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SUMMARY

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Oversight of Gain-of-Function Research with Pathogens: Issues for Congress

The term *gain of function* (GOF) refers to any genetic mutation in an organism that confers a new or enhanced ability. Such changes often occur naturally. Additionally, scientists can induce such changes to organisms through experimentation. *GOF research* covers a broad area of scientific inquiry. One area of GOF research is the study of both naturally occurring and experimentally induced changes in viruses to better understand transmission, infection, and pathogenesis. Current U.S. policy focuses on GOF research that involves altered or enhanced pathogens with the potential to cause a pandemic. Some scientists argue that this research is needed to better understand how viruses evolve in order to develop better medical countermeasures and surveillance regimes for emerging pathogens. Others argue that GOF research does not lead to the development of medical countermeasures and that other types of research, such as computer modeling, could be as effective as GOF. They further argue that an accident or deliberate misuse of GOF research has the potential to impact the larger public, potentially globally. This concern leads some observers to argue that the risks of such research outweigh any potential benefits.

Congress may be faced with competing and, in some instances, conflicting national and international priorities when weighing options addressing the risks and benefits of GOF and life sciences research more broadly. Determining whether changes to U.S. biosafety and biosecurity policies are necessary to minimize risks, maximize benefits, and better incorporate and address stakeholder concerns involves weighing complex and intertwined policy issues. Experts on each side invoke the public's well-being as reasoning for their positions.

Overlapping policies and guidance address aspects of biosafety and biosecurity associated with GOF research in the United States—some impose requirements, some provide guidelines, some apply only to research with select biological agents, and some apply only to federally funded research. These policies and guidance include federal regulation of research with select biological agents and toxins, best-practice guidance for microbiological and biomedical laboratories, and agency guidance on funding research with dual use potential and pathogens with enhanced pandemic potential, addressing the institutions and researchers conducting such research. Policies related to GOF research have evolved over time. In 2024, the *United States Government Policy for Oversight of Dual Use Research of Concern and Pathogens with Enhanced Pandemic Potential* (2024 policy), covering GOF and other issues, was released. It is scheduled to take effect in May 2025.

The outlook for the oversight system for life sciences research is uncertain under the Trump Administration. On January 20, 2025, the White House issued a presidential memorandum directing executive agencies to consider postponing the effective date of any rules that have been issued but have not taken effect, in order to review any questions of fact, law, and policy that the rules may raise. Until a decision has been made pursuant to the presidential memorandum on whether the 2024 policy will be instituted in May 2025, previous policies issued by the White House, such as the *Recommended Policy Guidance for Departmental Development of Review Mechanisms for Potential Pandemic Pathogen Care and Oversight* and the Department of Health and Human Services' *Framework for Guiding Funding Decisions About Proposed Research Involving Enhanced Potential Pandemic Pathogens (P3CO)*, would still apply to federally funded GOF research. Topics for congressional oversight could include how agencies might implement the 2024 policy, its impact on scientific research and risk management generally, and its impacts on U.S. government and industry scientific competitiveness.

Policy options for Congress on GOF research could include

- independent federal review or a ban on federally funded GOF research (see S. 738, S. 854, and H.R. 1864);
- limits on where such research is permitted (e.g., restrictions based on prescribed standards for how to design, construct, commission, operate, or maintain laboratories where such research is conducted);
- development of safer alternatives that could still expand scientific understanding of how viruses evolve into potential pandemic pathogens and how to monitor and combat them;
- increased support for biosafety and biosecurity research; and
- establishment of a federal *biorisk* management policy intended to align oversight across federal agencies and provide a consistent review process for research institutions.

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Introduction

Gain of function (GOF) refers to any genetic mutation in an organism that confers a new or enhanced ability.[1] Such changes often occur naturally. Additionally, scientists can induce some changes to organisms through experimentation. *GOF research* covers a broad area of scientific inquiry. The term entered public policy debates and became more commonly used in 2011 when it was used to describe two controversial research projects on H5N1 avian influenza virus funded by the National Institutes of Health (NIH).[2] Subsequent U.S. policies have narrowly defined GOF research such that it refers only to studies of pathogens with pandemic potential.[3]

Congress may face competing and, in some instances, conflicting national and international priorities when weighing options to address the risks and benefits of GOF and life sciences research more broadly. These assessments may involve complex and intertwined policy issues that revolve around whether changes to U.S. biosafety and biosecurity policies are necessary to minimize risks, maximize benefits, and better incorporate and address stakeholder concerns.

A key area of emerging infectious disease research is the study of both naturally occurring and experimentally induced changes in viruses. Such research aims to improve understanding of virus transmission, infection, and pathogenesis.[4] Some of this research involves changing the genetic code of an organism or virus to observe how such changes affect its key properties. Through such experiments, scientists hope to improve their understanding of human-pathogen interactions, better understand how viruses evolve and mutate, and further public health preparedness by making better vaccines and treatments.

