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PUBLIC HEALTH PREPAREDNESS

HHS Could Improve Oversight of Research Involving Enhanced Potential Pandemic Pathogens

Accessible Version

GAO Highlights

Highlights of [GAO-23-105455](#), a report to congressional committees

Why GAO Did This Study

Research involving pandemic pathogens is crucial to ensure the nation's ability to prepare for, respond to, and recover from public health threats. For example, such research resulted in COVID-19 vaccines and therapeutics to prevent severe disease or death. However, a number of incidents and research projects—including research that enhanced the transmissibility of influenza between mammals—have raised questions about the adequacy of HHS oversight of the safety of such research.

The CARES Act includes a provision for GAO to report on ongoing federal efforts to prepare for, respond to, and recover from COVID-19. This report examines the extent to which HHS's oversight Framework for enhanced potential pandemic pathogen research is effective; and gaps that exist in HHS's broader oversight of such research, among other things.

GAO reviewed HHS's oversight policies and programs as well as documentation for selected research grants. GAO also assessed the Framework against GAO's elements of effective oversight. GAO interviewed HHS officials and select subject matter experts from the research biosafety and biosecurity community.

What GAO Recommends

GAO is making three recommendations to improve HHS's oversight of research, including developing and documenting a standard for "reasonably anticipated" and assessing the risk of statutory limitations. HHS neither agreed nor disagreed with two of the recommendations and agreed with the third.

View [GAO-23-105455](#). For more information, contact Mary Denigan-Macauley at (202) 512-7114 or DeniganMacauleyM@gao.gov.

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What GAO Found

The Department of Health and Human Services (HHS) oversees high-risk research involving potential pandemic pathogens, which are defined as likely highly transmissible and virulent, and capable of causing significant morbidity or mortality. SARS-CoV-2, which causes COVID-19 disease, is an example of a pandemic pathogen. In 2017, HHS developed an oversight policy (the Framework) that requires funding agencies to refer proposed research that is "reasonably anticipated to create, transfer, or use enhanced potential pandemic pathogens" to the Department for an additional review of associated risks and benefits, among other things.

Researcher conducting high-risk research



Source: Centers for Disease Control and Prevention. | GAO-23-105455

GAO found that HHS's Framework does not fully meet the key elements of effective oversight identified in past work. For example, the Framework does not provide a standard to help funding agencies interpret what "reasonably anticipated" means. Until HHS develops and documents such a standard, the Framework allows for subjective and potentially inconsistent interpretations of the requirement—leaving HHS without assurance the department is reviewing all necessary research proposals.

HHS also oversees research involving certain pandemic pathogens through its Federal Select Agent Program—a list-based program regulating the possession, use, and transfer of certain pathogens. However, HHS faces trade-offs in adding newly emerged pathogens, like SARS-CoV-2, to the list because, as officials told GAO, doing so would impede the public health response by burdening diagnostic and treatment facilities with additional reporting and inspection requirements. The statute authorizing the Federal Select Agent Program limits HHS's ability to waive or postpone these requirements during public health emergencies for a maximum of 60 days. HHS has not assessed the risk this limitation poses to its oversight of known pandemic pathogens. Until the risk of this statutory limitation is assessed and action taken to mitigate any risks, HHS will continue to face tradeoffs between impeding public health response efforts and allowing high-risk research involving known pandemic pathogens to be conducted without appropriate HHS oversight.

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January 18, 2023

Congressional Committees

High-risk life science research has been a topic of interest in recent congressional hearings.¹ High-risk research that results in the acquisition of new or enhanced biological characteristics in microorganisms is of particular concern, as it can involve enhancing the transmissibility or virulence of pathogens.² By enhancing these features, this research typically aims to improve understanding of pathogens, their interactions with human hosts, and their pandemic potential. It can be used to better inform public health and preparedness efforts and develop medical countermeasures. For example, this type of research led to the development of influenza vaccines.

Oversight to ensure the biosafety and biosecurity of pandemic pathogens is a responsibility shared across multiple departments. Generally, the Department of Health and Human Services (HHS) and its component agencies—including the Administration for Strategic Preparedness and Response (ASPR),³ the National Institutes of Health (NIH), the Food and Drug Administration (FDA), and the Centers for Disease Control and

¹See *Revisiting Gain of Function Research: What the Pandemic Taught Us and Where Do We Go From Here?* Hearing before the Subcomm. on Emerging Threats and Spending Oversight of the S. Comm. on Homeland Security and Governmental Affairs, 117th Cong., (2022).

Life sciences covers all sciences relating to living organisms, encompassing biology, biotechnology, genomics, pharmaceutical and biomedical research and techniques.

²National Science Advisory Board for Biosecurity, *Recommendations for The Evaluation And Oversight Of Proposed Gain-Of-Function Research*, May 2016.

³On July 22, 2022, HHS designated ASPR, which was formerly the Office of the Assistant Secretary for Preparedness and Response, as a stand-alone agency within the Department and announced that ASPR's name changed to the Administration for Strategic Preparedness and Response. According to HHS, the change will allow ASPR to mobilize a coordinated national response to future disasters and emergencies more effectively and efficiently.

Prevention (CDC)—are most directly involved in leading public health preparedness and response efforts, and associated research.⁴

Over the last 10 years, a number of incidents have led to questions about the nature and adequacy of U.S. government oversight of pathogens with pandemic potential and laboratory safety more generally. Such incidents included HHS-funded research in 2012 that involved the manipulation of avian influenza viruses to create human pathogens with pandemic potential, as well as unrelated laboratory safety lapses that could have released dangerous pathogens.⁵

In 2017, HHS instituted a new oversight framework for HHS-funded enhanced potential pandemic pathogen research (hereafter referred to as the Framework). The Framework defines a potential pandemic pathogen as being “likely highly transmissible and likely capable of wide and uncontrollable spread in human populations” and “likely highly virulent and likely to cause significant morbidity and/or mortality in humans.” It further defines an enhanced potential pandemic pathogen as one resulting from the enhancement of the transmissibility and/or virulence of a pathogen.⁶ This new Framework was developed in response to guidance from the White House Office of Science and Technology Policy (OSTP) recommending federal departments adopt a department-level

⁴Several federal departments and agencies share biodefense responsibilities to assess, prevent, and respond to biological threats. In these efforts, HHS coordinates with the Department of Homeland Security, the Department of Defense, and the Department of Agriculture among others on biosafety.

⁵Concerns about the risks of this type of research, which may be referred to as gain of function, were heightened after the publication of two separate experiments in 2012 that demonstrated how highly pathogenic avian influenza—an influenza strain that has increased ability to cause disease and mortality in birds—could be manipulated in the lab to produce genetic mutations that allowed the virus to become transmissible between mammals. In addition, concerns about laboratory safety and biosecurity were renewed in light of serious safety lapses at federal laboratories. For instance, in June 2014, CDC staff inadvertently transferred live *Bacillus anthracis* bacteria—which they erroneously believed had been inactivated by an experimental procedure—to a different laboratory, resulting in the potential exposure of many workers to a highly virulent strain of the pathogen that causes anthrax disease. In July 2014, FDA researchers discovered that vials of viable smallpox virus had been left in the cold room of an FDA laboratory instead of in appropriately secure repositories. See GAO, *High Containment Laboratories: Recent Incidents of Biosafety Lapses*, [GAO-14-785T](#) (Washington, D.C.: July 16, 2014) for more information.

⁶Enhanced potential pandemic pathogens do not include naturally occurring pathogens that are circulating in or have been recovered from nature, regardless of their pandemic potential.

pre-funding review mechanism for federally funded research that is anticipated to create, transfer, or use enhanced pathogens with pandemic potential.⁷ White House OSTP works with the White House National Security Council to coordinate policy across the federal government.

The CARES Act includes a provision for GAO to conduct and report on its monitoring and oversight of activities and funds to prepare for, respond to, and recover from COVID-19.⁸ This report focuses on HHS's oversight of research with potential pandemic pathogens, which HHS funds to assess the pandemic potential of emerging infectious agents such as viruses, and to inform public health and preparedness efforts. Specifically, in this report, we

1. describe how HHS uses its Framework and other programs to oversee federally funded research involving enhanced potential pandemic pathogens;
2. assess the extent to which HHS's Framework has the elements of effective oversight;
3. examine what gaps exist in HHS's broader oversight of research involving enhanced potential pandemic pathogens; and
4. assess the extent to which HHS oversees privately funded research.

To describe how HHS uses its Framework and other programs to oversee federally funded research involving enhanced potential pandemic pathogens, we reviewed federal regulations, guidance, and policies that HHS and its agencies use to oversee this research. In particular, we focused on how HHS and its agencies oversee the biosafety and biosecurity of this research. Biosafety includes the practices and equipment that ensure that lab workers, the community, and the environment are protected from infectious pathogens and biological hazards. Biosecurity includes the practices to ensure the protection and control of biological materials in laboratories to protect them from theft, loss, or misuse. We interviewed HHS officials, including those from NIH, CDC, and FDA about how they conduct and coordinate oversight.

⁷Office of Science and Technology Policy, *Recommended Policy Guidance for Departmental Development of Review Mechanisms for Potential Pandemic Pathogen Care and Oversight (P3CO)*, (Washington, D.C.: Jan. 2017).

