of pandemic potential policy debate was that although the majority of experts weighed in thoughtfully and seriously about how to appropriately balance what they saw as both necessary benefit and high-consequence risk for this research, there was a small, but passionate, number of scientists who saw no value in the research or thought the likely benefit was minimal and far outweighed by the risk of misuse or accidental release and advocated for a total ban in public funding or an outright legal prohibition (to be fair, there was also a vocal minority who saw no need for any additional oversight). Although that point of view was heard substantively during the policy debate, policymakers ultimately allowed the research to move forward with additional oversight.

On December 19, 2017, HHS released their *Framework for Guiding Funding Decisions about Proposed Research Involving Enhanced Potential Pandemic Pathogens*[31] *and* NIH lifted their funding pause[32]. The framework required funding proposals that met the ePPP definition described by OSTP to undergo a multidisciplinary Department-level review before funding decisions were made. Importantly, the concept of additional scrutiny for high-risk pathogen experiments was not new to HHS; prior to the 2017 framework, they had already been reviewing certain influenza studies under the HHS *Framework for Guiding Department of Health and Human Services Funding Decisions about Research Proposals with the Potential for Generating Highly Pathogenic Avian Influenza H5N1 Viruses that are Transmissible among Mammals by Respiratory*

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[30]NSABB Meeting Materials (2014, Oct. 22) https://osp.od.nih.gov/events/national-science-advisory-board-for-biosecurity-nsabb-meeting-20141022/

[31]HHS framework for guiding funding decisions about proposed research involving enhanced potential pandemic pathogens (2021, Sept. 27): https://www.phe.gov/s3/dualuse/Pages/p3co.aspx

[32] https://www.nih.gov/about-nih/who-we-are/nih-director/statements/nih-lifts-funding-pause-gain-function-research

Droplets[33]*.* This process was put in place in 2013 in response to the two influenza publications that had begun the "gain of function" debate.

The P3CO approach to reducing the risk of experiments involving potential pandemic pathogens has notable positive attributes and flaws. It is an appropriately rigorous process, involving government experts across a range of expertise – including infectious disease, security, public health, biosafety, policy, and communications – and because it takes place before funding decisions are made, there is opportunity both to decide *not* to fund the research with taxpayer dollars or to ensure the correct risk mitigation measures are built into the terms and conditions of the award. Unfortunately, the pre-funding decision nature of the review, is also a major weakness, because it inherently limits transparency of the process. Prior to funding, grant applications are subject to high degrees of confidentiality, to protect the intellectual property therein. Even Federal advisory committees, which statute generally deems to be highly public bodies, enter closed session when making funding decisions. This lack of transparency around high-risk research decisions was publicly criticized in 2019[34], leading to the Trump Administration charging the NSABB to revisit the question of transparency and public communication around the P3CO process in early 2020[35] (not surprisingly, that process was quickly derailed by the COVID-19 pandemic).

- **Terms and conditions of award:** In thinking about the opportunities and gaps in oversight of federally funded research, it is important not to forget the terms and conditions of research grants and contracts, through which policies are frequently implemented, augmented, or held to account. For example, while the BMBL is not a regulatory document, it is often included in the terms and conditions of NIH awards, indicating an expectation of "compliance" with that guidance document. Because violation in a term and condition of a federal grant can lead to significant consequences for institutions (who are the awardees, rather than individual scientists), from defunding to debarment, institutions frequently comply with "requirements" in research award terms as if they had the strength of regulation or law. It is not unusual for funding agencies to add specific terms and conditions for high-risk research, such as requiring foreign facilities to undergo inspection by Select Agent officials, although they are not subject to U.S. law and regulation.