Naturally occurring and experimentally induced GOF mutations may affect several different traits of a virus. The environmental conditions in which a virus operates (e.g., inside a host vs. in a laboratory) can also impact potential mutation. Experiments where researchers did not intend to increase virulence or transmissibility could do just that. Thus, biosafety and biosecurity processes emphasize accounting for unintended consequences to protect laboratory workers and prevent accidental releases.[5]

This report discusses biosafety- and biosecurity-related issues associated with a subset of GOF research involving pathogens. It provides an overview of what GOF research on such pathogens

[1] Amber Dance, "The Shifting Sands of 'Gain-of-Function' Research," *Nature*, vol. 598, no. 7882 (2021), pp. 554-557, https://doi.org/10.1038/d41586-021-02903-x.

[2] Kelsey Lane Warmbrod et al., "COVID-19 and the Gain of Function Debates: Improving Biosafety Measures Requires a More Precise Definition of Which Experiments Would Raise Safety Concerns," *EMBO Reports*, vol. 22, no. 10 (2021), https://doi.org/10.15252/embr.202153739 (hereinafter Warmbrod et al., "COVID-19 and the Gain of Function Debates").

[3] White House Office of Science and Technology Policy (OSTP), *U.S. Government Gain-of-Function Deliberative Process and Research Funding Pause on Selected Gain-of-Function Research Involving Influenza, MERS, and SARS Viruses*, 2014; OSTP, *Recommended Policy Guidance for Departmental Development of Review Mechanisms for Potential Pandemic Pathogen Care and Oversight (P3CO)*, 2017, https://obamawhitehouse.archives.gov/sites/default/files/microsites/ostp/p3co-finalguidancestatement.pdf; U.S. Department of Health and Human Services (HHS), *Framework for Guiding Funding Decisions About Proposed Research Involving Enhanced Potential Pandemic Pathogens (P3CO)*, 2017; and OSTP, *United States Government Policy for Oversight of Dual Use Research of Concern and Pathogens with Enhanced Pandemic Potential*, May 2024 (hereinafter 2024 policy).

[4] *Pathogenesis* is the process by which a disease develops, including its onset and progression.

[5] *Biosafety* is a framework that describes the use of specific practices, training, safety equipment, and specially designed buildings to protect the worker, community, and environment from an accidental exposure or unintentional release of infectious agents and toxins. *Biosecurity* refers to the protection from, control of, and accountability for high-consequence biological agents and toxins, and critical relevant biological materials and information within laboratories to prevent unauthorized possession, loss, theft, misuse, diversion, and accidental or intentional release.

entails, the history of concerns with such research, the potential benefits and risks of conducting such research, U.S. oversight mechanisms for such research, and issues that Congress may consider in the context of research involving potential pandemic pathogens.

History of Concern with GOF Research

Concern with research involving pathogens and other life sciences is not new. There have been long-standing biosafety and biosecurity concerns surrounding the use of pathogens and other life-sciences-related research since infectious diseases were recognized as potential weapons against people and armies.[6] In one instance, representatives from various Army facilities convened in 1955 to share knowledge and experiences regarding the three principal biological warfare laboratories of the United States. This meeting was the first Biological Safety Conference in the United States.[7] Subsequent concerns arising from biosafety and biosecurity events associated with life sciences research have prompted subsequent actions to establish oversight mechanisms and address perceived risks (see **Figure A-1**).

Concerns over certain types of GOF research—specifically the risk of accidental release of a deadly pathogen and security risks associated with publishing study results—emerged in 2011-2012 around a set of studies funded by NIH on respiratory transmission of the highly pathogenic avian influenza virus H5N1.[8] Since then, policymakers, scientists, and the public have debated the magnitude of potential risks and benefits of GOF research involving pathogens, how to weigh those risks and benefits appropriately, and to what extent community engagement and transparent decisionmaking should have a role in determining those risk and benefits.[9]

Policy concerns and debates regarding the H5N1 studies, along with a series of contemporaneous but unrelated government laboratory biosafety incidents, 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.[10] As part of this pause, NIH's National Institute of Allergy and Infectious Diseases sent 18 letters to 14 institutions identifying research projects and contracts they believed were subject to the pause.[11]

As part of the 2014 pause, 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

[6] Stefan Riedel, "Biological Warfare and Bioterrorism: A Historical Review," *Baylor University Medical Center Proceedings*, vol. 17 (2004), pp. 400-406.

[7] Manuel S. Barbeito and Richard H. Kruse, "A History of the American Biological Safety Association Part I: The First 10 Biological Safety Conferences 1955-1965," American Biological Safety Association, https://absa.org/about/hist01/.

[8] Martin Enserink, "Scientists Brace for Media Storm Around Controversial Flu Studies," *Science*, November 23, 2011.

[9] Michael J. Selgelid, "Gain-of-Function Research: Ethical Analysis," *Science and Engineering Ethics*, vol. 22, no. 4 (2016), pp. 923-964.

[10] OSTP, *U.S. Government Gain-of-Function Deliberative Process and Research Funding Pause on Selected Gain-of-Function Research Involving Influenza, MERS, and SARS Viruses*, 2014.

