Recommendations to Strengthen the US Government's Enhanced Potential Pandemic Pathogen Framework and Dual Use Research of Concern Policies

The purpose of this document is to provide recommendations to the US Government (USG) and the National Science Advisory Board on Biosecurity (NSABB)[1] as revisions are being developed regarding oversight of enhanced potential pandemic pathogen (ePPP) research and dual-use research more broadly.

Research in the life sciences, especially research with microbial agents, addresses major challenges in medicine, public health, and the environment, and offers important benefits. However, life science research can also pose risks, particularly in the realm of enhancing potential pandemic pathogens (PPP) and other dual-use challenges. COVID-19 has shown the global impact of a highly transmissible virus that causes mortality and morbidity. Experiments that create the possibility of initiating such a pandemic require rigorous assessment. Increased access to the ability to create and engineer pathogens, driven partly by continued advancements in general purpose tools and methods, presents new challenges for carefully governing this work.

Research involving potential pandemic pathogens could lead to modified pathogens capable of spreading beyond control; modified pathogens with the ability to evade existing countermeasures; or, published and publicly available information that could enable subsequent synthesis of such pathogens. The White House Office of Science and Technology's (OSTP) "Recommended Policy Guidance for Departmental Development of Review Mechanisms for Potential Pandemic Pathogen Care and Oversight (P3CO)"[2] and the US Department of Health and Human Services' (HHS) "Framework for Guiding Funding Decisions about Proposed Research Involving Enhanced Potential Pandemic Pathogens,"[3] taken together, were important and useful developments in diminishing risks related to research that enhances the pandemic potential of pathogens. We will refer to these two documents taken together as the **ePPP Framework** for the remainder of this document. Similarly, the "United States Government Policy for Oversight of Life Sciences Dual Use Research of Concern"[4] (DURC) was an important step forward. However, there are critical gaps in these guidance documents that need to be addressed as part of the current USG review process and concomitant NSABB review. The USG has an extraordinary obligation to prevent USG funding or approval of work that could start an epidemic or pandemic, as well as to provide international leadership in this realm.

The goals of the recommendations in this document are to:

- Diminish the risk that US science could inadvertently initiate epidemics or pandemics

1 https://osp.od.nih.gov/biotechnology/national-science-advisory-board-for-biosecurity-nsabb/

2 https://www.phe.gov/s3/dualuse/Documents/P3CO-FinalGuidanceStatement.pdf

3 https://www.phe.gov/s3/dualuse/Documents/P3CO.pdf

4 https://www.phe.gov/s3/dualuse/Documents/us-policy-durc-032812.pdf

- Clarify scope and the decision-making process associated with governance of ePPP research and dual-use science
- Increase transparency around US policy and decision making on these issues
- Minimize or eliminate disruption of scientific work that does not pose these risks.

RECOMMENDATIONS

1. **Modify and expand the scope of pathogens to be governed by the ePPP Framework**

   We recommend 3 modifications to the intent and scope of the ePPP Framework:

   a. The existing ePPP Framework defines a PPP as a pathogen meeting both criteria of high transmissibility and high virulence. The virulence criterion states that a PPP "is likely highly virulent and likely to cause significant morbidity and/or mortality in humans." In the absence of an explicit quantitative criterion, prior to the COVID-19 pandemic, this criterion could plausibly have been interpreted as requiring pathogens that are only above a certain threshold of infection fatality rate (IFR), such as SARS-CoV-1 and highly pathogenic avian influenza H5N1. However, the experience of COVID-19 in 2019-22 has shown that with a sufficient level of transmissibility, a pathogen with an IFR considerably lower than 1% can cause global societal and economic disruption, widespread mortality, and collapse of health systems. **We recommend that the ePPP Framework be modified to make explicit that conferring efficient human transmissibility on a pathogen of even modest virulence should be considered as creation of an ePPP, and therefore covered by the ePPP Framework.**

   b. The ePPP Framework is unclear as to whether it governs research that (i) is reasonably anticipated to enhance an existing potential pandemic pathogen (PPP) vs. (ii) is reasonably anticipated to enhance virulence or transmissibility of any pathogen to make it become an ePPP, irrespective of whether the starting pathogen meets the criteria of transmissibility and virulence for a PPP. Interpretation (i) includes only a subset of the experiments that would be included in interpretation (ii). Given the possibility that engineering or directed evolution of pathogens could confer new epidemic or pandemic potential to viral families that do not now possess it, the ePPP Framework should not be limited to pathogens already recognized as having pandemic potential. Experiments reasonably anticipated to change the host range of pathogens in ways that could lead to efficient human transmission should also be governed by the ePPP Framework. **Because the risk of creating an ePPP does not depend on the starting point, but rather on the end-product, we recommend the ePPP Framework be broadened to incorporate research that could enhance the virulence or transmissibility of any pathogen to produce an ePPP (interpretation (ii)).** For example, if researchers were to propose experiments reasonably anticipated to make a filovirus or a lyssavirus highly transmissible among humans, then that work should be governed by the ePPP Framework, even though the starting virus did not have pandemic potential.

