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Subcommittee on Emerging Threats and Spending Oversight

For the Hearing "Revisiting Gain of Function Research"

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Chair Hassan and members of the Committee:

Thank you for inviting me to discuss gain-of-function research and its oversight. I am Board of Governors Professor of Chemistry and Chemical Biology at Rutgers, The State University of New Jersey, and Laboratory Director at the Waksman Institute of Microbiology. I direct a biomedical research laboratory and serve as project leader on two National Institutes of Health (NIH) research grants. I conduct research on the mechanism of bacterial RNA synthesis and on the development of new antibacterial therapeutic agents able to treat bacterial infections resistant to current drugs. My research involves both priority public health bacterial pathogens (e.g., the pathogens responsible for Staph infections, Strep infections, and tuberculosis) and priority biodefense bacterial pathogens (e.g., the pathogens responsible for anthrax, plague, and tularemia). I am a member of the Institutional Biosafety Committee of Rutgers University, and I have been a member of the Working Group on Pathogen Security of the state of New Jersey, the Controlling Dangerous Pathogens Project of the Center for International Security Studies, and the Biosecurity Advisory Board of the Center for Civilian Biodefense. Here, I discuss the definition of gain-of-function research of concern, risks and benefits of the research, US oversight of the research, and recommended steps to strengthen US oversight of the research. In my written comments, I also include an appendix addressing the origin of SARS-CoV-2 and the possibility that lapses in US oversight of gain-of-function research of concern contributed to the origin of SARS-CoV-2. My assessments are based on information in published NIH, Health and Human Services (HHS), Office of Science and Technology Policy (OSTP), and Congressional Research Service (CRS) documents, on published press reports, on published scientific papers, and on my knowledge of biosafety and biosecurity standards for work with pathogens.

Gain-of-function research of concern

Definition

Gain-of-function research of concern is defined as research activities reasonably anticipated to increase a potential pandemic pathogen's transmissibility, pathogenesis, ability to overcome immune response, or ability to overcome a vaccine or drug. Some definitions also include research activities reasonably anticipated to reconstruct an extinct or eradicated potential pandemic pathogen.

Gain-of-function research of concern involves the creation of *new health threats*--health threats that did not exist previously and that might not come to exist by natural means for tens, hundreds, thousands, or tens of thousands of years.

Most gain-of-function research of concern to date has been performed in the US with US funding or overseas with US funding.

Gain-of-function research of concern is a small part of biomedical research (less than 0.1% of all biomedical research and less than 1% of virology). However, because gain-of-function research of concern can cause pandemics, this small part of the biomedical research enterprise is highly consequential and requires effective oversight.

Risks

Gain-of-function research of concern poses high--potentially existential--risks. Gain-of-function research of concern poses both material risks and information risks.

Gain-of-function research of concern poses *material risks* by creating new or enhanced potential pandemic pathogens. If a resulting new potential pandemic pathogen is released into humans, either by accident or deliberately, this can cause a pandemic.

Gain-of-function research of concern poses *information risks* by providing information on the construction and properties of new potential pandemic pathogens. Publication of the research provides instructions--step-by-step "recipes"--that can be used by a rogue nation, organization, or individual to construct a new potential pandemic pathogen and release it to cause a pandemic. With current biotechnology, the technical means to do this are within the reach of most nations. With improvements in biotechnology in the next decade, the technical means to do this likely also will be within the reach of most sub-state organizations and individuals.

The risks posed by gain-of-function research of concern are *inherent risks*. In some cases, the risks can be mitigated, but in no case can the risks be eliminated.

Benefits

Gain-of-function research of concern provides limited benefits.

Gain-of-function research of concern can advance scientific understanding and, in some cases, can do so more quickly than alternative research strategies.

However, gain-of-function research of concern has no civilian practical applications. In particular, gain-of-function research of concern is not needed for, and does not contribute to, the development of vaccines and drugs. (Companies develop vaccines and drugs against pathogens that exist and circulate in humans. Not against pathogens that do not yet exist and do not yet circulate in humans.)

Gain-of-function research of concern is performed because it is easy and fast (much faster and much easier than vaccine or drug development) and because, it is fundable and publishable. Not because it is needed.

Risk-benefit assessment and risk-mitigation review

Because gain-of function research of concern poses high--potentially existential--risks and provides limited benefits, the risk-benefit ratio for the research almost always is unfavorable and in many cases is extremely unfavorable.

Therefore, it is imperative that gain-of function research of concern be subject to national- or international-level oversight to ensure that, before the research is started, risk-benefit assessment is performed, risk-benefit profiles are acceptable, and mitigable risks are mitigated..