[11] Jocelyn Kaiser, "Moratorium on Risky Virology Studies Leaves Work at 14 Institutions in Limbo," *Science*, 2014, https://www.science.org/content/article/moratorium-risky-virology-studies-leaves-work-14-institutions-limbo. Follow-up letters sent to some institutions clarified which research project may have been subject to the pause. CRS was unable to identify with certainty which of the 36 initial projects were ultimately paused.

that is anticipated to create, transfer, or use enhanced pathogens with pandemic potential.[12] Implementation of a review and reporting process with the described attributes allowed agencies to support GOF research on pathogens of this type. Responding to the OSTP guidance, the Department of Health and Human Services (HHS) released its *Framework for Guiding Funding Decisions About Proposed Research Involving Enhanced Potential Pandemic Pathogens (P3CO)* in December 2017.[13] HHS was the only agency that developed and released a GOF review process that addressed the 2017 OSTP GOF guidance and the only federal agency that has reported GOF research funding involving enhanced potential pandemic pathogens.

The coronavirus disease 2019 (COVID-19) pandemic and interest in its origin have refocused attention on GOF research (see the text box **Origins of COVID-19 and Gain of Function (GOF)**). One 2014 NIH-funded study by the EcoHealth Alliance, "Understanding the Risk of Bat Coronavirus Emergence,"[14] was conducted at the Wuhan Institute of Virology in China. Results were published in 2016.[15] In that experiment, researchers inserted spike proteins from eight different coronaviruses into a single bat coronavirus called WIV1. Spike proteins help a virus bind to its host. The study showed that the virus modified with the additional eight spike proteins could infect human cells.[16]

Some stakeholders have argued that the 2014 pause on GOF research should have included this study and that it should have been subsequently reviewed under the 2017 HHS P3CO guidance.[17] Others have argued that the research did not meet the requirements of the 2014 pause because the research did not enhance transmissibility, as both the modified and the original virus are able to infect human cells.[18] 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.[19]

[12] OSTP, *Recommended Policy Guidance for Departmental Development of Review Mechanisms for Potential Pandemic Pathogen Care and Oversight (P3CO)*, 2017, https://obamawhitehouse.archives.gov/sites/default/files/microsites/ostp/p3co-finalguidancestatement.pdf.

[13] HHS, *Framework for Guiding Funding Decisions About Proposed Research Involving Enhanced Potential Pandemic Pathogens (P3CO)*, 2017.

[14] National Institutes of Health (NIH), "Understanding the Risk of Bat Coronavirus Emergence," NIH RePORTER, https://reporter.nih.gov/project-details/9819304.

[15] Vineet D. Menachery et al., "SARS-Like WIV1-CoV Poised for Human Emergence," *Proceedings of the National Academy of Sciences, USA*, vol. 113, no. 11 (2016), pp. 3048-3053, https://doi.org/10.1073/pnas.1517719113.

[16] "What Is 'Gain-of-Function' Research?," *The Economist*, November 1, 2021.

[17] Warmbrod et al., "COVID-19 and the Gain of Function Debates."

[18] Warmbrod et al., "COVID-19 and the Gain of Function Debates."

[19] Declan Butler, "Engineered Bat Virus Stirs Debate over Risky Research," *Nature*, 2015, https://doi.org/10.1038/nature.2015.18787; and U.S. Congress, House Oversight and Government Reform Committee, Select Subcommittee on the Coronavirus Pandemic, *After Action Review of the COVID-19 Pandemic: The Lessons Learned and a Path Forward*, 118th Cong., 2nd sess., December 4, 2024.

Origins of COVID-19 and Gain of Function (GOF)

The coronavirus disease 2019 (COVID-19) pandemic and interest in its origin have refocused attention on GOF. In 2021, a group of scientists called for investigation into the origins of COVID-19, stating that "we must take hypotheses about both natural and laboratory spillovers seriously until we have sufficient data."[20] During the 118th Congress in December 2024, the House Committee on Oversight and Accountability's Select Subcommittee on the Coronavirus Pandemic examined whether a laboratory incident potentially involving GOF experiments could have contributed to the COVID-19 pandemic. The subcommittee's report states that "SARS-CoV-2, the virus that causes COVID-19, likely emerged because of a laboratory or research[-]related accident."[21] A separate report released by the subcommittee's minority Members states that the subcommittee did not conclusively identify the virus's origin. Rather the minority's report asserts that two hypotheses of its origin remain plausible: a natural origin or a laboratory or research-related accident.[22] The debates around the origins of COVID-19 continue to evolve as new information becomes available.

Benefits and Risks of GOF Research with Pathogens

For many infectious diseases, the primary medical countermeasure is vaccination.[23] However, vaccines can lose their efficacy as a result of changes in the pathogen. For example, the first vaccines for influenza were introduced in the 1940s; new influenza vaccines are developed annually as influenza viruses undergo antigenic drift (small changes or mutations) that can reduce vaccine efficacy.[24] A main argument for conducting GOF experiments is that viruses are constantly mutating. As one virologist stated, "We can either wait for something to arise, and then fight it, or we can anticipate that certain things will arise, and instead we can preemptively build our arsenals. ... That's where [GOF] research can come in handy."[25] Proponents of GOF research assert that understanding and predicting how these changes occur could aid in the development of vaccines that work against mutations of a virus.[26] Some scientists argue that

> attention to mutations specifically identified by GOF studies allows experts to assess the relevance of specific molecular determinants in relation to virologic and epidemiological factors considered for pandemic preparedness and is of particular relevance for decisions

[20] Jesse D. Bloom et al., "Investigate the Origins of COVID-19," *Science*, vol. 372, no. 6543 (2021), p. 694, https://doi.org/10.1126/science.abj0016.