c. A growing number of practitioners are capable, with increasing ease, of synthesizing viruses in the laboratory. For these individuals, the availability of a viral genome sequence is equivalent to the availability of the virus itself. The existing ePPP Framework does not give adequate attention to this reality. For example, there is insufficient attention to oversight and control of sequence information about ePPPs, including the significant risks posed by computational methods for designing PPPs with enhanced properties, e.g., using artificial intelligence (AI) approaches. There also is insufficient attention to anticipatory local biosafety measures at the locations where efforts to synthesize the physical realization of potential ePPPs might take place. **We recommend that the ePPP Framework address and establish oversight of sequence information about ePPPs, the risks related to computational methods for designing PPPs, and biosafety measures related to synthesis of ePPPs.**

2. Assess and Detail Risks and Benefits

a. **Articulate risks that must be considered in the ePPP Framework review process.** Categories of risks that must be considered in the ePPP review process are not stated in the current ePPP Framework. We recommend that the newly updated ePPP Framework is explicit that the ePPP review process should evaluate the risk and potential consequences of accidents, deliberate theft of an isolate, and insider diversion, as well as the risk that information about or from the research could subsequently be used in ways leading to accidents or deliberate harm. The ePPP Framework risk assessment also should include considerations of unintentional outcomes over the course of the research, in addition to the intended outcome. Many methodologies in the life sciences can cause off-target effects, such as pushing an individual microbial strain to change or causing a microbial population to evolve in unpredicted ways. The ePPP risk assessment should include considerations of ethical, legal, societal, and security ramifications of the work, in addition to risks to the laboratory and its staff. The updated ePPP Framework should provide guidance to scientists who are proposing this type of work, both in terms of expertise required and the process to be used. For example, one goal of this process should be to ensure the scientific community is doing its own rigorous risk assessments, before the USG initiates its formal ePPP Framework.

b. **Reconsider the relationship between ePPP creation and vaccine development and between ePPP creation and surveillance**. At present, Section II.C. of the HHS Framework[5] reads:

"To the extent that transmissibility and/or virulence of PPPs are modified in the following categories of studies, the resulting pathogens are not considered to be enhanced PPPs for the purposes of this Framework:

- Surveillance activities, including sampling and sequencing; and
- Activities associated with developing and producing vaccines, such as generation of high growth strains."

5 https://www.phe.gov/s3/dualuse/Documents/P3CO.pdf

- We fully recognize that surveillance activities restricted to the sequencing of samples and isolates are of important benefit and of relatively little risk. However, surveillance activities increasingly include efforts to assess the clinical or public health relevance of newly discovered sequences of potential pathogens by expressing entire viral genome sequences or portions of these genome sequences within the "backbone" of a known viral genome as a chimera. These chimeras may constitute ePPPs. Thus, we recommend this work be subject to the ePPP Framework.

- Vaccine development activities generally pose fewer risks related to the production of ePPPs because these activities are designed and intended to yield products of low or minimal virulence. However, efforts to create transmissible vaccines raise issues similar to those mentioned in recommendation 1 (a) (the disproportionate risks associated with transmissibility). Thus, we recommend that vaccine development work be judged based on the properties of the anticipated product, rather than assumed in all cases to be associated with lesser risks.

c. **Distinguish between practical and realizable benefits and unsupported claims of benefit.** Will the benefits of the research result in new public health, medical, or pharmaceutical approaches that reduce the risks posed by this pathogen? For example, if the primary potential benefit is improving public health surveillance but there is not a framework in place for public health to use the potentially improved system, then that potential benefit should not be weighted as highly as it otherwise could be. Similarly, if the proposed benefit is to provide new vaccines, but vaccine manufacturers do not judge the proposed research to be useful or relevant to their work, that should be taken into account. How critical is the information that would be gained by the proposed work; how long will it take for possible benefits to be realized; are there other safer ways of attaining comparable information; how consequential are the risks? We recommend that assessment of benefits provide answers to the above questions.

d. **Consider the possibility that generalizing from ePPP findings could be misleading.** A broad concern is that the information gained from studies on any particular pathogen is of uncertain relevance to characterizing pathogens of subtly different genetic sequence from those studied, as has been documented repeatedly in the case of influenza.[6] Therefore, we recommend that risk-benefit assessments consider the possibility that the information could mislead and cause harm to these efforts. For example, inaccurate understanding of the requirements for transmissibility due to generalization from experimental enhancements could lead to inaction following identification of a virus that lacks properties believed to be necessary for transmissibility.