⁸Pub. L. No. 116-136, § 19010(b), 134 Stat. 281, 580 (2020). All of GAO's reports related to the COVID-19 pandemic are available on GAO's website at <https://www.gao.gov/coronavirus>.

To examine the extent to which HHS's oversight of enhanced potential pandemic pathogen research has elements of effective oversight, we assessed HHS's policies, agency guidance, and other documentation against GAO's key elements of effective oversight. GAO identified five key elements of effective oversight in prior work in areas where low-probability adverse events can have significant and far-reaching effects. For example, we have applied these elements in assessing federal oversight of nuclear safety, oil and gas management, and high-containment laboratories.⁹ These elements are:

- **Ability to Perform Reviews.** The organization conducting oversight should have the ability to perform reviews, including the working knowledge necessary to review compliance with requirements.
- **Transparency.** The organization conducting oversight should provide access to key information, as applicable, to those most affected by operations.
- **Technical Expertise.** The organization conducting oversight should have sufficient staff with the expertise to perform sound safety and security assessments.
- **Independence.** The organization conducting oversight should be structurally distinct and separate from the entities it oversees.
- **Enforcement Authority.** The organization conducting oversight should have clear and sufficient authority to require that entities achieve compliance with requirements.

We also obtained and reviewed documentation for the two awards that involved enhancement of potential pandemic pathogens to make them more transmissible and that were reviewed under the Framework. We reviewed the documentation to examine how HHS oversaw the biosafety and biosecurity of the research. Additionally, we interviewed 10 subject matter experts, comprising nine individual researchers, academics, scientific advisory board members, and one organization representing biosafety officers. These subject matter experts were selected because of their roles as current or former members of National Science Advisory Board for Biosecurity (NSABB)—a federal advisory committee that addresses issues related to biosecurity and dual use research—

⁹See GAO, *High Containment Laboratories: Coordinated Actions Needed to Enhance the Select Agent Program's Oversight of Hazardous Pathogens*, [GAO-18-145](#) (Washington, D.C.: Oct. 19, 2017).

membership in the Association for Biosafety and Biosecurity, or authorship of recently published academic articles related to the enhancement of potential pandemic pathogens.¹⁰ We interviewed these experts about identified and potential risks of research with potential pandemic pathogens. We accessed and reviewed the recorded webcast of NSABB meetings and stakeholder engagement meetings to obtain perspectives from other members of the research biosafety and biosecurity community.¹¹

To identify any gaps that exist in HHS's oversight of research involving enhanced potential pandemic pathogens, we reviewed federal regulations, guidance, and policies that HHS and its agencies use to oversee this research to identify their scope and applicability. In evaluating this information, we compared policies and procedures against federal internal control standards related to assessing and managing risk.¹² We also obtained and reviewed publicly available documentation on a research grant that involved studying potential pandemic pathogens rather than enhancing the pathogens' functions and, thus, did not fall within HHS's oversight of research involving potential pandemic pathogens. We reviewed the documentation to examine how NIH identified risks and oversaw the biosafety and biosecurity of the research. We interviewed HHS and agency officials from NIH and CDC about how they conduct and coordinate their oversight. We interviewed officials from OSTP and the National Security Council about broader federal oversight in this area. We also interviewed subject matter experts described above to obtain their perspective on federal oversight of high-risk research.

¹⁰Selected experts came from a broad range of academic and industry backgrounds representing disciplines such as epidemiology, veterinary medicine, microbiology, immunology, biosafety, and biosecurity. Our findings from interviews with these experts are not generalizable to the entire spectrum of biological research experts.

¹¹NIH held stakeholder engagement meetings on April 27, 2022, and June 29, 2022, to gather feedback to help inform evaluations of the Framework and dual use research of concern (DURC) policies, respectively. These sessions were recorded and available for view on NIH's website: (April Session) <https://videocast.nih.gov/watch=45230>; (June session) <https://videocast.nih.gov/watch=45698>. NIH held a meeting on September 21, 2022, to share NSABB's preliminary findings and recommendations for public input. That session was recorded and available for view on <https://videocast.nih.gov/watch=46218>.

¹²GAO, *Standards for Internal Control in the Federal Government*, GAO-14-704G (Washington, D.C.: Sept. 10, 2014). Internal control is a process effected by an entity's oversight body, management, and other personnel that provides reasonable assurance that the objectives of an entity will be achieved.

To assess the extent to which HHS oversees privately funded research, we reviewed federal regulations, guidance, and policies governing research biosafety and biosecurity and examined their scope and applicability. In evaluating this information, we compared policies and procedures against the federal internal control standards related to using quality information and managing risk. We also reviewed past GAO work on this topic.¹³ We interviewed HHS and agency officials as well as officials from the White House OSTP and the National Security Council about federal oversight for privately funded research.

We conducted this performance audit from September 2021 to January 2023 in accordance with generally accepted government auditing standards. Those standards require that we plan and perform the audit to obtain sufficient, appropriate evidence to provide a reasonable basis for our findings and conclusions based on our audit objectives. We believe that the evidence obtained provides a reasonable basis for our findings and conclusions based on our audit objectives.

Background

HHS leads the federal public health and medical response to potential biological threats and emerging infectious diseases. Within HHS, ASPR coordinates HHS policy development in research biosafety and biosecurity in collaboration with other departmental, agency, and outside experts.¹⁴ Other HHS agencies—including NIH, CDC, and FDA—conduct their own research—known as intramural research—to identify and prepare for public health threats. They also review, provide guidance, and fund research conducted by others—known as extramural research—that may involve public health risks. This extramural research is typically conducted at universities, medical schools, private biotechnology companies, and other research institutions. For example, HHS—including NIH, and FDA—in partnership with the Department of Defense,

¹³GAO, *High-Containment Laboratories: National Strategy for Oversight is Needed*. [GAO-09-574](#) (Washington, D.C.: Sept. 21, 2009).

¹⁴ASPR leads the HHS Biosafety and Biosecurity Coordinating Council, an intradepartmental group established by the HHS Immediate Office of Secretary, to provide a mechanism to share best practices, enhance visibility across HHS agencies, and coordinate biosafety and biosecurity policy development as well as oversight activities. The HHS Biosafety and Biosecurity Coordinating Council includes members from CDC and NIH, among others.

implemented Operation Warp Speed, which provided financial support and oversight of nonfederal partners to accelerate the development of COVID-19 vaccines and therapeutics to prevent severe disease and death.¹⁵

Funding agencies are responsible for conducting ongoing oversight of research through monitoring compliance with the terms and conditions of the award. NIH is the primary federal agency that conducts and supports biomedical research, and provides oversight in a variety of ways:¹⁶

- As a funding agency, NIH manages and administers federal awards to ensure that federal funding is expended, and associated programs are implemented in accordance with statutory and other grant requirements. To do so, NIH monitors grantee performance and use of NIH funds.¹⁷ In addition to its standard grants policy, NIH may incorporate specific terms and conditions reflecting the specific risks of the research. For example, NIH requires grantees to provide periodic progress reports describing research findings, and NIH may add biosafety terms to subsequent grant awards based on those reports.¹⁸
- NIH also provides biosafety and biosecurity guidance. For example, NIH, in conjunction with CDC, develops and disseminates *Biosafety in*

¹⁵GAO, *COVID-19: Federal Efforts Accelerate Vaccine and Therapeutic Development, but More Transparency Needed on Emergency Use Authorizations*, [GAO-21-207](#) (Washington, D.C.: Nov. 17, 2020).

¹⁶According to NIH, approximately 95 percent of NIH budget goes to support research. This includes grants and subawards to support research conducted outside the United States. CDC and FDA also fund research, with 5 percent of CDC's funding supporting research grants. FDA did not provide information about the percentage of agency funding dedicated to supporting research grants.

¹⁷Grantees must monitor the activities of subrecipients, including foreign subrecipients, to ensure that subawards are used for authorized purposes in compliance with relevant laws and the terms and conditions of the subaward.

¹⁸The Policy Statement requires that grantees report at least annually on budget information, but NIH has the flexibility to specify the elements for reporting and require more frequent reporting. The grant terms and conditions include requirements for the content and frequency of the progress reports. Progress reports include sections to report whether the major goals of the research have changed, accomplishments toward those goals, and plans for the next reporting period to accomplish the research goals.

Microbiological and Biomedical Laboratories, an advisory document recommending best biosafety practices to researchers.¹⁹

NIH comprises 27 institutes and centers. These institutes and centers both conduct and support biomedical research specific to their unique missions, which generally focus on a specific disease (e.g., cancer), a particular organ (e.g., eye), or a stage in life (e.g., childhood). NIH's National Institute of Allergy and Infectious Diseases (NIAID) conducts and supports basic and applied research aimed at understanding, treating, and ultimately preventing the spread of infectious diseases. Among the institutes, NIAID has a unique mandate that requires it to respond to emerging public health threats, including emerging and re-emerging infectious diseases (such as COVID-19 and mpox, respectively).²⁰ Among the institutes, NIAID is most directly involved in supporting or conducting research with potential pandemic pathogens.