[21] U.S. Congress, House Committee on Oversight and Accountability, Select Subcommittee on the Coronavirus Pandemic, *After Action Review of the COVID-19 Pandemic: The Lessons Learned and a Path Forward*, 118th Cong., 2nd sess., December 4, 2024, p. 1, https://oversight.house.gov/wp-content/uploads/2024/12/2024.12.04-SSCP-FINAL-REPORT-ANS.pdf.

[22] U.S. Congress, House Committee on Oversight and Accountability, Select Subcommittee on the Coronavirus Pandemic, *Partisan Probes over Pandemic Prevention and Preparedness*, minority report, 118th Cong., 2nd sess., December 2024, p. 6, https://oversightdemocrats.house.gov/sites/evo-subsites/democrats-oversight.house.gov/files/evo-media-document/SSCP%20Democratic%20Final%20Report.pdf.

[23] Medical countermeasures are Food and Drug Administration (FDA)-regulated products that may be used in the event of a public health emergency stemming from a terrorist attack with a biological, chemical, or radiological/nuclear material or a naturally occurring emerging disease. See FDA, "What Are Medical Countermeasures?," October 1, 2024, https://www.fda.gov/emergency-preparedness-and-response/about-mcms/what-are-medical-countermeasures.

[24] Surface proteins of influenza viruses are "antigens," which means they are recognized by the immune system and are capable of triggering an immune response, including production of antibodies that can block infection. See Centers for Disease Control and Prevention, "How Flu Viruses Can Change: 'Drift' and 'Shift,'" https://www.cdc.gov/flu/php/viruses/change.html?CDC_AAref_Val=https://www.cdc.gov/flu/about/viruses/change.htm.

[25] Amber Dance, "The Shifting Sands of 'Gain of Function' Research," *Nature*, vol. 598, no. 7882 (2021), pp. 554-557, https://doi.org/10.1038/d41586-021-02903-x.

[26] S. Schultz-Cherry et al., "Influenza Gain-of-Function Experiments: Their Role in Vaccine Virus Recommendation and Pandemic Preparedness," *mBio*, vol. 5, no. 6 (2014), https://doi.org/10.1128/mbio.02430-14 (hereinafter Schultz-Cherry, "Influenza Gain-of-Function Experiments").

> relating to the production of manufacturing seeds and trial lots and the stockpiling of vaccines.[27]

Others similarly argue that GOF experimentation is needed to better understand medical countermeasures across virus families and move the field from "one bug, one drug" to "one drug, many bugs."[28]

Another argument raised in favor of continued GOF experimentation is that it will help us better understand how viruses become *zoonotic*, or obtain the ability to transmit from animals to humans. In the early 2000s, the number of human infections with avian H5N1 influenza resulting from close contact with birds increased. This zoonotic transmission raised particular concern because the disease's case fatality rate was estimated at about 60%.[29] For comparison, one estimate of the U.S. case fatality rate for COVID-19 is 1.1%.[30] At that time, H5N1 had not yet acquired mammalian transmissibility, and there were no confirmed cases of human-to-human transmission.[31] Currently, H5N1 influenza is not known to spread easily from human to human. To date, most human H5N1 influenza cases have been associated with animal exposures, with very few cases due to human-to-human transmission. Yet many uncertainties persist around if and when the H5N1 influenza virus might adapt to spread more easily among humans, potentially resulting in a pandemic. Proponents of GOF research argue that experiments are needed to understand how a virus such as H5N1 can adapt, particularly as it relates to human-to-human transmissibility.

A major concern among some biosafety and biosecurity experts is that an accidental or deliberate release of a modified virus could pose a "grave, and completely novel, threat to human health,"[32] potentially causing a pandemic by evading natural immunities or effectiveness of available medical countermeasures. Some observers have raised additional concerns that publication of data from GOF research could pose a safety and security threat even if the research is conducted under governmental oversight measures.[33]

Conducting a risk-benefit assessment could aid in determining the potential advantages of any medical countermeasure that may result from GOF research and the risks associated with a potential laboratory accident or deliberate misuse. However, some researchers have suggested that a risk-benefit assessment is unlikely to determine reliably whether the risks of GOF research

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[27] Schultz-Cherry, "Influenza Gain-of-Function Experiments."

[28] Timothy P. Sheahan and Ralph S. Baric, "Is Regulation Preventing the Development of Therapeutics That May Prevent Future Coronavirus Pandemics?," *Future Virology*, vol. 13, no. 3 (2018), pp. 143-146, https://doi.org/10.2217/fvl-2017-0143.

[29] Michael J. Imperiale et al., "The Silver Lining in Gain-of-Function Experiments with Pathogens of Pandemic Potential," *Methods in Molecular Biology*, vol. 1836 (2018), pp. 575-587.

[30] For one source of estimates of COVID-19 case fatality rates by country until March 10, 2023, see Johns Hopkins University & Medicine, "Mortality Analyses," March 16, 2023, https://coronavirus.jhu.edu/data/mortality.