Effective oversight includes three components:

First, research proposals that include gain-of function research of concern must be identified

Second, a risk-benefit assessment and a risk-mitigation review must be performed. This entails enumerating anticipated risks, enumerating anticipated benefits, weighing risks and benefits, and reaching a decision either (i) to proceed as proposed, (ii) to proceed with additional risk mitigation, or (iii) not to proceed.

Third, compliance with the decision from the risk-benefit assessment and risk-mitigation review must be mandated, monitored, and enforced.

US oversight of gain-of-function research of concern

US oversight, before 2014

Before 2014, there was no national-level US oversight of gain-of-function research of concern.

US oversight, 2014-2017

In 2014-2017, there was a moratorium on federal funding for "selected gain of function research," defined as research activities reasonably anticipated to increase transmissibility or pathogenicity of influenza, SARS, or MERS viruses. The policy was referred to as the "US Government Research Funding Pause on Selected Gain-of-Function Research Involving Influenza, MERS, and SARS Viruses," or, for short, as the "Pause." (https://www.phe.gov/s3/dualuse/documents/gain-of-function.pdf).

Under the Pause, 18 projects were paused.

However, at least 7 of the 18 projects that were paused were allowed to re-start almost immediately (based on a certification by the NIH Director that the projects were "urgently necessary to protect the public health or national security"). More important, other projects that met the definition for coverage under the Pause--including a project on engineering of SARS- and MERS-related coronaviruses by EcoHealth Alliance and the Wuhan Institute of Virology--were not paused, due to the failure of the NIH to identify and flag all covered projects

US oversight, 2018-present

In 2018-present, there has been a requirement for HHS-Secretary-level risk-benefit assessment prior to awarding HHS funding for "research involving enhanced potential pandemic pathogens,"

defined as research activities reasonably anticipated to increase transmissibility or pathogenicity of a potential pandemic pathogen. The policy is referred to as the "HHS Framework for Research Involving Enhanced Potential Pandemic Pathogens," or, for short, as the "P3CO Framework" (https://www.phe.gov/s3/dualuse/documents/p3co.pdf).

Under the P3CO Framework, covered projects are to be identified and flagged by HHS funding agencies (i.e., the NIH and the CDC), and covered projects are to be reviewed by a committee appointed by the HHS Secretary (i.e., the HHS P3CO Committee).

The P3CO Framework applies to funding for proposed research and operates before funding and conduct of the research (not after completion of the research). Accordingly, identification of covered projects coverage under the policy is based on proposed research and evaluates "reasonably anticipated" results of the proposed research (not results after completion of the research). The "reasonably anticipated" standard employed by the policy is equivalent, in all respects, to the "reasonable person" standard employed in US administrative and civil law.

The definitions of the research activities covered by the P3CO Framework, and the definitions of research activities exempted from the P3CO Framework, are clear. They are as clear as in any US statute or rule having a "reasonable person" standard. The policy covers research activities reasonably anticipated to increase the transmissibility or the pathogenicity of a potential pandemic pathogen, including research activities in which neither the pathogen to be modified nor the enhanced pathogen to be generated is known to infect humans.

In principle, the P3CO Framework provides for risk-benefit assessment and risk-mitigation review for gain-of-function research of concern. *However, in practice, the P3CO Framework largely has existed only on paper.* In the four-and-one-half years since the policy was

announced, *only three projects have been reviewed*: two projects that had been carried over from the Pause, and one new project. Most covered projects--including the project on engineering of SARS- and MERS-related coronaviruses by EcoHealth Alliance and the Wuhan Institute of Virology--were not reviewed, due to a failure by the NIH to identify covered projects, flag them, and forward them to the HHS P3CO Committee for review. In addition, the HHS P3CO Committee has operated with complete non-transparency and complete unaccountability. The names and agency affiliations of its members have not been disclosed, its proceedings have not been disclosed, and even its decisions have not been disclosed.

Shortcomings in US oversight of gain-of-function research of concern

Current US oversight of gain-of-function research of concern has serious shortcomings:

- Responsibility for oversight is assigned to federal agencies that perform research and/or fund research. This constitutes an inherent conflict of interest.

- Oversight applies only to HHS-funded research.

- Oversight is not codified in regulations with force of law, and, as a result, compliance is neither mandated, monitored, nor enforced.

- Oversight is undermined by the failure of federal research funding agencies to identify covered projects, flag them, and forward them to the HHS P3CO Committee for review.

- Oversight is not transparent and accountable, neither at the level of the federal research funding agencies, nor at the level of the HHS P3CO Committee .