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[33] Framework for guiding U.S. Dept of HHS Funding Decisions about research proposals on HPAI H5N1: https://www.phe.gov/s3/dualuse/Documents/funding-hpai-h5n1.pdf

[34] Lipsitch and Inglesby (2019, Feb. 27) "The U.S. is funding dangerous experiments it doesn't want you to know about." *Washington Post,* Opinion. https://www.washingtonpost.com/opinions/the-us-is-funding-dangerous-experiments-it-doesnt-want-you-to-know-about/2019/02/27/5f60e934-38ae-11e9-a2cd-307b06d0257b_story.html

[35] NSABB Meeting materials (202, Jan 23): https://osp.od.nih.gov/events/national-science-advisory-board-for-biosecurity-nsabb-meeting-20200123/

- **New OSTP Policy on DURC/PEPP:** In response to the 2022 National Biodefense Strategy and appropriations language passed by Congress, OSTP has released an updated policy for oversight of DURC and pathogens with enhanced pandemic potential (PEPP), essentially combining and expanding the two previous policies[36]. The new policy expands the scope of oversight to many more biological agents, but simplifies the oversight schema into Category 1 experiments (previously DURC) and Category 2 experiments (previously P3CO), encourages voluntary oversight for both non-federally funded research and DURC research that might fall outside the defined scope of the policy, and increases communication between the researcher (PI or principal investigator), institutions, and federal agencies. Otherwise, the processes of local, agency, and federal departmental level review are fairly similar with previous policies, although it specifies some more independence and interagency collaboration for PEPP review at the Department level. The OSTP policy is an important and positive step forward for our evolving biosecurity oversight framework, particularly in looking beyond human health to agricultural pathogens, but the devil will ultimately be in the details of implementation, which is awaiting further agency guidance.

Second, throughout this evolving policy discussion, the central question and challenge has not really changed: how do we appropriately balance risk and benefit of high-consequence research when there is inherent uncertainty on both sides of the equation? We undertake scientific inquiry, or research, because there are questions about the world around us for which we have no answers. Nature's ability to surprise us feels infinite, which is why we are always vulnerable to the next emerging health threat. That also means that when we ask scientific questions or perform experiments, we will lack clarity around whether or when we will realize benefit from that research or if it will pose risks that outweigh those benefits. Well-meaning technical experts can – and experience teaches us *will* – disagree on the magnitude of benefit and risk. Moreover, there will always be some level of subjectivity as to what constitutes an acceptable level of risk relative to the benefit and vice versa. In fact, we are seeing in real time how powerful new artificial intelligence (AI) technologies are creating extraordinary new benefits and evolving biosecurity risks – and accelerating the time where pathogen-based systems for risk identification will be obsolete. There are no easy or perfect answers, and we learn as we go, which is why our policies appropriately continue to evolve.

The risk that a pathogen, whether naturally emerging or re-emerging or manipulated in a laboratory, is constantly changing and is subject to a number of factors which are themselves constantly changing. These might include not just the severity of the disease caused and method of transmission, but also whether the disease is endemic or widespread in a given area,

[36] U.S. government policy for oversight of dual use research of concern and pathogens with enhanced pandemic potential. (May 2024) https://www.whitehouse.gov/wp-content/uploads/2024/05/USG-Policy-for-Oversight-of-DURC-and-PEPP.pdf

the availability of countermeasures, and our understanding of the pathogen itself and what measures are needed to contain or combat it. The magnitude of risk will shift over time, depending on the imminency of the threat. For example, once it became clear that COVID-19 was widespread, and we had few effective countermeasures, it would not have made sense to limit research for BSL-4 laboratories, despite the dangerousness of the virus, because that would have drastically reduced the innovation capacity dedicated to addressing the urgent need for vaccines, diagnostics, and treatments.

Working with pathogens in a laboratory clearly introduces the risk of infection to workers in the laboratory and, in theory, increases the risk that pathogens could escape the lab through theft or accident. It is worth noting that there is very little evidence of occurrence of the latter scenario – pathogens escaping from a laboratory and causing an outbreak of disease - in the history of biomedical research[37][38], but the risk is not zero, which is why both worldwide norms and standards for biosafety and biosecurity need to be high and research oversight is important. However, we also know that the risk of naturally occurring diseases, particularly through zoonotic spillover is also increasing, due to the impact of urbanization, deforestation, climate change, and other activities that bring humans into close proximity with animals[39]. Oversight mechanisms for reducing the risk of working with laboratory pathogens need to be carefully weighed against the risk of creating barriers to the development of new countermeasures against biological risks.

