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Global Pandemics: Gain-of-Function Research of Concern

Introduction

Gain-of-Function (GOF) research is a broad area of scientific inquiry where 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 either 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, infection, and pathogenesis of viruses. Through such knowledge, scientists hope to improve our understanding of human-pathogen interactions, aid in assessments of potential pandemic pathogens, and further public health preparedness. Some analysts have raised concerns that studies designed to understand how viruses might evolve may have the potential to generate pathogens that affect humans with the potential to cause a pandemic. To focus attention on this small subset of studies, the scientific and policy communities have begun to use the terms *gain of function research of concern* (GOFROC) and *enhanced potential pandemic pathogens* (PPP). However, all three terms (GOF, GOFROC, PPP) have been used interchangeably in some public discussions and media.

Risks and Benefits

Scientists and the public have debated the risks and benefits of GOF research. Some in the scientific community argue that the research is needed to better understand how viruses evolve, in order 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.

Concerns over GOF research first 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; seven of them subsequently received exemptions from the pause.

Current Oversight Mechanisms

As part of the 2014 pause on GOF research, OSTP initiated a deliberative process to evaluate the risks and potential 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 is 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 GOF, GOFROC, or PPP 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 (P3CO)* in December 2017. The HHS P3CO framework releases HHS from the 2014 GOF research pause. HHS appears to be the only agency that has developed a GOF review process that addresses the 2017 OSTP GOF guidance, and the only federal agency that has reported GOF research funding.

Key Components of HHS P3CO Framework

P3CO establishes an additional review process for research proposals that have gone through the normal scientific review process, have been determined to be scientifically sound, and are reasonably anticipated to create, transfer, or use enhanced potential pandemic pathogens (PPPs), defined as PPPs resulting from the enhancement of the transmissibility and/or virulence of a pathogen. To be subject to this extra scrutiny, an enhanced PPP must satisfy two criteria:

1. It is likely highly transmissible and likely capable of wide and uncontrollable spread in human populations; and
2. It is likely highly virulent and likely to cause significant morbidity and/or mortality in humans.

The P3CO review process examines what the experiment will produce (an enhanced PPP). If a proposal meets these criteria, it is to go through an independent, HHS-level, multidisciplinary P3CO review committee to determine, in part, whether the research is scientifically sound; the pathogen is considered to be a credible source of a potential future human pandemic; the potential risks compared to the potential benefits to society are justified; there is no feasible

alternative method to address the same question in a manner that poses less risk; the investigators have demonstrated the capacity and commitment to conduct the research safely and securely; research results are expected to be responsibly communicated; the research will be subject to ongoing federal oversight; and the research is ethically justifiable.

Based on this review, the P3CO review committee reports to the HHS funding agency (i.e., NIH) whether the research is acceptable, not acceptable, acceptable on the condition that certain experiments are modified, or acceptable on the condition that certain risk mitigation measures are employed at the federal and institutional level. The funding agency makes the final determination on whether or not the project will be funded and must report its decision to HHS and OSTP.

Since the implementation of the P3CO policy, three research projects have been reviewed and approved. Two of these projects had originally been awarded in 2013 and were subject to the 2014 pause. Those projects were subsequently reviewed in 2018 under the P3CO policy and were approved to continue. Both projects concluded in 2019. The third project, while approved with additional risk mitigation measures, ultimately shifted to utilize alternative approaches that do not involve enhanced PPP research.

CRS has not identified any publicly released data on how many projects, if any, have been referred into P3CO review and subsequently retracted from consideration by their principal investigators. Such data might help policymakers understand whether, and how many, research projects do not go forward due to the requirements of the P3CO policy.

COVID-19 and GOF

The emergence of COVID-19 and debates on its origin have refocused attention on GOF. A particular focus has been the NIH funding of the EcoHealth Alliance study, *Understanding the Risk of Bat Coronavirus Emergence*, which collaborated with scientists at the Wuhan Institute of Virology. Some have argued this project should have been captured by the 2014 pause on GOF research and reviewed under the HHS P3CO guidance. NIH asserts that the research project did not meet the criteria of either policy.

Looking Ahead

In addition to P3CO, multiple federal policies and guidelines governing the funding and oversight of life sciences research could also capture components of GOF research (**Table 1**). These require certain biosafety and biosecurity protocols to be implemented at the institutions where the research will be conducted. Several near-term federal activities are examining how these federal regulations, policies, and guidelines address oversight of GOF research and whether they produce duplicative requirements, inefficiencies, or coordination challenges.

In January 2020, the HHS Secretary charged the National Science Advisory Board for Biosecurity (NSABB), a federal advisory committee that addresses issues related to biosecurity and dual use research, with reviewing the dual use research of concern (DURC) policies and the P3CO guidance.

Table 1. Select Policies for Life Science Research

Federal Policy/Guidelines	Description
NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules	Outlines science-based safety practices for creating and handling recombinant and synthetic nucleic acid molecules, and organisms and viruses containing such molecules. Also articulates responsibilities of institutions, investigators, and Institutional Biosafety Committees.
HHS Screening Framework Guidance for Providers of Synthetic Double-Stranded DNA	Aims to reduce the risk that synthetic DNA will be deliberately misused to create dangerous organisms.
United States Government Policy for Institutional Oversight of Life Sciences Dual Use Research of Concern (DURC)	Addresses institutional oversight of DURC, which includes policies, practices, and procedures to ensure the identification of DURC and that risk mitigation measures are implemented if needed.
Federal Select Agent Program (FSAP)	Oversees the possession, use, and transfer of biological select agents and toxins that have the potential to pose a severe threat to public, animal or plant health, or to animal or plant products.

Source: HHS; U.S. Federal Select Agent Program.

NSABB is to review and provide recommendations regarding the balance between security and transparency when sharing PPP research information. It should also recommend whether or how to incorporate the P3CO policy into DURC. In February 2022, NSABB's charge was updated to reevaluate DURC definitions; support for international ePPP research; and whether the P3CO framework effectively balances the benefits, biosafety, and biosecurity risks of ePPP research. In September 2022, the NSABB issued preliminary draft findings and recommendations (https://osp.od.nih.gov/wp-content/uploads/NSABB_P3CO_WG_Preliminary_Draft_Findings_and_Recommendations.pdf). NSABB's final recommendations are anticipated in late 2022 or early 2023.

Section 19010 of the Coronavirus Aid, Relief, and Economic Security (CARES) Act (P.L. 116-136) requires the Government Accountability Office to examine the extent to which HHS oversight addresses biosafety and biosecurity risks—including consideration of DURC, FSAP, and P3CO—and whether these programs are duplicative.

For additional information, see CRS Report R47114, *Oversight of Gain of Function Research with Pathogens: Issues for Congress*, by Todd Kuiken.

Todd Kuiken, Analyst in Science and Technology Policy

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