6 https://elifesciences.org/articles/18491

3. **Clarify and Restructure Processes of Review, Communication, Biosafety and Biosecurity, and Transparency**

   a. **Define the meaning of "responsible communication of results."** The ePPP Framework and Dual Use Research Guidance refer to the need for investigators to responsibly communicate, but there is no identified process for this. When these policies call for "responsible communication of results," this presupposes there are existing approaches and pathways to safely and practically do so. But such approaches are not clearly defined and developed. We recommend that formal pathways for responsible communication be developed if the recommendation for responsible communication continues to be part of the ePPP Framework and Dual Use Research Guidance going forward. Fulfilling this recommendation would help avoid false reassurance that there is a clearly developed path for "responsible communication."

   b. **Expand the stakeholders involved in the review and approval process.** To thoroughly assess risks and benefits, many types of expertise are needed, including experts in science, biosafety, biosecurity, public health, vaccine manufacturing, and bioethics. Nongovernmental expertise should be sought out and included in each review process. Clinical and public health expertise should be part of the ePPP review since in the event of an epidemic or pandemic resulting from the work, these experts would be key players in the response. Representatives of civil society also should be included, given the widespread ramifications. In addition to including a broad range of experts in the review and approval process, we recommend that a published summary of the expertise involved should be part of every ePPP review.

   c. **Recuse any individual whose agency is funding or participating in the proposed ePPP work from decision making in the ePPP review process.** Experts involved in the ePPP review process should be subject to conflict-of-interest rules that allow them to provide expert input but require them to recuse themselves from the decision-making process.

   d. **Define the necessary standards for biosafety and biosecurity to carry out approved research.** There is a lack of familiarity with biosecurity especially among life scientists, even those working with pathogens. Biosecurity is not often covered in degree programs or other training avenues. For biosafety, there are large differences in how institutions choose to train students and new staff. All life scientists working with infectious agents should have rigorous training in both biosafety and biosecurity.

      The USG policy states that the researcher and institution must have the demonstrated capacity to conduct ePPP research safely and securely, but no specific guidelines or baseline standards for demonstrating this capacity are defined. We recommend that these safety and security standards be clearly defined in the updated ePPP Framework, including standards for managing information hazards. If ePPP research is approved by the federal government, state and local authorities should be consulted to ensure that biosafety and biosecurity standards

can be met. If state and local authorities do not believe that relevant biosafety and biosecurity standards can be met, the work should not proceed. A USG-sponsored expert group related to this ePPP review process should lead the development of biosafety and biosecurity standards for ePPP (and other high consequence work).

e. **Require institutions that conduct ePPP work to have robust health surveillance systems in place for laboratory staff.** If an accident were to occur, quickly identifying any affected individuals and mitigating impact would be critical. Local and/or state public health officials should be included in the institution's public health surveillance mechanism. We recommend that the ePPP Framework require that all institutions permitted to conduct ePPP work have robust health surveillance systems in place.

f. **Create guidelines for when and how to assess agents created during ePPP research.** While some ePPP research methods are targeted and seek to achieve explicit intended outcomes, other methods (such as serial passage) are not targeted, and the end result cannot be predicted accurately. We recommend the development of guidelines covering when and how researchers test the products of their work to ascertain potential increased transmissibility and/or virulence. For example, how should researchers testing products determine if a characteristic of interest has been enhanced? At what point in the research should such testing be done? If the product has enhanced transmissibility, to whom should this be reported? Such information is critical for ensuring that appropriate biosafety and biosecurity measures are taken to protect the laboratory staff and broader community.