Strengthening US oversight of gain-of-function research

Rationale

Lapses in US oversight of gain-of-function research of concern may have caused the current pandemic (see Appendix 1), and could cause future pandemics The US government funded high-risk gain-of-function research and high-risk enhanced potential pathogen research at the Wuhan Institute of Virology in 2016-2019. The research overlapped the US Government Research Funding Pause on Selected Gain-of-Function Research Involving Influenza, MERS, and SARS Viruses (the Pause) that was in effect in the 2014 to 2017, and met the criteria to be paused, but was not paused. The research also overlapped the HHS Framework for Research Involving Enhanced Potential Pandemic Pathogens (the P3CO Framework) that has been in effect in 2018 to the present, and met the criteria for federal risk-benefit review under the P3CO Framework, but did not undergo federal risk-benefit review under the P3CO Framework. The research was performed at biosafety level 2--a biosafety level that is inadequate for research with potential pandemic pathogens. The research may have generated SARS-CoV-2 or a proximal progenitor, and an accident in the research may have been responsible for entry of SARS-CoV-2 or a proximal progenitor into the human population.

These facts--and these statements indeed are facts--are an indictment of the current system of US oversight of gain-of-function research of concern and are a testament that strengthening US oversight of gain-of-function research of concern is essential.

Moving forward, any effective system of US oversight of gain-of-function research of concern must address the shortcomings of the current system:

Recommendations

- **Responsibility for US oversight of gain-of-function research of concern should be assigned to a single, independent federal agency that does not perform research and does not fund research. The oversight of research on fissionable materials by the Nuclear Regulatory Commission provides a precedent and a model.**

    - **US oversight of gain-of-function research of concern should cover all US and US-funded research, irrespective of funding source, classification status, and research location.**

    - **US oversight of gain-of-function research of concern should be codified in regulations with force of law and should be mandated, monitored, and enforced--in the same manner that US oversight of human-subjects research and vertebrate-animals research is codified in regulations with force of law and is mandated, monitored, and enforced.**

- **The US should call on other nations to adopt similar systems of oversight of gain-of-function research of concern.**

- **The US should call for an additional, international-level layer of oversight for the highest-risk, highest-consequence subset of gain-of-function research of concern. The oversight of research on smallpox virus by the World Health Organization Advisory Committee on Variola Virus Research provides a precedent and a model.**

Appendix 1: Origins of SARS-CoV-2

SARS-CoV-2 may have entered humans through a research-related accident.

The genome sequence of SARS-CoV-2 indicates that its progenitor was a bat coronavirus.

Bat coronaviruses are present in nature in multiple parts of China. Therefore, the first human infection could have occurred as a natural accident, with a virus passing from a bat to a human, possibly through another animal. There is clear precedent for this. The first entry of the SARS virus into the human population occurred as a natural accident in a rural part of Guangdong province in 2002.

But bat coronaviruses also are collected and studied by laboratories in multiple parts of China, including the Wuhan Institute of Virology. Therefore, the first human infection also could have occurred as a research-related accident, with a virus accidentally infecting a field-collection staffer or a laboratory staffer, followed by transmission from the staffer to the public. There also is clear precedent for this. The second, third, fourth and fifth entries of the SARS virus into human populations occurred as a laboratory accident in Singapore in 2003, a laboratory accident in Taipei in 2003, and two separate laboratory accidents in Beijing in 2004.

At this point in time, there is no scientific or other secure basis to assign relative probabilities to the natural-accident hypothesis and the research-related-accident hypothesis. Nevertheless, there are three lines of circumstantial evidence that should be noted:

First, the outbreak occurred in Wuhan, a city of 11 million persons that is more than 800 miles from, and outside the flight range of, known bat colonies with SARS-related coronaviruses.

Second, the outbreak occurred in Wuhan, on the doorstep of the laboratory that conducts the world's largest research project on bat viruses, that has the world's largest collection of bat viruses, and that possessed and worked with the bat virus that, at the time SARS-CoV-2 emerged, was the world's closest known relative of SARS-CoV-2. The laboratory actively searched for new bat viruses in bat colonies in caves in remote rural areas in Yunnan province, brought those new bat viruses to Wuhan, and then mass-produced, genetically manipulated, and studied those new bat viruses, year-round, inside Wuhan.

Third, the bat-SARS-related-coronavirus projects at the Wuhan Institute of Virology, including projects involving the construction and initial characterization of novel chimeric SARS-related coronaviruses having enhanced viral growth and enhanced lethality, used personal protective equipment (usually just gloves; sometimes not even gloves) and biosafety standards (usually just biosafety level 2) that would pose high risk of infection of field-collection or laboratory staff upon contact with a virus having the transmission properties of SARS-CoV-2.