A common theme in the debate about oversight of dual use pathogen research has always been a striking lack of consensus among scientific experts. In some ways, this is a hallmark of scientific research itself: if we knew the answers, there would be no reason to pursue the scientific question. But, as described in the history of DURC policy above, this makes it both hard to easily define the research we are trying to oversee and to evaluate the potential risk and benefits of such research. However, there is a difference between healthy debate and overweighing a minority opinion against overwhelming expertise and scientific evidence. Minority views are critically important in science, history has taught us they can lead to paradigm shifting understanding, and questioning the status quo forces more rigorous examination of the evidence and helps shape the next set of experiments. Fairness and equality are integral American values, and part of what has long made us the envy of the world, but it also leaves us vulnerable to false equivalencies. There is risk in the scientific equivalent of

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[37] Gryphon Scientific. (Dec. 2015) Risk and benefit analysis of gain of function research. https://osp.od.nih.gov/wp-content/uploads/2015/12/Risk%20and%20Benefit%20Analysis%20of%20Gain%20of%20Function%20Research%20-%20Draft%20Final%20Report.pdf

[38] Gronvall. (2021, Nov 26) The contested origins of SARS-CoV-2. *Global Politics and Strategy,* 63(6):7-36. https://www.tandfonline.com/doi/full/10.1080/00396338.2021.2006442

[39] Esposito *et al*. (2023, May) The impact of human activities on zoonotic infection transmissions. *Animals (Basel)*, 13(10): 1646. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10215220/#:~:text=New%20studies%20have%20shown%20that,in%20zoonotic%20pandemics%20as%20well.

'minority rule', and we need to be appropriately skeptical of a vocal minority of scientific views serving as the foundation for evidence-based science and public health policy.

Finally, the U.S. has served for decades as the worldwide leader in biological sciences, as well developing policy tools and practices to reduce biological risk. From the early days of biosecurity conversations following the 2001 anthrax attack, it has been clear that there is a tension between those two, particular set against the stage of international competition and collaboration. While that was an initially a conversation about whether the U.S. could maintain science leadership if it created risk-mitigation measures that reduced our scientists' ability to innovate, the conversation has shifted as other nations, from Europe to Asia, have expanded their research capacity and talent for investigating viral pathogens. This is particularly true in the wake of the global effort to combat the COVID-19 pandemic. It is imperative that the U.S. not lose either the claim to research excellence or the interrelated ability to drive the norms and standards by which laboratories conduct research around the world. Funding of infectious disease research through international collaborations, the cultivating of foreign talent in U.S. laboratories, and the building of research capacity through training and infrastructure around the world provides the U.S. with levers to expect and enforce global biosafety and biosecurity norms and, in doing so, reduce worldwide risk associated with pathogen research.

Third, in thinking about policies to reduce risk of pathogen research, we can't lose sight of the risk of limiting innovation or creating rigid frameworks that are not agile enough to respond to new and emerging threats. The reason this policy discussion has continued for more than two decades is because it has always been clear that research on high-consequence pathogens is critical and necessary for developing the countermeasures needed to protect human, animal, and plant health. Simply put, if we make it too hard for scientists to conduct and communicate the finding of experiments that expand our knowledge of pathogen function, pathology, and evolution, we will be less prepared for the next emerging biological threat. It is very easy to become focused on the risk of ***doing*** the research and lose sight of the risk of ***not doing*** the research. Additionally, in an increasingly competitive global environment we must consider how best reduce safety and security vulnerabilities in a way that does not stifle American innovation or competitiveness.