In addition to oversight through grant review, some research involving pathogens that have the potential to pose a severe threat to human health—such as the Ebola and mpox viruses—is considered to pose higher risk to public health and safety, and may also be subject to other oversight governing the use of these pathogens.

¹⁹NIH also developed and administers the *NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules (NIH Guidelines)*. These guidelines detail safety practices and containment procedures for research involving manipulated or laboratory-created nucleic acid molecules (i.e., genetic building blocks) including the creation and use of organisms and viruses containing these molecules. In addition to providing biosafety guidance for a broad array of work with nucleic acids, the *NIH Guidelines* are a term and condition of NIH funding and they require researchers and institutions receiving NIH funds to obtain prior approval from the NIH director for any work involving the deliberate transfer of drug resistance traits to bacteria.

²⁰Mpox was formerly known as monkeypox. The World Health Organization recommended the name change in November 2022.

Viruses Subject to the Federal Research Funding Pause between 2014-2017

Influenza Virus: In 2009, the most recent influenza pandemic, primarily affected children and young adults and led to over 12,000 deaths in the United States.

MERS-CoV: Has been found in camels and was first reported in Saudi Arabia in 2012. It has since spread to 27 countries, including the United States and led to 894 deaths as of July 2022. Most people infected with MERS developed fever, cough, and shortness of breath. MERS fatality rate is approximately 35 percent.



A veterinarian extracts blood samples from a camel's neck.

SARS-CoV: A viral respiratory illness first reported in Asia in February 2003. It spread to 29 countries, infecting over 8,000 people and resulting in over 770 deaths. SARS case fatality rate is approximately 10 percent. Since 2004, no SARS cases have been reported.



A health provider in the process of acquiring information from a SARS patient in a clinical setting.

Source: The Centers for Disease Control and Prevention (CDC) (information, photos), World Health Organization (information). | GAO-23-105455

In the fall of 2014, the U.S. government paused funding for a specific type of high-risk research that results in the acquisition of new or enhanced biological characteristics in microorganisms—referred to as gain-of-function research. Specifically, the U.S. government paused funding for gain-of-function research that was anticipated to enhance the transmissibility or pathogenicity of influenza viruses, Middle East Respiratory Syndrome, and Severe Acute Respiratory Syndrome (SARS) coronaviruses.²¹ At the same time, the U.S. government embarked on a process to re-evaluate the risks and benefits of gain-of-function research and to develop policies to govern the funding and oversight of such research. During this time, the U.S. government sought input from the NSABB and other stakeholders on the risks and benefits of research involving potential pandemic pathogens, as well as recommendations for strengthening oversight.

In 2016, NSABB found that a small subset of gain-of-function research entails risks that were potentially significant enough to warrant additional oversight, and recommended that such research be subjected to additional review and oversight. Specifically, NSABB recommended the federal government take the following actions:

1. develop an additional, multidisciplinary review for any gain-of-function research that could generate a pathogen that is: a) highly transmissible and likely capable of wide and uncontrollable spread in human populations; and b) highly virulent and likely to cause significant morbidity and/or mortality in humans prior to determining whether such research is acceptable for funding. If funded, such projects should be subject to ongoing oversight at the federal and institutional levels;
2. utilize an advisory body designed for transparency and public engagement as part of the U.S. government's ongoing evaluation of oversight policies for gain-of-function research of concern;
3. consider ways to ensure that gain-of-function research of concern conducted within the United States or by U.S. companies be subject to oversight, regardless of funding source.²²

²¹See <https://obamawhitehouse.archives.gov/blog/2014/10/17/doing-diligence-assess-risks-and-benefits-life-sciences-gain-function-research> accessed August 24, 2021. The National Institutes of Health (NIH) identified 21 projects or awards that contained experiments that were subject to the research funding pause.

²²National Science Advisory Board for Biosecurity, *Recommendations for The Evaluation And Oversight Of Proposed Gain-Of-Function Research*, May 2016.

HHS's Framework and Other Programs for Overseeing Federally Funded Enhanced Potential Pandemic Pathogen Research

HHS's 2017 Framework establishes a departmental-level review process for research proposals that are submitted for HHS funding and involve enhanced potential pandemic pathogens. According to the Framework, this includes research proposals to enhance the transmissibility or virulence of pathogens that already have the likely potential to cause wide and uncontrollable disease, resulting in significant morbidity and mortality in human populations.

The Framework's definition of an enhanced potential pandemic pathogen specifically excludes naturally occurring pathogens that are circulating in or have been recovered from nature, regardless of their pandemic potential. The Framework also excludes projects that consist of surveillance activities, including sampling and sequencing of pathogens, and activities associated with developing and producing vaccines, such as generating virus strains that replicate quickly (for an example of the research excluded under the Framework, see app. II).

The departmental-level review is layered onto a funding agency's standard grant review process and provides non-binding recommendations for the funding agency to consider in deciding whether to fund a research grant proposal (see fig. 1).

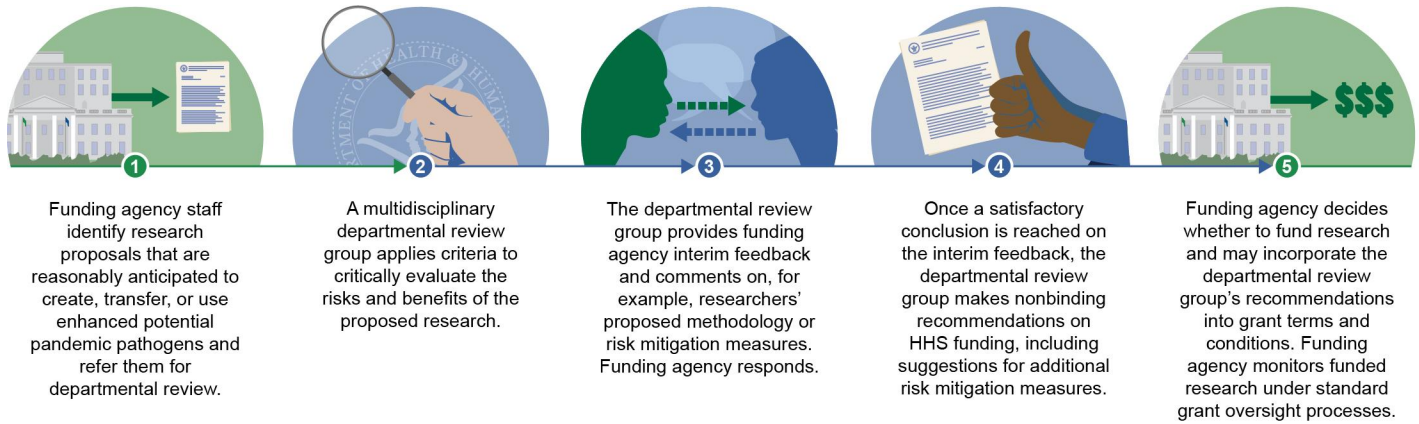
Potential and Enhanced Potential Pandemic Pathogens

The U.S. Department of Health and Human Services defines a potential pandemic pathogen as being "likely highly transmissible and likely capable of wide and uncontrollable spread in human populations" and "likely highly virulent and likely to cause significant morbidity and/or mortality in humans."

It further defines an enhanced potential pandemic pathogen as one resulting from the enhancement of the transmissibility and/or virulence of a pathogen.

Source: HHS. | GAO-23-105455

Figure 1: Department of Health and Human Services (HHS) Process for Reviewing Research Considered for Funding That Involves Enhanced Potential Pandemic Pathogens



Source: GAO analysis of HHS documentation. | GAO-23-105455

Department of Health and Human Services (HHS) Review Criteria for Assessing Certain High-Risk Research Proposals

- The research has been evaluated by an independent expert review process (whether internal or external) and has been determined to be scientifically sound.
- 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.
- 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.
- 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.
- 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.
- 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.
- 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.
- 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 potential pandemic pathogens.

Source: HHS. | GAO-23-105455

Specifically, under the Framework, HHS funding agencies are to conduct a review of research proposals that are being considered for federal funding to identify research proposals that are reasonably anticipated to create, transfer, or use enhanced potential pandemic pathogens. If the funding agency determines that the research fits the scope, the funding agency then refers such research proposals to a multi-disciplinary departmental review group, coordinated by ASPR, to assess the risks, benefits, and the researchers' capacity to ensure biosafety. According to the Framework, a multidisciplinary departmental review will be conducted in order to guide HHS funding decisions, and it will be based upon the identified criteria.

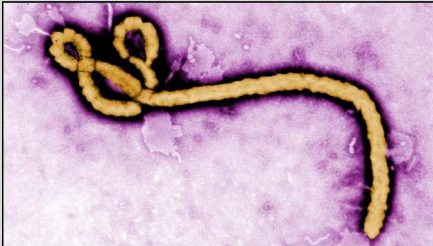
After its review, the departmental review group makes a nonbinding recommendation to the relevant HHS funding agency, which the agency considers in deciding whether to fund the research or impose additional risk-mitigation measures as a condition of funding the research. If the funding agency moves forward with funding the research proposal, the funding agency is responsible for incorporating any additional requirements into the grant and conducting oversight to ensure compliance through its standard grant oversight responsibilities. The funding agency must report its decision to the departmental review group and OSTP. ASPR officials told us they may require that funding agencies notify ASPR if the approved research results in unexpected outcomes.