SARS-CoV-2 may have entered humans through US-funded gain-of-function research and lapses in US oversight of gain-of-function research.

The research at the Wuhan Institute of Virology included activities that met the definition of "selected gain of function research" in the US policy in effect in 2014-2017 and that met the definition of "enhanced potential pandemic pathogen research" in the US policy in effect in 2018-present. Using US funding, provided by the NIH in 2014-2019, the Wuhan Institute of Virology: (1) constructed novel chimeric SARS-related coronaviruses that combined the spike gene of one bat SARS-related coronavirus with the rest of the genetic information of another bat SARS-related coronavirus, (2) showed that resulting viruses efficiently infected human airway

cells and efficiently replicated in human airway cells, and (3) showed that the resulting viruses exhibited up to 10,000-fold enhancement of viral growth in lungs, and up to 4-fold enhancement of lethality, in mice engineered to display human receptors on airway cells ("humanized mice").

Although this research met the definition of selected gain-of-function research in the US policy in effect in 2014-2017 (the Pause) and exceeded--by more three orders of magnitude--the threshold set by the NIH for enhancement of viral growth that should trigger immediate cessation of work, and although the NIH was informed of project objectives and results in annual project progress reports in 2016-2018, the NIH failed to flag the project as being covered by the policy, failed to pause the project as required by the policy, and failed to stop the project as required by the Terms and Conditions of the grant.

Although the research also met the definition of enhanced potential pandemic pathogen research in the US policy in effect in 2018-present (the P3CO Framework), and although the NIH was informed of project objectives and results in a proposal for renewal of the grant for 2019-2024, the NIH failed to identify the project as being covered by the policy, and failed to forward the proposal to the HHS P3CO Committee for the risk-benefit assessment required by the policy.

On October 20, 2021, in response to a request from the Ranking Member of the House Oversight Subcommittee, the NIH Acting Director, Lawrence A. Tabak, D.D.S., Ph.D., released a letter on NIH-funded research on bat SARS-related coronaviruses conducted at the Wuhan Institute of Virology and Wuhan University in 2014-2019 (https://www.documentcloud.org/documents/21674679-tabak-letter-to-comer-oct-20-2021). The Tabak letter addressed: (1) NIH funding under grant AI110964, awarded by the NIH to EcoHealth Alliance with subcontracts to the Wuhan Institute of Virology and Wuhan University;

(2) the virus WIV1 SHC014 S (mis-rendered as "SHC014 WIV1"), a virus constructed and characterized in Wuhan using NIH funding under NIH grant AI110964;; and (3) the possibility that the virus WIV1 SHC014 S was a proximal progenitor of SARS-CoV-2.

WIV1 SHC014 S is a novel chimeric SARS-related coronavirus that combines the spike gene of one bat SARS-related coronavirus with the rest of the genetic information of another bat SARS-related coronavirus. It is an artificial, laboratory-constructed virus that has no counterpart in viruses that circulate in nature. It is one of at least three artificial, laboratory-constructed chimeric coronaviruses that were constructed by EcoHealth Alliance and its Wuhan partners using NIH funding and that were shown to infect human airway cells, to replicate in human airway cells, and to exhibit 10,000-fold higher viral growth and higher lethality than the parental natural coronavirus in infection studies in mice engineered to display human receptors on airway cells ("humanized mice"; https://theintercept.com/document/2021/09/08/understanding-the-risk-of-bat-coronavirus-emergence/; https://republicans-oversight.house.gov/wp-content/uploads/2021/10/Year-5-EHAv.pdf).

The year-4 progress report for the first 5-year term of the NIH grant (submitted to the NIH in March 2018) and the proposal for the second term 5-year term of the NIH grant (submitted to the NIH in November 2018) reported the construction of the three chimeras, the 10,000-fold enhanced viral growth in humanized mice of the three chimera, and the enhanced pathogenicity in humanized mice of one of the three chimeras (https://theintercept.com/document/2021/09/08/understanding-the-risk-of-bat-coronavirus-emergence/).

The year-5 proposal for the first 5-year term of the NIH grant (submitted to NIH in August 2021, more than two years overdue, and released to the Ranking Member of the House Oversight Subcommittee together with the Tabak letter) reported that the chimeras exhibited enhanced viral growth in brains as well as in lungs of humanized mice, and exhibited 2- to 4-fold increased lethality in humanized mice (https://republicans-oversight.house.gov/wp-content/uploads/2021/10/Year-5-EHAv.pdf).