g. **Incorporate transparency into the approval process.** We recommend that scientists, local institutions, funders, public health officials, other government agencies, and the public have access to the information about the risk and benefit assessments related to ePPP-related research, including proposed methods and pre-research assessments. This process could be modeled on the Registered Reports model used for clinical trials and other life science research to enhance reproducibility and ensure adequate ethical analysis. The Registered Reports model can provide an additional benefit to researchers because the journal that publishes the methods and risk-benefit assessment prior to commencing research also typically agrees to publish the results of the work, even if they are inconclusive or null. In addition to enabling peer review through Registered Reports, the deliberations of the USG body deciding on approval of any ePPP research should be made public, especially any dissenting opinions or recusals.

h. **Engage investigators as partners in the effort to identify and properly evaluate ePPP experiments.** The vast majority of investigators wish to engage in responsible actions that minimize ePPP risk while maximizing benefits. By analogy to questions about DURC, we recommend that grant proposals should include a question about whether the work is reasonably anticipated to give rise to an ePPP. The answer to this question should include an explanation and rationale. Moreover, research evolves from the moment of funding as it progresses. Research not initially likely

to generate an ePPP may become so as it evolves. Therefore, we also recommend that a similar question be included on annual progress reports to further assess and justify whether the current experimental plan and evidence-to-date could give rise to an ePPP.

4. **Expand Reach of ePPP Framework**

   a. **Broaden the ePPP Framework to apply to non-federally funded research.** There are no formal mechanisms in place to track ePPP research in all work domains across the United States. ePPP risks can emerge from diverse settings, including universities and research institutions that conduct research funded by private entities or philanthropies. Pharma and biotech companies self-fund research or otherwise conduct work using non-federal funds. Such work currently falls outside of the ePPP Framework, despite the 2016 NSABB recommendation[7] that all ePPP work be subject to oversight, regardless of funding source. We recommend that the USG develop new federal policies, guidance, and/or legislation to close this gap in governance.

   b. **Require all USG agencies to implement the ePPP Framework.** The ePPP Framework is currently not binding on all agencies that oversee or fund relevant life sciences research; only HHS has a policy. We recommend that all federal agencies be required to implement the ePPP Framework. Importantly, any federal officials conducting reviews and controlling the oversight process must be distinct and separate from any investigators within the agency or institution proposing this work (similar to recommendation 3 (c)).

   c. **Strengthen USG outreach to other governments to catalyze ePPP Framework and Dual Use policy development by other governments.** The 2017 OSTP P3CO guidance[8] committed to international engagement on this topic. That does not appear to have happened. We recommend the USG work with other governments to put analogous policies in place.

5. **Revise USG DURC Policy**

   a. **Expand the scope of the policy to include additional pathogens.** Currently, only 15 agents are included in the "United States Government Policy for Institutional Oversight of Life Sciences Dual Use Research of Concern." However, dual-use research occurs with many pathogens that are not included in this list. We recommend that DURC policy apply to all human pathogens. Policies must also take into account how closely animal, plant, and human ecosystems are intertwined. Dual-use research for animals and plants may have major consequences for human health through both direct and indirect mechanisms. We recommend that the USG Dual Use guidance is expanded to include animal and plant pathogens with similar

7 https://osp.od.nih.gov/wp-content/uploads/2016/06/NSABB_Final_Report_Recommendations_Evaluation_Oversight_Proposed_Gain_of_Function_Research.pdf

8 https://www.phe.gov/s3/dualuse/Documents/P3CO-FinalGuidanceStatement.pdf

properties to those highlighted for human pathogens. For this change in scope to be realized, the US Department of Agriculture (USDA) would need to implement an analogous Dual Use guidance.

b. **Expand the types of experiments included in the policy.** Currently, there is a list of 7 categories of experiments covered in the "United States Government Policy for Institutional Oversight of Life Sciences Dual Use Research of Concern." While these 7 categories are all appropriate, we recommend including additional categories of concern covering work that provides pathways or approaches for substantially shortening the timeline for, lowering the costs of, or decreasing the required sophistication for *de novo* synthesis of highly pathogenic organisms, or for engineering them with new traits. For example, research that results in making it significantly easier to synthesize a pathogen like the Ebola virus should be considered to fall within a category of experiment covered by USG DURC policy.

c. **Clarify requirements for the risk assessment and risk mitigation plan.** Similar to the needs described above for the ePPP Framework, DURC policies also need to provide more direction and detail concerning risk assessment and risk mitigation plans. We recommend that the USG provide more explicit direction concerning the types of risks researchers must consider, how to weigh the risks, and how to determine if the risk mitigation plans that are proposed are sufficient.

We, the undersigned,* respectfully submit these recommendations on 29 June 2022:

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