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Global Pandemics: Gain-of-Function Research of Concern

Gain-of-function (GOF) research is a broad area of scientific inquiry that examines how and why an organism gains a new property or an existing property is altered. The terms *gain of function* and *loss of function* refer to any genetic mutation in an organism that, respectively, confers a new or enhanced ability or causes the loss of an ability. Such changes often occur naturally. Additionally, scientists can induce some changes to organisms through experimentation.

A key area of GOF research is the study of both naturally occurring and experimentally induced changes in organisms to better understand the transmission, infectious properties, and pathogenesis of viruses. Some argue that GOF research may improve understanding of human-pathogen interactions, aid in assessments of potential pandemic pathogens, and further public health preparedness. Others have raised concerns that studies designed to understand how viruses might evolve may generate pathogens that affect humans and have the potential to cause a pandemic.

To focus attention on this small subset of studies that involve GOF-type research, the scientific and policy communities use terms such as *GOF research of concern* (GOFROC); *enhanced potential pandemic pathogens*; and most recently, *pathogens with enhanced pandemic potential* (PEPPs). However, these terms have, and can be, used interchangeably in some public discussions and media.

Risks and Benefits

Scientists and the public have debated the risks and benefits of GOF research, which also has been of interest to Congress. Some in the scientific community argue that this research is needed to better understand how viruses evolve and to develop better medical countermeasures and surveillance regimes for emerging pathogens. Further, they assert that this research can be conducted responsibly with proper biosafety and security protocols. Others argue that the risks outweigh any potential benefits and that alternative experiments should be considered. Multiple federal policies and guidelines govern the funding and oversight of life sciences research broadly, which includes GOF research (see **Table 1**). These require certain biosafety and biosecurity protocols to be implemented at the institutions where the research is to be conducted. These policies and guidelines do not currently apply to GOF research.

History of Oversight Mechanisms

Concerns over GOF research emerged in 2011-2012 around a set of studies funded by the National Institutes of Health (NIH) on respiratory transmission of the highly pathogenic avian influenza virus H5N1. At that time, the debate centered on the security risks of publishing the results of these studies and whether the research should have been allowed to proceed, considering the risk of accidental release. These debates, along with a series of government laboratory biosafety incidents not associated with the H5N1 studies, led the White House Office of Science and Technology Policy (OSTP) to issue *U.S. Government Gain-of-Function Deliberative Process and Research Funding Pause on Selected Gain-of-Function Research Involving Influenza, MERS, and SARS Viruses* in October 2014. This initial pause affected 18 federally funded research projects and contracts; 7 of them subsequently received exemptions from the pause.

As part of the 2014 pause, OSTP initiated a deliberative process to evaluate the potential risks and benefits of GOF research with potential pandemic pathogens. In January 2017, OSTP released *Recommended Policy Guidance for Departmental Development of Review Mechanisms for Potential Pandemic Pathogen Care and Oversight (P3CO)*, which described attributes of federal agency review and reporting processes for the additional oversight of federally funded research that would be anticipated to create, transfer, or use enhanced pathogens with pandemic potential. Agency implementation of a review and reporting process with the described attributes would allow an agency to support certain types of GOF research.

Following the OSTP guidance, the Department of Health and Human Services (HHS) released *Framework for Guiding Funding Decisions About Proposed Research Involving Enhanced Potential Pandemic Pathogens* (HHS P3CO Framework) in December 2017. Consequently, the issuance of the HHS P3CO Framework excused HHS from the 2014 GOF research pause. HHS was the only agency that developed a GOF review process in response to the 2017 OSTP GOF guidance and the only federal agency that has reported GOF research funding.

COVID-19 and GOF

The emergence of COVID-19 and debates on its origin have refocused attention on GOF and particularly the NIH funding of the EcoHealth Alliance study Understanding the Risk of Bat Coronavirus Emergence, in which scientists from the United States and the Wuhan Institute of Virology collaborated. Some have argued that this project should have been captured by the 2014 pause on GOF research and reviewed under the HHS P3CO guidance. In testimony to the House Select Committee on the Coronavirus Pandemic, NIH reportedly concluded that the research project did not meet the criteria of the 2014 pause on GOF research or the 2017 HHS P3CO guidance.