The Terms and Conditions of the first 5-year NIH grant stated (https://theintercept.com/document/2021/09/08/understanding-the-risk-of-bat-coronavirus-emergence/):

> Per the letter dated July 7, 2016 to Mr. Aleksei Chmura at EcoHealth Alliance, should any of the MERS-like or SARS-like chimeras generated under this grant show evidence of enhanced virus growth greater than 1 log over the parental backbone strain you must stop all experiments with these viruses and provide the NIAID Program Officer and Grants Management Specialist, and Wuhan Institute of Virology Institutional Biosafety Committee with the relevant data and information related to these unanticipated outcomes.

The term "1 log" means "a factor of 10". EcoHealth Alliance and its Wuhan partners created novel chimeras of SARS-related coronaviruses that showed enhanced viral growth by greater than a factor of 10,000...which exceeded, *by three orders of magnitude*, the trigger point for stopping work and reporting results to NIH under the Terms and Conditions of the NIH grant.

The Tabak letter confirms that research reported in the reported in the year-4 and year-5 progress reports of the first 5-year grant and in the renewal proposal for the second 5-year grant--research

in Wuhan that generated a potential pandemic pathogen with a greater than 10,000-fold enhanced viral growth, enhanced pathogenicity, and enhanced lethality in humanized mice-- occurred. The Tabak letter thus confirms that NIH funds supported gain-of-function research of concern and construction and characterization of an enhanced potential pandemic pathogen--a pathogen reasonably anticipated, indeed likely, to have enhanced transmissibility and/or pathogenicity in humans--in Wuhan.

The Tabak letter reveals that EcoHealth Alliance and it Wuhan partner failed to report to NIH in a timely manner that they had obtained evidence of enhanced viral growth greater than 1 log over the parental backbone strain. Thus the Tabak letter confirms that EcoHealth Alliance and its Wuhan partner violated the Terms and Conditions of the first 5-year grant,

The Tabak letter also reveals that EcoHealth Alliance failed to submit the year-5 progress report for the first 5-year grant report until more than two years after the submission deadline. Thus the Tabak letter also confirms that EcoHealth Alliance and its Wuhan partner again violated the Terms and Conditions of the first 5-year grant,

The Tabak letter correctly states that WIV1 SHC014 S and the other novel chimeric SARS-related viruses reported to the NIH by EcoHealth Alliance and its Wuhan partners in their 2018 grant progress report and 2018 grant renewal proposal are insufficiently closely related to SARS-CoV-2 to have served as a proximal progenitor of SARS-CoV-2.

However, the Tabak letter leaves unstated the crucial fact that the NIH has received no information on novel chimeric SARS-related viruses constructed by EcoHealth Alliance and its Wuhan partners subsequent to the 2018 grant progress report and 2018 grant renewal proposal., and therefore that the NIH cannot rule out the possibility that the project created a proximal

progenitor of SARS-CoV-2, and cannot even rule out the possibility that the project used NIH funding to create a proximal progenitor of SARS-CoV-2.

The Tabak letter also leaves unanswered the questions of why the NIH, which was provided with relevant data in March of 2018 and again in November of 2018, and which became aware of the failure to submit the year-5 progress report in 2019: (1) failed to act on the violations of the Terms and Conditions of the first 5-year grant, (2) awarded a second 5-year grant period despite the violations of the Terms and Conditions of the first 5-year grant, (3) awarded a second 5-year grant period for a project that proposed continuation of enhanced potential pandemic pathogen research--specifically proposing to construct and characterize additional novel chimeric SARS-related coronaviruses--without forwarding the proposal for HHS-level risk-benefit review as required under the HHS P3CO Framework, and (4) falsely asserted that NIH funding had not supported gain-of-function research or enhanced potential pandemic pathogen research in Wuhan.

Appendix 2

Policy document: US Government Research Funding Pause on Selected Gain-of-Function Research Involving Influenza, MERS, and SARS Viruses (https://www.phe.gov/s3/dualuse/documents/gain-of-function.pdf).

Policy document: HHS Framework for Research Involving Enhanced Potential Pandemic Pathogens (https://www.phe.gov/s3/dualuse/documents/p3co.pdf).

U.S. Government Gain-of-Function Deliberative Process and Research Funding Pause on Selected Gain-of-Function Research Involving Influenza, MERS, and SARS Viruses

October 17, 2014

U.S. Government Gain-of-Function Deliberative Process and Research Funding Pause on Selected Gain-of-Function Research Involving Influenza, MERS, and SARS Viruses

Gain-of-function studies, or research that improves the ability of a pathogen to cause disease, help define the fundamental nature of human-pathogen interactions, thereby enabling assessment of the pandemic potential of emerging infectious agents, informing public health and preparedness efforts, and furthering medical countermeasure development. Gain-of-function studies may entail biosafety and biosecurity risks; therefore, the risks and benefits of gain-of-function research must be evaluated, both in the context of recent U.S. biosafety incidents and to keep pace with new technological developments, in order to determine which types of studies should go forward and under what conditions.