As scientists, we are not always humble when describing the magnitude of what we do not know about the world around us. It is easier to focus on the excitement of discoveries and advancement, and the rate of discovery in the life sciences in recent decades has accelerated dramatically, spurred by public investment in scientific research. However, each new or re-emerging virus reminds us how little we know about these bits of "bad news wrapped in protein", as Nobel laureate Sir Peter Medawar once said. As sophisticated as our ability to rapidly assess viral genomics and structure have become, we are still a long way from understanding or predicting how viral structure will relate to disease. Even as we speak, and despite decades of rigorous research on influenza viruses, the current H5N1 outbreak is re-writing the textbook on what we understand about avian flu. The riskiest experiments in

functional enhancement of dangerous pathogens are not taking place in the laboratory. They are happening in real time, in the real world, in naturally occurring viruses and other pathogens, and it is critical that we be able to learn how that evolution relates to health risk.

But there is more that can be done to strengthen the current system. The new OSTP policy for oversight of dual use research is an important step forward, but the details of implementation will be important, and resources are critical for training the broader swath of the scientific community who will be affected by the policy. There is more Congress can do to bolster the global approach to biosafety, which is primarily based on guidelines and professional practices, including encouraging adoption of international standards like ISO 35001 and developing a non-punitive safety reporting system akin to the ASIAS system used by the aviation industry. Finally, global health security and prevention of the next pandemic requires rigorous support of capabilities that allow us to rapidly respond to new and emerging threats, by strengthening surveillance systems, adopting a One Health approach to zoonotic diseases, and investing in the research and manufacturing capacity to meet the goals of rapid development of diagnostics, vaccines, and treatments often referred to as the '100 Day Mission'. All of these should stand on the principles of transparency, continued U.S. leadership in driving the highest norms and standards for research oversight and balancing the reduction of risk with the need for innovation.

- **Adopting and promulgating international biosecurity and biosafety standards:** The International Organisation of Standards (ISO) has recently released ISO 35001 "Biorisk management for laboratories and other related organisations" creating a consensus standard to which organizations could be held accountable for identifying, evaluration, controlling and monitoring the risks associated with the use of laboratory biorisks. Adoption of such a standard has been demonstrated to increase the quality of safety and security practices in laboratory settings[40]. Congress could consider what actions it could take to encourage widespread adoption and use of ISO 350001.

- **Enabling sharing and use of safety data:** A recommendation of the 2014 FESAP/FTAC-SAR was a non-punitive safety incident reporting system for laboratories working with high-risk pathogens to increase transparency for the public and creating a culture of learning and improvement for laboratory biosafety and biosecurity. While not implemented, this remains a sound idea and could be built on the public-private partnership model[41] of similar systems in the aviation safety community, like the

[40] Calilhan *et al* (2021, Dept. 13) Considerations for laboratory biosafety and biosecurity during the COVID 19 pandemic: applying the ISO:350001:2019 standard and high-reliability organizations principles. *Applied Biosafety,* 26(3): https://www.liebertpub.com/doi/10.1089/apb.20.0068

[41] Described in greater detail in the testimony of Dr. Charles Clancy before the House Select Committee on Strategic Competition between the U.S. and CCP (pg.6 of attached document): https://selectcommitteeontheccp.house.gov/sites/evo-

Aviation Safety Information and Analysis Sharing System (ASIAS)[42], or the cybersecurity community's CVE system[43]. I would encourage Congress to consider how to stand up such a system for reporting of biological incidents from publicly and privately funded laboratories.

- **Increasing security awareness and preparation of the research community:** For those of us who have been working in biorisk policy for many years, it can be easy to lose sight of how little experience most researchers have with thinking about their research in a security context. Previous examinations have shown that when researchers are made aware of security risks, they will voluntarily act to reduce risk[44]. Given that policy proposals will expand the scope of research that will be subject to biosecurity expectations, and to ensure that the scientific community is an expert and engaged partner in biorisk reduction, Congress could require and provide resources for security training related to biological risk and emerging technologies for federally funded scientists.

- **Supporting applied biosafety and biosecurity research:** Experts, stakeholders, and policymakers largely agree with the need for an evidence- and risk-based system for ensuring biosafety and biosecurity[45], but that presumes we know what works best in various settings and situations. The need for federal investment in applied biosafety and biosecurity research has long been recognized by interagency groups[4647] and third party validators[4849], yet has no materialized. Congress could support such investment and create mechanisms for best practices discovered to be incorporated into federal oversight requirements.