Recent Updates to Oversight Mechanisms

OSTP released its most recent policy update on this issue in May 2024, with an effective date of May 6, 2025. The *United States Government Policy for Oversight of Dual Use Research of Concern and Pathogens with Enhanced Pandemic Potential* (2024 policy) is a framework for reviewing and conducting oversight of certain types of federally funded life sciences research. The policy addresses oversight of research on biological agents and toxins that, when enhanced, may pose risks to public health, agriculture, food security, economic security, or national security. The 2024 policy, if implemented, will supersede previous policies and guidance. It also is anticipated to replace the HHS P3CO Framework.

Key Components of the 2024 Policy

The 2024 policy is to create two categories of research for review, Category 1 and Category 2, that require certain standards of review and oversight based on the biological agent or toxin used and the type of research being conducted. Category 1 research is dual-use research of concern (DURC), the meaning of which has been expanded from previous DURC policies. One major change is that all research involving individual agents and toxins listed under the Federal Select Agent Program is now considered Category 1. This potentially expands the number of research proposals that meet the qualifications of DURC compared with previous policies. Category 1 research is subject to oversight by both research institutions and the federal funding agency. Category 2 is considered research involving pathogens with enhanced pandemic potential (PEPPs), which meet the following criteria:

- A pathogen that is likely capable of wide and uncontrollable spread in a human population and would likely cause moderate to severe disease and/or mortality in humans. Referred to as a PPP.
- A type of PPP resulting from experiments that enhance a pathogen's transmissibility or virulence, or disrupt the effectiveness of preexisting immunity, regardless of its progenitor agent, such that it may pose a significant threat to public health, the capacity of health systems to function, or national security. Referred to as PEPP.

Category 2 research would be subject to oversight by research institutions and federal funding agencies, if applicable, because of heightened potential for biosafety and biosecurity risks.

Congressional Considerations

In the 118th Congress, the Senate Committee on Homeland Security and Governmental Affairs reported S. 4667, Risky Research Review Act, which would have established a life sciences research security board within the executive branch to review proposed federal funding that constituted high-risk life sciences research and vote whether or not an agency may fund such research. In the 119th Congress, the bill was reintroduced in the Senate (S. 854) and introduced in the House (H.R. 1864). Congress may choose to examine the relationship among the intentions of S. 854, H.R. 1864, and the 2024 policy, should it take effect.

On January 20, 2025, the White House issued a memorandum directing executive agencies to consider postponing the effective date for any rules that have been issued but have not taken effect, to review any questions of fact, law, or policy that the rules may raise. Congress may choose to continue the current oversight system for life sciences research, introduce new models for review (such as the board proposed in S. 4667), or wait to evaluate how the Trump Administration addresses GOF research, including whether and how executive agencies implement the 2024 OSTP policy. Congress could also be concerned about the potential implementation of the 2024 policy, its potential impact on scientific research and risk management generally, and its potential impacts on U.S. government and industry scientific competitiveness.

Table 1. Selected U.S. Policies for Biosafety and Biosecurity Oversight

Federal Policy/Guidelines	Description
NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules	Requires institutional review with a focus on the concepts of risk assessment, risk group classification of agents, physical and biological containment levels, practices, personal protective equipment, and occupational health
Federal Select Agent Program	Oversees the possession, use, and transfer of biological select agents and toxins that have the potential to pose a severe threat to the public, animal or plant health, or to animal or plant products
United States Government Policy for Oversight of Dual Use Research of Concern and Pathogens with Enhanced Pandemic Potential	Addresses oversight of research on biological agents and toxins that, when enhanced, may pose risks to public health, agriculture, food security, economic security, or national security
Framework for Nucleic Acid Synthesis Screening	Provides guidance to providers of synthetic nucleic acids and manufacturers of benchtop nucleic acid synthesis equipment on how to screen purchase orders to identify nucleic acid sequences of concern and assess customer legitimacy

Source: CRS.

For additional information on GOF research and federal oversight of laboratory biosafety and biosecurity, see CRS Report R47114, *Oversight of Gain-of-Function Research with Pathogens: Issues for Congress*, by Todd Kuiken, and CRS Report R48155, *Oversight of Laboratory Biosafety and Biosecurity: Current Policies and Options for Congress*, by Todd Kuiken.

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