In light of recent concerns regarding biosafety and biosecurity, effective immediately, the U.S. Government (USG) will pause new USG funding for gain-of-function research on influenza, MERS or SARS viruses, as defined below. This research funding pause will be effective until a robust and broad deliberative process is completed that results in the adoption of a new USG gain-of-function research policy[1]. Restrictions on new funding will apply as follows:

> *New USG funding will not be released for gain-of-function research projects that may be reasonably anticipated to confer attributes to influenza, MERS, or SARS viruses such that the virus would have enhanced pathogenicity and/or transmissibility in mammals via the respiratory route. The research funding pause would not apply to characterization or testing of naturally occurring influenza, MERS, and SARS viruses, unless the tests are reasonably anticipated to increase transmissibility and/or pathogenicity.*

In parallel, we will encourage the currently-funded USG and non-USG funded research community to join in adopting a voluntary pause on research that meets the stated definition.

The deliberative process that will ensue during the period of the research pause will explicitly evaluate the risks and potential benefits of gain-of-function research with potential pandemic pathogens. The presumptive benefits that are generally identified in pursuing this type of research are stated in terms of enhanced ability for earlier awareness of naturally emerging dangerous pandemic pathogens or in the development of medical products in anticipation of such emergence.

However the relative merits of gain-of-function experimental approaches must be compared ultimately to potentially safer approaches. The deliberative process will offer recommendations for risk mitigation, potential courses of action in light of this assessment, and propose methodologies for the objective and rigorous assessment of risks and potential benefits that might be applied to the approval and conduct of individual experiments or classes of experiments. Although the gain-of-function studies that fall within the scope of research subject to the funding pause will be a starting point for deliberations, the suitability of other types of gain-of-function studies will be discussed. It is feasible that the discussion could lead to suggestions of broadening the funding pause to include research with additional pathogens,

[1] An exception from the research pause may be obtained if the head of the USG funding agency determines that the research is urgently necessary to protect the public health or national security.

however, federal Departments and Agencies who fund, support, or perform research should be consulted prior to any additional pathogens being added to the scope of the funding pause.

The deliberative process is envisioned to be time-limited, to involve two distinct, but collaborating, entities, and to be structured to enable robust engagement with the life sciences community. As a first step, the National Science Advisory Board for Biosecurity (NSABB) will be asked to conduct the deliberative process described above and to draft a set of resulting recommendations for gain-of-function research that will be reviewed by the broader life sciences community. The NSABB will serve as the official federal advisory body for providing advice on oversight of this area of dual use research, in keeping with federal rules and regulations.

As a second step, coincident with NSABB recommendations, the National Research Council (NRC) of the National Academies then will be asked to convene a scientific conference focused on the issues associated with gain-of-function research and will include the review and discussion of the NSABB draft recommendations. This NRC conference will provide a mechanism both to engage the life sciences community as well as solicit feedback on optimal approaches to ensure effective federal oversight of gain-of-function research. The life sciences community will be encouraged to provide input through both the NRC and NSABB deliberative processes.

The NSABB, informed by NRC feedback, will deliver recommendations to the Secretary of Health and Human Services, the Director of the National Institutes of Health, and the heads of all federal entities that conduct, support, or have an interest in life sciences research (including the Assistants to the President for Homeland Security and Counterterrorism and for Science and Technology). The final NSABB recommendations and the outcomes of the NRC conference will inform the development and adoption of a new U.S. Government policy governing the funding and conduct of gain-of-function research. Upon adoption of a federal gain-of-function policy, the U.S. Government will declare the end of the research funding pause.

The life sciences community will be informed of progress at regular intervals. The estimated time-line is six months for completion of the two deliberative steps (culminating in delivery of the NSABB recommendations to the HHS Secretary) and three months for the development, approval, and publication of the policy, with the goal of completing the entire process in less than one year from declaration of the research funding pause.