Since the Framework's implementation in 2017, HHS has reviewed three research proposal submissions, all referred by NIH as of September

2022.²³ Of these three proposals, NIH adopted the departmental group recommendation for two of the studies. Both studies involved highly pathogenic avian influenza viruses—influenza strains that have increased ability to cause disease and mortality in avian species—and both have since concluded.²⁴ The third proposal, also involving influenza, was determined to be acceptable for funding with additional risk mitigation measures by the departmental review group. According to NIH, the agency decided to fund the proposal after the proposal was revised to use alternative methodologies that did not involve enhanced potential pandemic pathogen research.

Examples of Select Agents

The Ebola virus is highly lethal and can cause severe illness and death in humans from hemorrhagic fever. Case fatality rates average 50 percent and can reach 90 percent. The Ebola virus caused an epidemic from 2014–2016 that ended with more than 28,600 cases and 11,325 deaths. The Centers for Disease Control and Prevention (CDC) have listed the Ebola virus as a select agent.



The filamentous and curved morphology of an Ebola virus particle.

Source: The Centers for Disease Control and Prevention (CDC) (information, photos), World Health Organization (information). | GAO-23-105455

According to CDC officials, enhanced potential pandemic pathogen research is not typically the type of research the agency funds, and the agency had not received any funding requests for such work as of September 2022. According to FDA officials, the agency has also not funded research related to enhanced potential pandemic pathogens.

Beyond the Framework, HHS and its agencies have other programs in place that are not specifically focused on enhanced potential pandemic pathogens, but may provide additional oversight. Specifically,

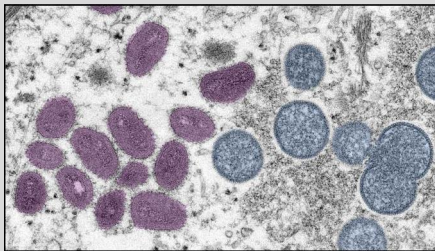
- **Federal Select Agent Program.** The Federal Select Agent Program regulates the possession, use, and transfer of certain hazardous pathogens and toxins, which are designated as select agents because they have the potential to pose a severe threat to human, animal, or plant health and safety. Under this program, the CDC's Division of Select Agents and Toxins (DSAT), is responsible for developing and maintaining a list of select agents that have the potential to pose a severe threat to public health and safety. Specifically, in developing and maintaining the list, CDC must assess (1) the effect on human health of exposure to the agent or toxin; (2) the degree of contagiousness of the agent or toxin and the methods by which the agent or toxin is transferred to humans; (3) the availability and effectiveness of pharmacotherapies and immunizations to treat and prevent any illness resulting from infection by the agent or toxin; and (4) any other criteria, including the needs of children and other

²³Specifically, all three proposals were referred for departmental review by National Institute of Allergy and Infectious Diseases.

²⁴Two of these projects had originally been awarded in 2013 and were subject to the 2014 funding pause. Those projects were subsequently reviewed in 2018 under the Framework policy and were approved to continue.

Examples of Select Agents Continued

The mpox virus is part of the same family of viruses as the virus that causes smallpox. One strain of the virus—the Congo Basin clade—is capable of causing severe illness with a fatality rate of 10 percent. It has been listed by the CDC as a select agent. The strain responsible for the 2022 outbreak is the West African clade, and symptoms are milder and rarely fatal. The West African clade is not listed as a select agent.



Mature (left) and immature (right) mpox virus particles.
Source: The Centers for Disease Control and Prevention (CDC) (information, photos), World Health Organization (information). | GAO-23-105455

- vulnerable populations.²⁵ CDC conducts periodic inspections of entities—including research institutions—that possess, use, or transfer these agents.²⁶ Some pandemic pathogens, such as the influenza strain that caused the 1918 pandemic, are select agents. Generally, laboratories and other entities that possess, use, or transfer these select agents must register with CDC, and must develop explicit biosecurity and biosafety plans and procedures that are reviewed by CDC inspectors.²⁷
- Dual use research of concern (DURC) policies.** Certain types of research conducted for legitimate purposes can also be utilized for harmful purposes. Such research is called “dual use research.” Dual use research of concern (DURC) is the subset of life sciences research that, based on current understanding, can be reasonably anticipated to provide knowledge, products, or technologies that also could be directly misapplied to pose a significant threat to public health, safety, or national security. The federal government’s DURC policies aim to strengthen institutional oversight of high-risk life sciences research by providing guidance to its agencies and research institutions on identifying research of concern. DURC policies specify a list of agents—all of which are also on the select agent list—and types of experiments that warrant assessment for the potential to involve DURC. DURC policy requires researchers to identify potential DURC research, and institutions to assess risk posed by such research and develop risk-mitigation plans. Funding agencies are responsible for reviewing and approving the risk mitigations plans. On a biannual basis, agencies report a list of DURC-related research to the Assistant to the President for Homeland Security and Counterterrorism. Research that enhances the transmissibility or virulence of certain potential pandemic pathogens could be subject to DURC.

All three programs—the Framework, Federal Select Agent Program, and DURC—applied to two of the three research proposals noted above that were referred for departmental review under the Framework. Both of the

²⁵42 U.S.C. § 262a(a)(1)(B).

²⁶The Federal Select Agent Program is jointly managed by CDC and the Department of Agriculture, with the Department of Agriculture responsible for overseeing the use of select agents and toxins that have the potential to pose a severe threat to animal or plant health or animal or plant products. 7 C.F.R. Part 331 and 9 C.F.R. Part 121 (2022); 42 C.F.R. Part 73 (2021).

²⁷See 42 C.F.R. §§ 73.7, 73.12 (2021).

proposed research projects involved highly pathogenic avian influenza, a pathogen with pandemic potential that is also a select agent and included in the DURC policies as well.²⁸ According to ASPR, CDC, and NIH officials, there is some coordination and information sharing among the programs. For example, CDC officials told us that key officials from the Select Agent Program are members of the departmental review group and that they provide biosafety and biosecurity recommendations in the context of the group's review of a specific proposal.

During the course of our review, in February 2022, NIH tasked NSABB with evaluating and providing recommendations on the scope and effectiveness of OSTP's guidance governing research with enhanced potential pandemic pathogens, the Framework and DURC.²⁹ HHS and OSTP officials told us that both the Framework and DURC policies are subject to periodic review. According to OSTP officials, this particular review was part of a broader review of biodefense policies in response to the President's January 2021 national security memo, which required a coordinated federal review of health security policies and strategies for reducing the risk of deliberate or accidental biological events.³⁰ NIH held

²⁸GAO previously examined the effectiveness of the Federal Select Agent Program in oversight of select agents and recommended that CDC take steps to improve the elements of effective oversight. See GAO, *High Containment Laboratories: Coordinated Actions Needed to Enhance the Select Agent Program's Oversight of Hazardous Pathogens*, [GAO-18-145](#) (Washington, D.C.: Oct. 19, 2017). CDC agreed with and implemented our recommendations.

²⁹In January 2020, HHS charged NSABB with providing recommendations to OSTP and HHS on balancing considerations regarding security and public transparency when sharing information about research involving enhanced potential pandemic pathogens as well as evaluating OSTP's policy guidance on overseeing this research and federal DURC policies. The charge was subsequently revised in 2022 to focus on review and evaluation of OSTP's guidance and HHS's Framework as well as DURC policies.

³⁰The White House, *National Security Memorandum on the United States Global Leadership to Strengthen the International COVID-19 Response and to Advance Global Health Security and Biological Preparedness*, (Washington, D.C.: Jan. 21, 2021). Subsequently, in October 2022, the White House released the *National Biodefense Strategy and Implementation Plan for Countering Biological Threats, Enhancing Pandemic Preparedness, and Achieving Global Health Security*, which updates the 2018 *National Biodefense Strategy*, and pushes for broader concerted effort by federal, state, and local governments to assess, prevent, prepare for, and respond to biological threats. Under this plan, the White House has tasked NSC and OSTP with leading an inter-departmental effort to develop and provide guidance for rigorous life sciences research biosafety and biosecurity norms and oversight and monitoring programs in all sectors worldwide. This includes completing the interagency review of efforts to strengthen responsible conduct for biological research and develop and operationalize interagency plans.

two public listening sessions in April and June 2022 to gather public input on the OSTP's guidance, the Framework and DURC. More recently, NIH convened a virtual meeting of the NSABB on September 21, 2022. The meeting included an update from the NSABB on its work and public comment on its preliminary findings and draft recommendations. According to NIH, NSABB will discuss draft findings and recommendations in the coming months.

HHS Framework for the Oversight of Research Involving Enhanced Potential Pandemic Pathogens Does Not Fully Meet Key Elements of Effective Oversight

The oversight provided by the Framework does not fully meet key elements of effective oversight previously identified by GAO.³¹ In particular, the Framework has oversight shortcomings related to two key elements—performing reviews and transparency.

HHS Lacks Assurance That All Relevant Research Proposals Are Referred for Departmental Review

The Framework requires funding agencies to refer proposed research that is “reasonably anticipated to create, transfer or use enhanced potential pandemic pathogens” for departmental review. The departmental review group can only review research that a funding agency has referred for departmental review. Yet, the Framework does not articulate a standard for what “reasonably anticipated” means.