[31] The virus has adapted to spread among certain mammal species such as cattle and cats. Currently, H5N1 influenza is not known to spread easily from human to human. To date, most human H5N1 influenza cases have been associated with animal exposures, with very few cases due to human-to-human transmission. See CRS In Focus IF12895, *H5N1 Avian Influenza: The Human Health Response*, by Kavya Sekar, Amanda K. Sarata, and Hassan Z. Sheikh.

[32] Marc Lipsitch and Barry R. Bloom, "Rethinking Biosafety in Research on Potential Pandemic Pathogens," *mBio*, vol. 3, no. 5 (2012), https://doi.org/10.1128/mbio.00360-12; see also Declan Butler, "Engineered Bat Virus Stirs Debate over Risky Research," *Nature*, 2015, https://doi.org/10.1038/nature.2015.18787; and Kevin M. Esvelt, "Manipulating Viruses Is Too Dangerous," *Washington Post*, October 7, 2021.

[33] Marc Lipsitch and Alison P. Galvani, "Ethical Alternatives to Experiments with Novel Potential Pandemic Pathogens," *PLOS Medicine*, vol. 11, no. 5 (2014) (hereinafter Lipsitch and Galvani, "Ethical Alternatives"); and Arturo Casadevall et al., "Redaction of Sensitive Data in Publication of Dual Use Research of Concern," *mBio*, vol. 5, no. 1 (2013), https://doi.org/10.1128/mbio.00991-13.

outweigh the benefits, partly because of the absence of data, presumption of future events, and subjectivity in evaluation of risk tolerance.[34] Publicly available data on the number of laboratory incidents associated with life sciences research are difficult to obtain. Certain data on laboratory incidents must be reported to NIH and other federal agencies depending on the biological agent used and funding mechanisms governing the research. Other data associated with laboratory incidents are not reported outside the institution where the work is being done. Reporting requirements for institutions vary, and no single repository collects all of this information. The lack of consolidated or comprehensive data arguably hampers the ability to predict how likely it is for a GOF virus to escape containment. However, some researchers assert that the lack of prior GOF research incident data does not mean that researchers and oversight bodies should avoid risk-benefit assessments, noting that these types of assessments are routinely done in other scientific fields with incomplete data.[35]

Questions have also been raised about the ethicality of GOF research on potential pandemic pathogens. Some observers and researchers argue that ethical principles would allow GOF research on potential pandemic pathogens only if public health benefits cannot be achieved by other, safer methods.[36] Some have suggested that safer experimental approaches exist that can enhance surveillance, prevention, and treatment of disease resulting from pandemic pathogens. They cite examples such as developing universal vaccines and antiviral drugs, and improving technologies and capabilities for rapid vaccine development and manufacturing,[37] including via the use of artificial intelligence with certain biological design tools and modeling.[38]

The general public is at the center of the debate, with experts on each side invoking the public's well-being as reasoning for their positions.[39] In this context, the public consists of all individuals who could become ill or die as a result of infection with a pathogen of pandemic potential, whether that occurs naturally, accidentally, or intentionally.[40] An accident or a deliberate misuse of a GOF virus strain has the potential to impact the larger public as well as those conducting or participating (e.g., as human subjects) in the research. Similarly, successful GOF research that leads to, for example, new medical countermeasures or increased vaccine efficacy provides broadly applicable benefits to the larger public. Some experts have called for GOF research to be evaluated under a broader ethical framework that includes input from and evaluation of risks to the public.[41] Others argue that the public should be included more broadly in the process of research assessment to determine what levels of risk are acceptable in contexts beyond GOF.[42]

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[34] Daniel J. Rozell, "Assessing and Managing the Risks of Potential Pandemic Pathogen Research," *mBio*, vol. 6, no. 4 (2015), https://doi.org/10.1128/mbio.01075-15.

[35] Arturo Casadevall and Michael J. Imperiale, "Risks and Benefits of Gain-of-Function Experiments with Pathogens of Pandemic Potential, Such as Influenza Virus: A Call for a Science-Based Discussion," *mBio*, vol. 5, no. 4 (2014).

[36] Nicholas G. Evans, "Ethical and Philosophical Considerations for Gain-of-Function Policy: The Importance of Alternate Experiments," *Frontiers in Bioengineering and Biotechnology*, vol. 6 (2018); and Lipsitch and Galvani, "Ethical Alternatives."

[37] Lipsitch and Galvani, "Ethical Alternatives."

[38] CRS Report R47849, *Artificial Intelligence in the Biological Sciences: Uses, Safety, Security, and Oversight*, by Todd Kuiken.

[39] Monica Schoch-Spana, "Public Engagement and the Governance of Gain-of-Function Research," *Health Security*, vol. 13, no. 2 (2015), pp. 69-73 (hereinafter Schoch-Spana, "Public Engagement").

[40] Schoch-Spana, "Public Engagement."

[41] Nicholas G. Evans et al., "The Ethics of Biosafety Considerations in Gain-of-Function Research Resulting in the Creation of Potential Pandemic Pathogens," *Journal of Medical Ethics*, vol. 41, no. 11 (2015), pp. 901-908.