U.S. Department of Health and Human Services

Framework for Guiding Funding Decisions about Proposed Research Involving Enhanced Potential Pandemic Pathogens

2017

Department of Health and Human Services Framework for Guiding Funding Decisions about Proposed Research Involving Enhanced Potential Pandemic Pathogens

Section I. Purpose and Principles

Research involving potential pandemic pathogens (PPPs) is essential to protecting global health and security. However, there are biosafety and biosecurity risks associated with undertaking such research that must be adequately considered and appropriately mitigated in order to help safely realize the potential benefits. The *HHS Framework for Guiding Funding Decisions about Proposed Research Involving Enhanced Potential Pandemic Pathogens* (*HHS P3CO Framework*) is intended to guide HHS funding decisions on individual proposed research that is reasonably anticipated to create, transfer, or use enhanced PPPs. This *HHS P3CO Framework* is responsive to and in accordance with the *Recommended Policy Guidance for Departmental Development of Review Mechanisms for Potential Pandemic Pathogen Care and Oversight* issued by OSTP on January 9, 2017[1] and supersedes the previous *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 Droplets*[2]. The *HHS P3CO Framework* ensures a multidisciplinary, department-level pre-funding review and evaluation of proposed research meeting the scope outlined herein to help inform funding agency decisions. In so doing, the *HHS P3CO Framework* seeks to preserve the benefits of life sciences research involving enhanced PPPs while minimizing potential biosafety and biosecurity risks.

Section II. Scope and Definitions

For the purposes of this *HHS P3CO Framework*:

A. A ***potential pandemic pathogen*** **(PPP)** is a pathogen that satisfies **both** of the following:

   1. It is likely highly transmissible and likely capable of wide and uncontrollable spread in human populations; and

   2. It is likely highly virulent and likely to cause significant morbidity and/or mortality in humans.

B. An **enhanced PPP** is defined as a PPP resulting from the enhancement of the transmissibility and/or virulence of a pathogen. Enhanced PPPs do not include naturally occurring pathogens that are circulating in or have been recovered from nature, regardless of their pandemic potential.

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[1] Recommended Policy Guidance for Departmental Development of Review Mechanisms for Potential Pandemic Pathogen Care and Oversight. U.S. Government, January 2017.

[2] 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 Droplets. U.S. Government, February 2013.

C. 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[3]:

   1. Surveillance activities, including sampling and sequencing; and

   2. Activities associated with developing and producing vaccines, such as generation of high growth strains.

D. Proposed intramural and extramural life sciences research that is being considered for funding and that has been determined by the funding agency as reasonably anticipated to create, transfer, or use enhanced PPPs is subject to additional HHS department-level review as outlined herein.

E. A pathogen previously considered by an agency to be an enhanced PPP should no longer be so considered if the HHS and the White House Office of Science and Technology Policy, in consultation with the Departments of Defense, Homeland Security, Agriculture, and Justice, generally acting through the Federal Bureau of Investigation, jointly determine, on the basis of additional information that has been developed about the risks or the benefits of that pathogen's creation, transfer, or use, that the department-level review processes outlined in this framework are no longer appropriate.

[3] For additional guidance and examples of activities that would and would not be considered to involve enhanced PPP see *Recommendations for the Evaluation and Oversight of Proposed Gain-of-Function Research.* National Science Advisory Board for Biosecurity, May 2016.

Box 1. Criteria for guiding HHS funding decisions on proposed research that involves, or is reasonably anticipated to involve, creation, transfer, or use of enhanced PPPs.

Department-level review of proposed research reasonably anticipated to create, transfer, or use enhanced PPPs will be based on the following criteria:

1) The research has been evaluated by an independent expert review process (whether internal or external) and has been determined to be scientifically sound;
2) The pathogen that is anticipated to be created, transferred, or used by the research must be reasonably judged to be a credible source of a potential future human pandemic;
3) An assessment of the overall potential risks and benefits associated with the research determines that the potential risks as compared to the potential benefits to society are justified;
4) There are no feasible, equally efficacious alternative methods to address the same question in a manner that poses less risk than does the proposed approach;
5) The investigator and the institution where the research would be carried out have the demonstrated capacity and commitment to conduct it safely and securely, and have the ability to respond rapidly, mitigate potential risks and take corrective actions in response to laboratory accidents, lapses in protocol and procedures, and potential security breaches;
6) The research's results are anticipated to be responsibly communicated, in compliance with applicable laws, regulations, and policies, and any terms and conditions of funding, in order to realize their potential benefit;
7) The research will be supported through funding mechanisms that allow for appropriate management of risks and ongoing Federal and institutional oversight of all aspects of the research throughout the course of the research; and
8) The research is ethically justifiable. Non-maleficence, beneficence, justice, respect for persons, scientific freedom, and responsible stewardship are among the ethical values that should be considered by a multidisciplinary review process in making decisions about whether to fund research involving PPPs.

Section III. Review and Oversight Framework

A. The identification, review, and oversight of research subject to department-level review will require responsibilities (Figure 1) of the:

- Funding agency considering funding the proposed research; and
- HHS.