³¹In 2008, we applied these elements to the area of nuclear safety oversight. In a 2017 report, we expanded the applicability of these five elements to the oversight of high-containment laboratories by the Federal Select Agent Program. See GAO, *Nuclear Safety: Department of Energy Needs to Strengthen Its Independent Oversight of Nuclear Facilities and Operations*, [GAO-09-61](#) (Washington, D.C.: Oct. 23, 2008) and GAO, *High-Containment Laboratories: Coordinated Actions Needed to Enhance the Select Agent Program's Oversight of Hazardous Pathogens*, [GAO-18-145](#) (Washington, D.C.: Oct. 19, 2017).

Key element of effective oversight*Ability to perform reviews*

The organization conducting oversight should have the ability to perform reviews, including the working knowledge necessary to review compliance with requirements.

Source: GAO. | GAO-23-105455

According to a key element of effective oversight, the organization conducting oversight should have the ability to perform reviews, including the working knowledge necessary to review compliance with requirements. Unclear standards for referral allow for subjective and inconsistent interpretation, and as a result, HHS may not have the opportunity to review all research proposals involving enhanced potential pandemic pathogens. The Framework refers to the 2016 NSABB report for examples of research that would and would not be considered to involve enhanced potential pandemic pathogens. However, these examples repeat the definition without providing specificity or articulating a standard for “reasonably anticipated.”³²

Experts we spoke with also noted there was a lack of clarity in the Framework’s definition of research subject to departmental review. Specifically, the phrase “reasonably anticipated” allows for subjective interpretation and covers a range of certainty regarding the intent of the research and the likelihood of the results. For example, one of the subject matter experts we spoke with told us the phrase could be interpreted to mean that it is more likely than not that research will result in an enhanced potential pandemic pathogen, whereas to others it could mean that the research is certain to result in an enhanced potential pandemic pathogen.

According to HHS and CDC officials, the Framework’s definition of research to be referred allows for subjective interpretation of what is reasonably anticipated to result in enhanced potential pandemic pathogens and acknowledged that additional clarity would be helpful. In contrast, NIH officials told us that the criteria for referral in the Framework are well defined and adequate. However, the NIH institute that is most directly involved in research with potential pandemic pathogens—NIAID—developed its own guidance for NIAID staff on how to determine whether a research proposal should be referred for departmental review, suggesting that additional clarity was needed.³³ In this guidance, it advises NIAID staff to err on the side of inclusion when identifying research that may involve enhanced potential pandemic pathogens.

³²National Science Advisory Board for Biosecurity, *Recommendations for The Evaluation And Oversight Of Proposed Gain-Of-Function Research*, May 2016.

³³As of September 2022, all research reviewed by the HHS departmental review group were referred by NIAID, one of the 27 components that make up NIH. Within NIH, NIAID is most directly involved in supporting or conducting research with potential pandemic pathogens.

Until HHS works with its funding agencies to develop and document a standard for “reasonably anticipated,” the Framework allows for subjective and potentially inconsistent interpretations of the criteria for determining which research proposals fall under the scope of the Framework. Consequently, HHS cannot ensure that funding agencies are referring all proposed research involving enhanced potential pandemic pathogens for departmental review.

HHS’s Departmental Review Process Lacks Transparency

HHS lacks transparency regarding the composition of the departmental review group. This lack of transparency impeded our ability to assess whether those conducting departmental review are equipped with appropriate technical expertise. Furthermore, HHS lacks transparency regarding how the departmental review group applies the Framework’s review criteria.

Key elements of effective oversight

Transparency

The organization should provide access to key information, as applicable, to those most affected by operations.

Technical expertise

The organization conducting oversight should have sufficient staff with the expertise to perform sound safety and security assessments.

Source: GAO. | GAO-23-105455

Composition of the departmental review group

HHS lacks transparency regarding the composition of the departmental review group. According to one of the key elements of effective oversight—transparency—the organization conducting oversight should provide access to key information, as applicable, to those most affected by operations. Key information includes information regarding the composition of the departmental review group and selection criteria for the review group membership. However, HHS does not publicly share the qualifications or expertise of those involved in the review process. Because little is known about the composition of the departmental review group, it is not clear whether the departmental review group is equipped with the full range of technical expertise needed to critically evaluate risks associated with proposed research involving enhanced potential pandemic pathogens.

The Framework lists the disciplines that should be represented in the review group, but does not identify the qualifications of the review group members or which HHS agencies are to be represented in the group.³⁴

³⁴The Framework specifies that the following disciplines should be represented during the department-level review: scientific research, biosafety, biosecurity, medical countermeasure 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.

Policymakers and the research community, including the experts we spoke with, as well as presenters at NSABB meetings, criticized the lack of transparency about the composition of the departmental review group. This practice is also inconsistent with other HHS research review protocols that identify the selection process for reviewers. For example, NIH publicly shares the selection criteria—including expertise requirements and individual qualifications—for reviewers who participate in the standard grant review process. In addition, NIH publicly shares the rules, responsibilities, and possible consequences for any actions that may threaten the integrity of its peer review process.³⁵

According to HHS's standard operating procedures for departmental review, the review group members are selected by the departmental review group Chair and confirmed by the Assistant Secretary for Preparedness and Response. However, the guidance is unclear as to the detailed selection process and criteria for the members and details regarding the appointment and tenure of the Chair.

This lack of transparency regarding the composition of the departmental review group impeded our ability to assess whether the Framework meets another key element of effective oversight—technical expertise. This key element states that the organization conducting oversight should have sufficient staff with the expertise to perform sound safety and security assessments.

The Chair of the departmental review group stated the confidentiality of review group members was intended to protect the privacy concerns and personal vulnerabilities of the members and maintain the integrity of the review process. For example, HHS officials told us that agency staff have faced threats to their personal safety related to their perceived involvement in gain-of-function research. Given the heightened concern about the risks posed by this type of research, and the safety of scientists, officials told us that there is a need to balance protection of

³⁵NIH publicly shares its selection process (NIH, "How Scientists Are Selected to Be Members of a Chartered Review Group" (Bethesda Md.: April 07, 2022), accessed Oct. 12, 2022. <https://public.csr.nih.gov/ForReviewers/BecomeARewriter/CharteredReviewers> and roles and responsibilities of its peer reviewers (NIH, "Maintaining Security and Confidentiality in NIH Peer Review: Rules, Responsibilities and Possible Consequences" (Bethesda Md.: December 30, 2021), accessed Oct. 12, 2022. <https://grants.nih.gov/grants/guide/notice-files/NOT-OD-22-044.html>). For details on how NIH shares non-sensitive key information about its peer reviewers, see NIH peer review policies and practices website (NIH, "Policy & Compliance: Peer Review Policies and Practices" (Bethesda Md.: June 12, 2022), accessed Oct. 21, 2022. <https://grants.nih.gov/policy/peer/index.htm>).

personal vulnerabilities and transparency. However, HHS was able to share some non-sensitive information about the composition of the review group and expertise of those involved. For example, the Chair of the committee told us that the departmental review group comprises HHS officials with appropriate technical expertise. In particular, as CDC officials confirmed, the Select Agent Program is represented in the departmental review group, fulfilling the requirements outlined in the Framework. By working with funding agencies to identify and share non-sensitive information about the composition of the review group—such as the qualifications or expertise of those who are involved in the review process—researchers, Congress and the public would have greater assurance that individuals with the appropriate expertise are conducting reviews of research involving enhanced potential pandemic pathogens.

Application of the review criteria

HHS also lacks transparency regarding its review process under the Framework. According to the transparency element of effective oversight, the organization conducting oversight should provide access to key information, as applicable, to those most affected by operations. This key information includes how the criteria are applied in the departmental group's review. However, HHS does not publicly share how the review group assesses the research proposals and applies the review criteria.

Although the Framework lists the evaluation criteria that the departmental review group must consider, HHS is not transparent about how those criteria are applied when evaluating research proposals and how they result in recommendations to the funding agency. Multiple experts we spoke with stated that transparency within HHS's departmental review process is important to understanding the application of the departmental evaluation criteria. During an NSABB listening session in April 2022, other members of the research community raised similar concerns. For example, one biosafety specialist noted that given the broad range of biosafety and biosecurity practices among researchers and institutions, without greater transparency in how the departmental review group applies criteria, it is unclear how the departmental review group can assess an institution's capacity to conduct research safely and securely. This specialist further noted that the public's awareness of research assessments of what levels of risk are acceptable, as well as public engagement in the process of establishing a minimum standard for biosafety practices and policies, are essential to the standard's dissemination.

HHS officials told us that departmental review is a pre-funding review, and as such, they do not want to compromise intellectual property by sharing details about the research assessment process.³⁶ Similarly, according to NIH, information about HHS's pre-funding reviews of specific proposals are not shared publicly in order to preserve confidentiality and to allow for candid critique and discussion of individual proposals.