[42] David Gillum et al., "Charting a New Course for Biosafety in a Changing World," *Issues in Science and Technology*, May 23, 2022, https://issues.org/new-course-biosafety-prevent-pandemics-gillum-moritz-lim-vogel/; and Marc Lipsitch and Barry R. Bloom, "Rethinking Biosafety in Research on Potential Pandemic Pathogens," *mBio*, vol. 3, no. 5 (2012).

Incorporating public input may be hampered by the lack of public engagement. There has been limited public engagement around GOF and the role that the U.S. government has in both the funding and oversight of GOF research.[43] Additionally, the use of different terms—GOF, GOF research of concern, pathogens with enhanced pandemic potential (PEPP), and engineered viruses—in public debates, media, and policies may cause confusion as to what research is being funded, what the risks and benefits are, and what policies do and do not cover.

Oversight of GOF Research Involving Pathogens

GOF research concerns are part of a larger policy debate on how best to manage biosafety and biosecurity associated with emerging technologies and life sciences research. The United States has multiple, overlapping policies that provide guidance and oversight for life sciences research, depending on the types of experiments and biological agents used (see **Figure 1**). Many of these policies and guidelines are framed around biosafety and biosecurity and were developed in response to specific events (see **Figure A-1**). While some oversight mechanisms are required by law, others are guidance issued by funding agencies and are mandatory only if the research is funded by the U.S. government. Privately funded research, or research conducted outside the United States, may therefore not be covered by certain U.S. oversight mechanisms. According to a 2023 study by Gryphon Scientific, a physical and life science consulting firm, an estimated "one quarter of human pathogen research performed in the United States occurs in the private sector."[44]

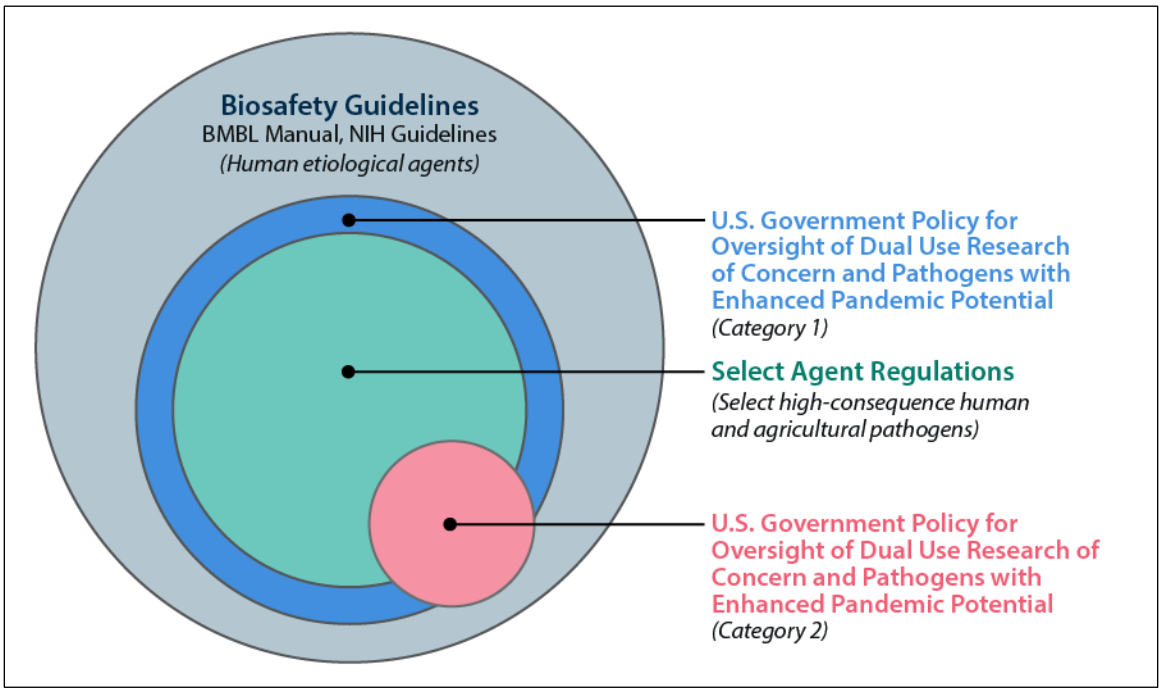
This section discusses specific policies and guidance that govern life sciences research broadly and could impact GOF research specifically, depending on the virus being used and the specific types of experiments being proposed. For a more in-depth analysis of federal policies and guidance that govern life sciences research, see CRS Report R48155, *Oversight of Laboratory Biosafety and Biosecurity: Current Policies and Options for Congress*, by Todd Kuiken.

[43] Schoch-Spana, "Public Engagement."

[44] Gryphon Scientific, *Characterizing Private-Sector Research on Human Pathogens in the United States*, 2023, p. 4, https://pandorareport.org/gryphon-scientific-characterizing-private-sector-research-on-human-pathogens-in-the-united-states-july-2023-funded-by-open-philanthropy.

Figure 1. Overlap of Selected U.S. Policies for Biosafety and Biosecurity Oversight

(oversight applies to specific agents, toxins, and/or types of experiments)



Source: CRS, adapted from National Science Advisory Board for Biosecurity, *Recommendations for the Evaluation and Oversight of Proposed Gain-of-Function Research*, May 2016, p. 28, https://osp.od.nih.gov/wp-content/uploads/2016/06/NSABB_Final_Report_Recommendations_Evaluation_Oversight_Proposed_Gain_of_Function_Research.pdf.