- **Increasing transparency around high-risk research review:** Although it remains critically important to protect intellectual property and the ideas of researchers, particularly in a

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subsites/selectcommitteeontheccp.house.gov/files/evo-media-document/Dr.%20Charles%20Clancy%20-%20SCC%20Testimony.pdf

[42]Aviation Safety Information Analysis and Sharing overview: https://portal.asias.aero/overview

[43] CVE program overview: https://cve.mitre.org/index.html

[44] National Academies (2009) Report in Brief: A survey of attitudes and actions on dual use research in the life sciences: https://nap.nationalacademies.org/resource/12460/pga_055298.pdf

[45] Blacksell *et al* (2023, Sept. 26) Investment in biosafety and biosecurity: the need for a risk-based approach and systematic reporting of laboratory accidents to mitigate laboratory-acquired infections and pathogen escapes. *The Lancet*, 4(11): E854-E855. https://www.thelancet.com/journals/lanmic/article/PIIS2666-5247(23)00288-4/fulltext

[46] FESAP Recommendation 1.6: https://www.phe.gov/s3/Documents/fesap-ftac-factsheet.pdf

[47] https://www.whitehouse.gov/wp-content/uploads/2022/04/04-2022-NSTC-ST-Biorisk-Research-Roadmap_FINAL.pdf

[48] Casagrande (2019, Aug. 6) CSIS Brief: Federal funding for biosafety research is critically needed: https://www.csis.org/analysis/federal-funding-biosafety-research-critically-needed

[49] *Ibid* https://www.liebertpub.com/doi/10.1089/apb.2022.0025

globally competitive environment, by not disclosing the content of pre-funded applications, the public has expressed a strong interest in knowing when, how, and what risk mitigations measures are in place for federally funded studies of pathogens enhanced for pandemic potential. Public trust in the oversight and outcomes of science is crucial to support and acceptance of the benefits of research, and transparency can help build that trust. Congress could consider ways to increase transparency around review of this research, perhaps by encouraging release of review committee proceedings immediately following funding decisions or creating special government employee (SGE) roles for designated members of the public.

- **Strengthening systems of pandemic preparedness and response:** As a nation, we need to be better prepared to respond to biological risk, regardless of whether they are naturally occurring, related to laboratory research, or the result of malicious action by a state actor or bioterrorist. Congress could support, through authorization and appropriations, the research, infrastructure, and capacity building needed to strengthen our public health systems, fulfill the 100 Day Mission, which aims to produce new safe and effective vaccines, therapeutics, and diagnostics within 100 days of the emergence of future threats, and could support the goals of the National Biodefense Strategy[50].

- **Adopting a One Health perspective:** The majority of infectious disease outbreaks arise from zoonotic causes, spilling over from animal populations to humans, in addition to other global health threats, such as antimicrobial resistance (AMR), emerging from human-animal intersections[51]. One Health recognizes that human health is closely connected to animal health and the environment and is an approach that should be integral to prevention, preparedness, and response for biological risks. Barriers for a One Health approach include lack of resources, siloed federal departments and agencies, lack of interdisciplinary collaboration between communities of experts, and non-interoperable data resources. While other nations have supported One Health policies and investments[52], the U.S. has not been a strong leader in this approach. Congress could support legislation and funding to strengthen One Health policies and to break down silos across the federal government and within the private sector.

Thank you for the opportunity to present these views, and I stand ready to discuss them further.

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[50] National Biodefense Strategy and Implementation Plan (Oct. 2022) https://www.whitehouse.gov/wp-content/uploads/2022/10/National-Biodefense-Strategy-and-Implementation-Plan-Final.pdf

[51] NASEM (2022, Jan. 11) Systematizing the One Health approach in preparedness and response efforts for infectious disease outbreaks: Proceedings of a workshop: https://www.ncbi.nlm.nih.gov/books/NBK579477/

[52] https://www.woah.org/en/the-quadripartite-launches-a-guide-to-support-countries-implement-one-health-approach/