Figure 1: Overview of Responsibilities under the HHS P3CO Framework

Entity	Responsibilities
Funding agency	• Conduct standard scientific merit review; • Refer proposed research that is reasonably anticipated to create, transfer, or use enhanced PPPs for departmental-level review; • Provide relevant information necessary for departmental-level review; • Participate in departmental-level review process, as requested; • Consider the recommendations resulting from the departmental-level review; • Make a funding decision, stipulating terms and conditions of award including additional risk mitigation measures if appropriate; • Report relevant information on funding decisions to HHS and OSTP; • Ensure implementation of and adherence to required risk mitigation procedures and other terms/conditions of award, if funded.
HHS	• Convene a multidisciplinary group to review proposed research that has been determined by the funding agency as being reasonably anticipated to create, transfer, or use enhanced PPPs; • Critically evaluate the proposed research including the risk/benefit assessment and proposed risk mitigation plan; • Consider the eight criteria for guiding HHS funding decisions (Box 1) and additional relevant factors and information; • Develop recommendations on acceptability for HHS funding, including suggestions for additional risk mitigation measures and/or terms and conditions of award, if funded.

B. The HHS department-level review will evaluate proposed research referred by the funding agency that meets the scope outlined in Section II. This review and evaluation will be guided by the criteria listed in Box 1. The evaluation will include consideration of a:

   - Risk/benefit analysis of the proposed research;
   - Risk mitigation plan; and
   - Additional relevant factors.

C. A department-level review will result in recommendations to the funding agency on whether the proposed research is acceptable for HHS funding and what, if any, additional risk mitigation measures should be incorporated into the terms and conditions of award, if funded.

D. If funded, research that is reasonably anticipated to create, transfer, or use an enhanced PPP may require additional risk mitigation strategies which may include, but are not limited to:

   - Modification of the design or conduct of the research;
   - Application of specific or enhanced biosecurity or biosafety and biocontainment measures;

- Evaluation of existing evidence of medical countermeasures (MCM) efficacy, or experiments conducted to determine MCM efficacy against agents or toxins resulting from the research; and
- Methodologies for responsible communication of results.

Section IV. HHS Department-level Review

A. Proposed research that is being considered for funding by the HHS funding agency, is deemed to be scientifically meritorious by an independent internal or external review process, and has been determined by the funding agency to be reasonably anticipated to create, transfer, or use enhanced PPPs must be referred for HHS department-level review.

B. The purpose of the department-level review is to provide a multidisciplinary, pre-funding review and evaluation of proposed research that meets the scope outlined in Section II to recommend whether HHS funding is appropriate, and if so, to help identify the appropriate risk mitigation strategies. The following disciplines should be represented during the department-level review: scientific research, biosafety, biosecurity, MCM development and availability, law, ethics, public health preparedness and response, biodefense, select agent regulations, and public health policy, as well as the funding agency perspectives and other relevant areas. The HHS department-level review group may include non-voting *ex officio* and/or *ad hoc* members from HHS and other federal departments and agencies as deemed appropriate by the Review Group Chair.

C. Extra care in the department-level review should be given to proposed research that is reasonably anticipated to:

- Enhance the harmful consequences of the pathogen;
- Disrupt immunity or the effectiveness of an immunization against the pathogen without clinical or agricultural justification;
- Confer to the pathogen resistance to clinically or agriculturally useful prophylactic or therapeutic interventions against that pathogen or facilitate the pathogen's ability to evade detection methodologies;
- Increase the stability, transmissibility, or the ability to disseminate the pathogen;
- Alter the host range or tropism of the pathogen;
- Enhance the susceptibility of a host population to the pathogen; or
- Generate or reconstitute an eradicated or extinct pathogen.

D. The HHS department-level review may result in the following recommendations:

- Research is acceptable for HHS funding;
- Research is not acceptable for HHS funding;
- Research is acceptable for HHS funding on the condition that certain experiments are modified;

- Research is acceptable for HHS funding on the condition that certain risk mitigation measures are employed at the federal and/or institutional level; or
- Other recommendations, as deemed appropriate.

For research determined to be not in accordance with all of the criteria for guiding HHS funding decisions on proposed research reasonably anticipated to create, transfer, or use enhanced PPPs, a recommendation will be that the research is not acceptable for HHS funding.

Section V. Evaluation of the HHS P3CO Review Process

HHS will periodically re-evaluate and modify this review process, as necessary, to reflect scientific advances and changes to the regulatory landscape. To help inform such evaluations, and to enhance transparency and public engagement in the review and oversight process for enhanced PPP research, HHS will periodically ask the National Science Advisory Board for Biosecurity to review the process described herein.