Notes: Circles depicting policies with oversight are meant to be estimates and are subject to interpretation and change. BMBL = *Biosafety in Microbiological and Biomedical Laboratories*; NIH = National Institutes of Health.

Biosafety in Microbiological and Biomedical Laboratories (BMBL) Guidelines

The Centers for Disease Control and Prevention (CDC) and NIH partner to publish *Biosafety in Microbiological and Biomedical Laboratories* (BMBL), which is the overarching guidance document for U.S. biosafety practices for protecting workers and preventing exposures in biological laboratories. The BMBL provides guidance for addressing the safe handling and containment of infectious microorganisms and hazardous biological materials.[45] Some federal agencies include adherence to the BMBL as a condition for receiving certain federal grants. In addition, some federal laws (see "Federal Select Agent Program (FSAP)") recommend the BMBL as guidance to assist entities in the development of biosafety and biocontainment plans.[46]

The BMBL describes four biosafety levels (BSLs)—a minimum set of safety practices and procedures, required safety equipment, and administrative and engineering controls—that must be applied to projects or activities conducted in laboratories. Each BSL is described in ascending order of containment based on the degree of the health-related risk associated with the work being

[45] Paul J. Meechan and Jeffrey Potts, *Biosafety in Microbiological and Biomedical Laboratories*, 6th ed., (Washington, DC: HHS, 2020), https://www.cdc.gov/labs/pdf/SF__19_308133-A_BMBL6_00-BOOK-WEB-final-3.pdf.

[46] 42 U.S.C. §73.12.

conducted.[47] Each BSL builds on the previous one (see **Table A-1**). The appropriate BSL for a research project is determined by the institution in which the work is being conducted, in consultation with the principal investigator, depending on the specific organism and types of experiment to be performed.

Some have raised concerns from an international context that while certain high-containment laboratories are state of the art, others may not be as well-equipped in terms of the facility itself, as well as training and screening of personnel and materials.[48] While the BMBL serves as an "advisory document recommending best practices for the safe conduct of work in biomedical and clinical laboratories,"[49] the Government Accountability Office (GAO) reported in 2013 that there were no national standards for how to design, construct, commission, operate, or maintain a high-containment laboratory.[50] Subsequent GAO studies have reviewed individual agency policies and made recommendations on how to improve laboratory safety and oversight.[51]

Federal Select Agent Program (FSAP)

FSAP is a regulatory program addressing biosecurity. The Public Health Security and Bioterrorism Preparedness and Response Act of 2002 (P.L. 107-188, as amended; 42 U.S.C. §362a) requires HHS to establish and regulate a list of biological agents and toxins that have the potential to pose a severe threat to public health and safety. The Agricultural Bioterrorism Protection Act of 2002 (Title II, Subtitle B, of P.L. 107-188) requires the U.S. Department of Agriculture (USDA) to establish and maintain a list of biological agents that have the potential to pose a severe threat to animal or plant health and safety or to the safety of animal or plant products. FSAP is managed jointly by the Division of Select Agents and Toxins at CDC and the Division of Agricultural Select Agents and Toxins at USDA. CDC and USDA share responsibility for some agents because they potentially threaten both humans and animals. By statute (42 U.S.C. §262a and 7 U.S.C. §8401), CDC and USDA are required to review and republish the lists of select agents and toxins on at least a biennial basis.[52]

FSAP has oversight of the people who have access to select agents and the facilities where select agents are used and stored, both of which must be registered with the program. According to the

[47] HHS, "Science Safety Security: Biosafety Levels," November 13, 2015.

[48] Ian W. Lipkin, "Biocontainment in Gain-of-Function Infectious Disease Research," *mBio*, vol. 3, no. 5 (2012).

[49] Paul J. Meechan and Jeffrey Potts, *Biosafety in Microbiological and Biomedical Laboratories*, 6th ed. (Washington, DC: HHS, 2020), p. iii, https://www.cdc.gov/labs/pdf/SF__19_308133-A_BMBL6_00-BOOK-WEB-final-3.pdf.

[50] U.S. Government Accountability Office (GAO), *High-Containment Laboratories: Assessment of the Nation's Need Is Missing*, GAO-13-466R, February 25, 2013, https://www.gao.gov/products/gao-13-466r. According to GAO, in May 2013, OSTP reported that it had been examining the need for national standards relating to designing, constructing, commissioning, maintaining, and operating high-containment laboratories through its Interagency Biorisk Management Working Group chartered in May 2012. According to GAO, an OSTP official stated that the group was chartered to collaborate on mechanisms for strengthening research laboratory biorisk management, which includes biosafety, biocontainment, and biosecurity.