We acknowledge the sensitivity and intricacy of departmental review. Those most involved in the review process—HHS and funding agencies—are best positioned to identify non-sensitive information that could be shared with the public. For example, NIH was able to provide a public description of its own review and referral process in its response to congressional inquiries.³⁷ Furthermore, HHS officials told us the departmental review group critically evaluates the proposal against each criterion. They told us that to assess, for example, an institution's capacity to conduct work safely, the departmental review group examines past history of adherence to biosafety and biosecurity practices, policies, and procedures. HHS has an opportunity to balance the need to preserve the integrity of the review process while improving transparency by sharing this type of information with researchers, Congress, and the public about how criteria are applied.

By working with its funding agencies to identify and share non-sensitive information about how HHS, in coordination with its funding agencies, conducts reviews and makes funding recommendations, researchers, Congress, and the public would have greater assurance that departmental review provides meaningful and effective suggestions to address biosafety and biosecurity concerns about research involving enhanced potential pandemic pathogens.³⁸ Moreover, doing so could enhance public confidence in the department's oversight as well as

³⁶Descriptions of research proposals reviewed by the departmental review group are made public upon funding agency's decision to fund the research (<https://www.phe.gov/s3/dualuse/Pages/ResearchReview-PPP.aspx>).

³⁷Letter from NIH Director Francis Collins to Senator Charles Grassley, July 28, 2021, https://www.grassley.senate.gov/download/national-institutes-of-health-to-grassley_-covid-origins-grant-oversight

³⁸For example, NIH's peer review policies and practices website (<https://grants.nih.gov/policy/peer/index.htm>) provides detailed guidelines regarding the peer review process, including review criteria, scoring guidance for reviews, rules about conflict of interest, and additional review considerations. For example, the NIH grant application scoring system is used to encourage reliable scoring of applications. The website contains information about detailed scoring procedures and examples in assigning impact scores and individual criterion scores in NIH peer review.

ensure the agency's goal to exemplify and promote the highest level of scientific integrity, public accountability, and social responsibility in the conduct of science.

Independent Reviews of Intramural and Extramural Research for Referral

Under the Framework, 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 potential pandemic pathogens is subject to additional departmental review. The Framework applies to funding for proposed research and operates before funding of the research. Therefore, HHS's oversight of such research begins with, and relies on, funding agencies to identify, flag, and refer them for additional review.

Key element of effective oversight

Independence

The organization conducting oversight should be structurally distinct and separate from the entities it oversees.

Source: GAO. | GAO-23-105455

According to a key element of effective oversight, to be independent, the organization conducting oversight should be structurally distinct and separate from the entities it oversees. Furthermore, OSTP guidance for reviewing enhanced potential pandemic pathogen research suggests departments and agencies are to vest oversight for their review mechanisms in offices that do not report to the head of the agency component that is proposing to fund such research. According to agency officials, funding agencies incorporate the reviews for referrals with their DURC reviews, which are performed by independent internal committees. Enhanced potential pandemic pathogen research is not typically the type of research that CDC or FDA funds. However, officials from CDC and FDA told us that both agencies would review research involving enhanced potential pandemic pathogens through their DURC review processes.³⁹ According to NIH documents and officials, NIH incorporates its review for referrals with its DURC review process. For example, as the institute conducting and funding the most research on enhanced potential pandemic pathogens, NIH developed procedures to help with an

³⁹CDC officials said that enhanced potential pandemic pathogen research is not typically the type of research the agency funds, but they would review such research proposals as they would for any proposals they receive involving dual use research of concern. Agency officials said there is no separate review mechanism for enhanced potential pandemic pathogen research proposals. FDA provided a directive outlining its internal process for reviewing enhanced potential pandemic pathogen research proposals with its DURC review panel, including a review by the Director of the Office of Laboratory Safety.

independent review process for both its extramural and intramural research proposals.⁴⁰ Specifically,

- Extramural research review: NIAID established a pre-departmental review committee and developed standard operating procedures outlining the institute's review process under the Framework. According to NIAID's standard operating procedures, at the institute-level, NIAID employs a two-stage review process to determine referrals: 1) program officer review to identify research that may be subject to the Framework, and 2) institute-level committee review of the research to determine referrals for departmental review.
- Intramural research review: NIAID leverages the NIH's existing internal independent review process to review its intramural research for referral. Specifically, NIH's DURC institutional review entity, comprising officials from NIH offices and component institutes, review intramural research protocols that may involve DURC. During the course of our review, NIH updated its DURC review policy for intramural research in September 2022 to require NIH's DURC institutional review entity to assess proposed intramural research for enhanced potential pandemic pathogens. According to NIH officials, the institutional review entity would determine whether to refer intramural research for departmental review based on the assessment.

HHS Enforcement Authority

Under the Framework, a departmental review is layered onto funding agencies' standard grants process. According to a key element of effective oversight, the organization conducting oversight should have clear and sufficient authority to require entities to achieve compliance with requirements. Under the Framework, HHS reviews research that has been referred for departmental review and makes recommendations to the funding agencies, which have the authority to determine whether to fund research or incorporate the recommended measures into the grant terms and conditions and oversee grantee compliance.⁴¹ Our analysis of the two research projects that NIAID funded following departmental

Key element of effective oversight

Enforcement authority

The organization should have clear and sufficient authority to require that entities achieve compliance with requirements.

Source: GAO. | GAO-22-105455

⁴⁰As of September 2022, all research reviewed by the departmental review group under the Framework were referrals from NIAID, an institute of NIH.

⁴¹HHS officials told us that during the development of the 2017 OSTP Guidance, the National Security Council determined that only the funding agency has the authority to determine whether to award funds and to impose conditions on the award of such funds.

review showed that the terms and conditions added to the awards were consistent with the departmental review group's recommendations. For example, NIAID added additional reporting requirements to the awards based on the departmental review group's recommendations.

HHS Faces Challenges Overseeing Research with Newly Emerged Potential Pandemic Pathogens during a Public Health Emergency

Under the DSAT program, CDC must maintain a list of pathogens that pose a severe threat to public health.⁴² CDC faces tradeoffs, however, between extending DSAT oversight to a newly emerged pandemic pathogen—for example, SARS-CoV-2, the virus responsible for the COVID-19 pandemic—and public health response activities (see text box). While adding a pathogen to the select agent list would allow CDC to oversee potentially high-risk research with the newly added select agent, this oversight could also impede the public health response activities during a pandemic by, for example, subjecting diagnostic and medical countermeasure development activities to DSAT's reporting and inspection requirements.

Centers for Disease Control and Prevention (CDC) Oversight of Research with SARS-CoV-2

In November 2021, CDC added specific Severe Acute Respiratory Syndrome (SARS) coronaviruses—SARS-CoV/SARS-CoV-2 chimeras—to the select agent list. These chimeras, which could have resulted in a new potential pandemic virus, are laboratory-created viruses that contain genetic material derived from two distinct viruses. The regulated chimeric viruses are explicitly limited to those that result from deliberately manipulating SARS-CoV-2 to incorporate genetic material from SARS-CoV, which is currently a select agent.

These chimeras were added to the select agent list after an institution's official voluntarily informed DSAT in April 2021 of planned research that could enhance a pandemic pathogen, SARS-CoV-2, according to CDC officials. In its interim final rule to add these chimeras to the select agent list, CDC noted that these experiments carried a significant potential risk of creating a chimeric virus that, if released, would result in a public health emergency requiring complicated and expensive response efforts, such as those seen during the COVID-19 pandemic.

⁴²The HHS Secretary is required to establish and maintain a list of each biological agent and toxin that has the potential to pose a severe threat to public health and safety. 42 U.S.C. § 262a(a)(1)(A).

CDC officials told us that they were able to add these specific SARS chimeric viruses to the select agent list because regulating these viruses would not interfere with the public health response. However, the addition of these SARS chimeras to the select agent list does not prevent research to make other SARS chimeras. For example, the results of research conducted at Boston University posted in October 2022 to create a chimera from two different SARS-CoV-2 strains is not covered by the Federal Select Agent Program because the research did not use genetic material from SARS-CoV and SARS-CoV-2.

Source: GAO analysis. | GAO-23-105455

Federal law authorizes CDC to exempt individuals or entities from DSAT requirements if it is determined an exemption is necessary to provide for the timely participation of the person or entity in the response to a public health emergency involving the listed agent.⁴³ This exemption authority gives CDC flexibility to determine which requirements to apply to specific individuals or entities. Such authority could allow for response activities such as diagnostic testing and medical countermeasure development that might otherwise be limited by the application of the full range of the DSAT requirements, while still allowing oversight of other research with the select agent. However, CDC can only exempt individuals or entities from DSAT's regulatory requirements for a maximum of 60 days, which may not be sufficient during an ongoing pandemic, such as the COVID-19 pandemic that had been ongoing for more than 2 years at the time of this report.⁴⁴

CDC officials agree this is a limitation. They told us they have not added SARS-CoV-2 to the select agent list because doing so would impede the pandemic public health response. For example, if CDC were to add SARS-CoV-2 to the select agent list during the COVID-19 pandemic, response efforts, such as important diagnostic work to track the spread of SARS-CoV-2, could be impeded due to the Federal Select Agent Program requirement to report each time a select agent is identified in patient samples. Additionally, research and medical countermeasure development efforts (such as COVID-19 therapeutics to prevent severe disease or death) could be slowed. This is because of the Federal Select Agent Program requirement that manipulation of the pathogen necessary to do this work only occur in laboratories that are registered with the Federal Select Agent Program and be performed by researchers who have undergone a background check.

⁴³42 U.S.C. § 262a(g)(3); 42 C.F.R. § 73.5(e) (2021).

⁴⁴The Secretary of HHS is authorized to exempt individuals or entities from DSAT regulations during a public health emergency, but these exemptions are limited to a 30-day period with a maximum extension of an additional 30 days.

CDC officials told us they have had discussions with HHS leadership concerning needs and challenges regarding the DSAT program, including the need for proposed legislative solutions. However, HHS leadership did not provide further details, leaving it unclear if HHS is considering possible changes to the DSAT program that would provide CDC with the flexibility to address the potential risks this program poses with respect to the limitation with the exemption period during a public health emergency.

Federal agencies are required to integrate risk management activities into their program management to help ensure they are effectively managing risks that could affect the achievement of agency objectives, according to the Office of Management and Budget's Circular A-123. In addition, federal internal control standards state that management should identify, analyze, and respond to risks related to achieving defined objectives. Without assessing and documenting the risk posed by the limitations in the duration of its existing exemption authority for public health emergencies, and taking any needed actions to mitigate any identified risks—including seeking legislative authority as needed—CDC will continue to face tradeoffs between impeding public health response efforts and allowing high-risk research involving known pandemic pathogens to be conducted without appropriate CDC oversight.

HHS Oversight of Privately Funded Enhanced Potential Pandemic Pathogen Research Is Limited

HHS's ability to oversee and regulate privately funded enhanced potential pandemic pathogen research is limited. Specifically, HHS does not conduct oversight of privately funded research, including enhancement of potential pandemic pathogens, if those pathogens are not select agents. For its part, the Framework applies only to grant applications submitted to HHS funding agencies. OSTP officials told us that the OSTP guidance and corresponding Framework were aimed at federally funded research because, at the time the guidance was developed, the understanding was that federal funding supported the majority of enhanced potential pandemic research.

The DURC policies apply only to institutions that receive federal funding for life science research and conduct research with any of the 15 agents or toxins listed in the policy, regardless of the funding source for that research. OSTP and White House National Security Council officials were

unable to provide information on the extent to which enhanced potential pandemic pathogen research is privately funded. OSTP officials told us that the scope of federal policies is under consideration as part of NSABB's current ongoing review of both the Framework and the DURC policies.

Of HHS's existing oversight, only the DSAT program oversees research conducted at privately funded institutions. However, its oversight is limited to its list of select agents and toxins. HHS does not have the responsibility or authority, under the Framework, the DURC policies, or the DSAT program, to license or regulate new laboratories unless use or storage of select agents or toxins is planned; as a result, it may not have knowledge of privately funded laboratories that are not registered with the Federal Select Agent Program.⁴⁵

HHS and its agencies' missions include identifying and preparing for public health threats. Federal internal controls standards require that federal agencies use, identify, and obtain quality information necessary to achieve their objectives, including identifying and addressing public health risks that could result from research with potential pandemic pathogens. A lack of knowledge about the scope and location of privately funded research being conducted means that there is a risk that an adverse public health event could result from unknown actors in unknown locations conducting high-risk research.

In 2009, we recommended that the National Security Advisor, in consultation with the Secretary of Health and Human Services, among others, identify a single entity charged with periodic government-wide strategic evaluation of high-containment laboratories.⁴⁶ The White House disagreed with the recommendation and the recommendation was not implemented. White House National Security Council staff we spoke with in September 2022 stated they have no position to share on this recommendation. We maintain that implementing this recommendation

⁴⁵Institutions that are registered with the Federal Select Agent Program must provide information on the specific laboratories where select agents and toxins will be used or stored, the specific select agents or toxins in each laboratory, and a description of the work for each select agent or toxin.

⁴⁶See GAO, *High-Containment Laboratories: National Strategy for Oversight is Needed*. [GAO-09-574](#) (Washington, D.C.: Sept. 21, 2009). In this report, we noted the increase in the number of high-containment laboratories had occurred across federal, state, academic, and private sectors. The Executive Office of the President (EOP) provided no comments to the report in 2009. In 2012, the EOP responded to GAO to note disagreement with the recommendation.

would provide the U.S. government with information that could be used to assess the risk posed by gaps in oversight of privately funded research with recently emerged potential pandemic pathogens and allow HHS to determine whether additional authorities are needed to address these risks.

Conclusions

Research involving potential pandemic pathogens is crucial for ensuring the nation's ability to prepare for, respond to, and recover from public health threats, such as COVID-19 and mpox. However, it also comes with risks. HHS has taken steps with the development of the Framework to strengthen oversight of research with potential pandemic pathogens. However, until HHS works with its funding agencies to develop and document a standard for "reasonably anticipated," the Framework allows for subjective and potentially inconsistent interpretations of the criteria for referral, potentially leaving HHS without the assurance that funding agencies are referring all the research proposals that should be referred for departmental review. Furthermore, by working with its funding agencies to identify and publicly share non-sensitive information about the departmental review process—including information on the composition and expertise of those involved in the review process, as well as how the evaluation criteria are applied—HHS would provide researchers, Congress and the public with greater assurance that the departmental review provides meaningful and effective suggestions to address biosafety and biosecurity concerns about research involving enhanced potential pandemic pathogens.

Moreover, HHS faces oversight gaps beyond the Framework. Specifically, until HHS and CDC assess and document the risks posed by the limitations of the existing DSAT exemptions for public health emergencies—including seeking any necessary legislative authority—as it deliberates changes to the DSAT program, CDC will continue to face tradeoffs between impeding public health response efforts and allowing high-risk research involving known pandemic pathogens to be conducted without appropriate CDC oversight.

We maintain that implementing our 2009 recommendation to charge a single federal entity with periodic government-wide strategic evaluations of high-containment laboratories would help HHS assess the risks posed by the lack of oversight of privately funded research that enhances potential pandemic pathogens, and develop mitigation plans, as needed.

Recommendations

We are making a total of three recommendations to HHS:

The Secretary of Health and Human Services should work with HHS funding agencies to develop and document a standard for “reasonably anticipated” to ensure consistency in identifying research for departmental review that is “reasonably anticipated to create, transfer or use enhanced potential pandemic pathogens.” (Recommendation 1)

The Secretary of Health and Human Services should work with HHS funding agencies to identify and share non-sensitive information with researchers, Congress, and the public about the departmental review process for research involving enhanced potential pandemic pathogens, including information on composition and expertise of those involved in the review process and how the evaluation criteria are applied. (Recommendation 2)

As HHS and CDC deliberate any changes to the DSAT program, the Director of the Centers for Disease Control and Prevention should assess and document the risk posed by the limitations of the existing DSAT exemptions for public health emergencies and seek legislative authority as needed. (Recommendation 3)

Agency Comments and Our Evaluation

We provided a draft of this report for advance review and comment to OSTP, the National Security Council, and HHS. National Security Council officials provided a technical comment, and OSTP officials told us they had no comments. HHS provided written comments, which we have reprinted in appendix I. HHS neither agreed nor disagreed with our first two recommendations to develop and document a standard for “reasonably anticipated” and share non-sensitive information about the departmental review. HHS stated that the department is committed to ensuring careful review and consideration of guidance to enhance the existing Framework and increase transparency. HHS further cited the ongoing work of the NSABB in evaluating the Framework, among other oversight policies and programs, and developing recommendations. HHS noted that the department expects this work to inform its future actions. HHS concurred with our third recommendation that HHS and CDC should assess and document risks posed by the limitations of the existing DSAT

exemptions and seek legislative authority as needed. HHS also stated that CDC is collaborating with HHS and the National Security Council to outline existing gaps and potential improvements to the Federal Select Agent Program.

We are sending copies of this report to the Secretary of Health and Human Services and appropriate congressional committees. The report is also available at no charge on the GAO website at <https://www.gao.gov>.

If you or your staff have any questions about this report, please contact me at (202) 512-7114 or at DeniganMacauleyM@gao.gov. Contact points for our Offices of Congressional Relations and Public Affairs may be found on the last page of this report. GAO staff who made key contributions to this report are listed in appendix III.

A handwritten signature in black ink that reads "Mary Denigan-Macauley". The signature is written in a cursive style with a large, stylized "M" at the beginning and a long, sweeping underline.

Mary Denigan-Macauley
Director, Health Care

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Committee on Appropriations
United States Senate

Chair
Ranking Member
Committee on Finance
United States Senate

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Ranking Member
Committee on Homeland Security and Governmental Affairs
United States Senate

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The Honorable Rosa L. DeLauro
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The Honorable Cathy McMorris Rodgers
Chair

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Ranking Member
Committee on Oversight and Accountability
House of Representatives

The Honorable Jason Smith
Chairman
The Honorable Richard Neal
Ranking Member
Committee on Ways and Means
House of Representatives

Appendix I: Comments from the Department of Health and Human Services



DEPARTMENT OF HEALTH & HUMAN SERVICES

OFFICE OF THE SECRETARY

Assistant Secretary for Legislation
Washington, DC 20201

December 19, 2022

Mary Denigan-Macauley
Director, Health Care
U.S. Government Accountability Office
441 G Street NW
Washington, DC 20548

Dear Ms. Denigan-Macauley:

Attached are comments on the U.S. Government Accountability Office's (GAO) report entitled, **"PUBLIC HEALTH PREPAREDNESS: HHS Could Improve Oversight of Research Involving Enhanced Potential Pandemic Pathogens"** (GAO-23-105455SU).

The Department appreciates the opportunity to review this report prior to publication.

Sincerely,

Melanie Anne Egorin

Melanie Anne Egorin, PhD
Assistant Secretary for Legislation

Attachment

GENERAL COMMENTS FROM THE DEPARTMENT OF HEALTH & HUMAN SERVICES ON THE GOVERNMENT ACCOUNTABILITY OFFICE'S DRAFT REPORT - "PUBLIC HEALTH PREPAREDNESS: HHS COULD IMPROVE OVERSIGHT OF RESEARCH INVOLVING ENHANCED POTENTIAL PANDEMIC PATHOGENS" (GAO-23-105455SU)

Recommendation 1

The Secretary of Health and Human Services should work with HHS funding agencies to develop and document a standard for "reasonably anticipated" to ensure consistency in identifying research for departmental review that is "reasonably anticipated to create, transfer or use enhanced potential pandemic pathogens."

HHS Response

HHS is committed to ensuring that it carefully reviews, considers, and incorporates guidance to enhance its existing framework. Earlier this year, the Acting NIH Director delivered a charge to the National Science Advisory Board for Biosecurity (NSABB) to review the scope and effectiveness of the USG's biosecurity policy frameworks governing research with enhanced potential pandemic pathogen (ePPP) and dual use research of concern (DURC). Specifically, the charge directed review of the White House Office of Science and Technology Policy's *Recommended Policy Guidance for Departmental Development of Review Mechanisms for Potential Pandemic Pathogen Care and Oversight* (OSTP P3CO Policy Guidance) and HHS's implementation of the OSTP guidance—the HHS P3CO Framework, as well as USG policies for the oversight of DURC.

The NSABB's final recommendations are anticipated in the coming months and will inform interagency and HHS deliberations about both the OSTP P3CO Policy Guidance and the HHS P3CO Framework to ensure we have robust policies and guidance in place. HHS will provide a future update to GAO in its Statement of Actions letter which is required by OMB Circular A-50 and 31 U.S.C. 720.

Recommendation 2

The Secretary of Health and Human Services should work with HHS funding agencies to identify and share non-sensitive information with researchers. Congress, and the public about the departmental review process for research involving enhanced potential pandemic pathogens, including information on composition and expertise, of those involved in the review process and how the evaluation criteria are applied.

HHS Response

HHS is committed to ensuring that it carefully reviews, considers, and incorporates guidance to increase transparency in the oversight of funding for research involving enhanced potential pandemic pathogens. In January 2020, the NIH Associate Director for Science Policy delivered a charge to the National Science Advisory Board for Biosecurity (NSABB) to provide recommendations regarding the balance between security and public transparency when sharing information about enhanced PPP research. The Working Group that is reviewing and evaluating the P3CO policy provided an update on its efforts during the NSABB September 22, 2022, meeting, including their efforts to enhance the transparency of the review process.

**GENERAL COMMENTS FROM THE DEPARTMENT OF HEALTH & HUMAN
SERVICES ON THE GOVERNMENT ACCOUNTABILITY OFFICE’S DRAFT
REPORT - “PUBLIC HEALTH PREPAREDNESS: HHS COULD IMPROVE
OVERSIGHT OF RESEARCH INVOLVING ENHANCED POTENTIAL PANDEMIC
PATHOGENS” (GAO-23-105455SU)**

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Recommendation 3

As HHS and CDC deliberate any changes to the DSAT program, the Director of the Centers for Disease Control and Prevention should assess and document the risk posed by the limitations of the existing DSAT exemptions for public health emergencies and seek legislative authority as needed.

HHS Response

HHS concurs with the recommendation. CDC, including DSAT, is continuing internal efforts and collaborating with HHS and the National Security Council to outline existing gaps and potential enhancements to the Federal Select Agent Program.

Agency Comment Letter

Text of Appendix I: Comments from the Department of Health and Human Services

December 19, 2022

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U.S. Government Accountability Office
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Washington, DC 20548

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Assistant Secretary for Legislation

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The NSABB's final recommendations are anticipated in the coming months and will inform interagency and HHS deliberations about both the OSTP P3CO Policy Guidance and the HHS P3CO Framework to ensure we have robust policies and guidance in place. HHS will provide a future update to GAO in its Statement of Actions letter which is required by OMB Circular A-50 and 31 U.S.C. 720.

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HHS Response

HHS concurs with the recommendation. CDC, including DSAT, is continuing internal efforts and collaborating with HHS and the National Security Council to outline existing gaps and potential enhancements to the Federal Select Agent Program.

Appendix II: National Institutes of Health Oversight of Surveillance of Naturally Occurring Pathogens

This appendix includes information on National Institutes of Health (NIH) oversight of a grant that involved surveillance of naturally occurring pathogens as an example of how oversight is conducted for a grant that does not fall within the Department of Health and Human Services oversight framework for enhanced potential pandemic pathogen research (the Framework).

According to NIH officials, a grant proposal examining the risk of bat Severe Acute Respiratory Syndrome (SARS)-like coronavirus emergence fell outside of the scope of the Framework because novel bat coronaviruses—novel coronaviruses that were found to have been naturally occurring and circulating among bats—had not been shown to infect humans; therefore the viruses being studied did not meet the definition of a potential pandemic pathogen.¹ Additionally, NIH officials told us that the experiments described by the researchers—the EcoHealth Alliance—were not anticipated to increase the virulence or transmissibility of these viruses in humans. NIH funded the research and oversaw it using its standard grant oversight process.

According to the agency's 2021 NIH Grants Policy Statement (Policy Statement), NIH references biosafety standards but does not monitor compliance with those standards. Specifically, NIH requires grantees to comply with Occupational Safety and Health Administration regulations for blood borne pathogens and occupational exposure to hazardous chemicals in labs and Nuclear Regulatory Commission standards and

¹National Institutes of Health, Response to Congressional Inquiry, October 20, 2021, <https://obamawhitehouse.archives.gov/blog/2014/10/17/doing-diligence-assess-risks-and-benefits-life-sciences-gain-function-research>. This inquiry stemmed from concerns about the source of the COVID-19 pandemic and U.S. funding of research conducted in a foreign country.

regulations, and recommends that grantees follow the Biosafety in Microbiological and Biomedical Laboratories' guidelines. As appropriate, NIH may reference other policies and programs (e.g., the Federal Select Agent Program), but does not require grantees to submit documented assurance of their compliance with these regulations and guidelines.² For example, NIH requires grantees to comply with the Division of Select Agents and Toxins' regulations, but officials told us that the agency relies on the Centers for Disease Control and Prevention to monitor compliance.

NIH requires grantees to provide periodic progress reports describing findings, and NIH may change terms and conditions for subsequent grant awards.³ For example, NIH monitored EcoHealth Alliance's progress reports and added a reporting measure when agency staff identified a risk. Specifically, after EcoHealth Alliance's year 2 progress reported the successful construction of SARS-like chimeras, NIH flagged it as a risk, and added a special condition to the 3rd year Notice of Award. This condition referenced a letter requiring work stoppage with MERS-like or SARS-like chimeras if the manipulated viruses showed a certain amount of increased growth when comparing the manipulated strains to the parental backbone strain. Officials told us that this work involved new viruses and there was a lack of data on virulence and transmissibility, therefore increased growth was selected to serve as an indicator that additional review of the research would be needed. According to NIH officials, they found that EcoHealth Alliance did not adequately monitor the activities of its subawardees and took action to terminate this part of the grant award. According to NIH, the agency will work with EcoHealth Alliance to renegotiate the aims and objectives of the grant before taking additional action.⁴

²The Policy Statement states that, if requested by the awarding institute or center, recipients should be able to provide evidence of consideration and practice of applicable safety standards.

³The Policy Statement requires that grantees report at least annually on budget information, but NIH has the flexibility to specify the elements for reporting and require more frequent reporting. The grant terms and conditions include requirements for the content and frequency of the progress reports. Progress reports include sections to report whether the major goals of the research have changed, accomplishments during the previous funding period toward those goals, and plans for the next reporting period to accomplish the research goals.

⁴National Institutes of Health, Response to Congressional Inquiry, August, 19, 2022, <https://obamawhitehouse.archives.gov/blog/2014/10/17/doing-diligence-assess-risks-and-benefits-life-sciences-gain-function-research>.

Appendix III: GAO Contact and Staff Acknowledgments

GAO Contact

Mary Denigan-Macauley, (202) 512-7114 or
DeniganMacauleyM@gao.gov

Staff Acknowledgments

In addition to the contact named above, Kelly DeMots (Assistant Director), Jasleen Modi (Analyst-in-Charge), Stella Chiang, Kevin Dong, Suhna Lee, Jenna Moody, and Janet Wilson made key contributions to this report. Also contributing were Samuel Amrhein and Jennifer Whitworth.

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