[51] U.S. GAO, *High-Containment Laboratories: Comprehensive and Up-to-Date Policies and Stronger Oversight Mechanisms Needed to Improve Safety*, GAO-16-305, March 21, 2016, https://www.gao.gov/products/gao-16-305; U.S. GAO, *High-Containment Laboratories: Coordinated Actions Needed to Enhance the Select Agent Program's Oversight of Hazardous Pathogens*, GAO-18-145, October 19, 2017, https://www.gao.gov/products/gao-18-145; U.S. GAO, *Laboratory Safety: FDA Should Strengthen Efforts to Provide Effective Oversight*, GAO-20-594, September 8, 2020, https://www.gao.gov/products/gao-20-594; and U.S. GAO, *HHS Could Improve Oversight of Research Involving Enhanced Potential Pandemic Pathogens*, GAO-23-105455, January 18, 2023, https://www.gao.gov/products/gao-23-105455.

[52] Federal Select Agent Program, "Select Agents and Toxins," May 6, 2024, https://www.selectagents.gov/sat/index.htm.

2023 FSAP annual report, 8,599 individuals[53] and 226 entities[54] were registered with FSAP.[55] Entities possessing select agents are required by law (42 U.S.C. §262a and 7 U.S.C. §8401) to develop explicit biosecurity and biosafety plans, as well as an incident response plan, all of which are reviewed and certified by the FSAP agency that has jurisdiction over the particular select agent. FSAP provides guidance documents that describe attributes that each plan must have.[56] The HHS Inspector General has authority to conduct investigations and to impose civil monetary penalties against any individual or entity for violations of the regulations.[57]

NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules

The *NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules* (NIH Guidelines) require certain safety practices and procedures to be in place when researchers are creating and handling recombinant and synthetic nucleic acid molecules[58] and organisms and viruses containing such molecules.[59] Compliance with NIH Guidelines is a condition of grant awards for recipients of funding from NIH. The guidelines are structured in a manner that applies to an entire research institution, even if a particular research project/experiment is not funded by NIH. Implementing certain aspects of the required safety practices and procedures may impact institutional research practices and policies more broadly.

For example, the NIH Guidelines describe and designate the responsibilities of institutions, investigators, and Institutional Biosafety Committees (IBCs). IBCs provide local review and oversight of research utilizing recombinant or synthetic nucleic acid molecules. Many institutions have chosen to assign their IBCs the responsibility of reviewing a variety of experiments that involve biological materials and other potentially hazardous agents. This additional responsibility is assigned entirely at the discretion of the institution.[60] The guidelines classify organisms into four risk groups based on their pathogenicity toward humans:

- Risk Group 1 agents "are not associated with disease in healthy adult humans."

[53] 42 C.F.R. §73.7(a) states that "an individual or entity shall not possess, use, or transfer any HHS select agent or toxin without a certificate of registration issued by the HHS Secretary," and 7 C.F.R. §331.7(a) states that "an individual or entity shall not possess, use, or transfer any select agent or toxin without a certificate of registration issued by the Administrator."

[54] An *entity* is defined in 7 C.F.R. §331.1 and 42 C.F.R. §73.1 as "any government agency (Federal, State, or local), academic institution, corporation, company, partnership, society, association, firm, sole proprietorship, or other legal [organization]." An entity is thus not limited to a single facility or to a single laboratory. An entity may possess one or multiple facilities, each facility containing one or multiple laboratories.

[55] Federal Select Agent Program, *2023 Annual Report of the Federal Select Agent Program*, 2023, p. 6, https://www.selectagents.gov/resources/publications/docs/FSAP-Annual-Report-2023_508.pdf.

[56] Federal Select Agent Program, *Select Agents and Toxins Biosafety/Biocontainment Plan Guidance*, July 2018, https://www.selectagents.gov/compliance/guidance/biosafety/index.htm, and Federal Select Agent Program, *Incident Response Plan Guidance*, August 2021, https://www.selectagents.gov/compliance/guidance/incident-response/index.htm.

[57] 42 U.S.C. §73.21.

[58] National Human Genome Research Institute, "Recombinant DNA Technology," March 7, 2025, https://www.genome.gov/genetics-glossary/Recombinant-DNA-Technology.

[59] HHS, *NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules*, April 2024, https://osp.od.nih.gov/wp-content/uploads/NIH_Guidelines.pdf.

[60] NIH, "FAQs on Institutional Biosafety Committee (IBC) Administration—April 2023," May 2024, https://osp.od.nih.gov/policies/biosafety-and-biosecurity-policy/faqs-on-institutional-biosafety-committee-ibc-administration-may-2019/.

- Risk Group 2 agents "are associated with human disease [that] is rarely serious and for which preventive or therapeutic interventions are often available."
- Risk Group 3 agents "are associated with serious or lethal human disease for which preventive or therapeutic interventions *may be* available."
- Risk Group 4 agents "are likely to cause serious or lethal human disease for which preventive or therapeutic interventions are *not usually* available."[61]

GOF-type experiments could fall under the NIH Guidelines if they are federally funded and depending on whether any components of the virus were synthesized or used recombinant DNA and whether they are associated with human disease.

U.S. Government Policy for Oversight of Dual Use Research of Concern and Pathogens with Enhanced Pandemic Potential

In May 2024, OSTP released a policy update on dual use research of concern (DURC) and research related to GOF. The *United States Government Policy for Oversight of Dual Use Research of Concern and Pathogens with Enhanced Pandemic Potential* (2024 policy) is "a unified federal oversight framework for conducting and managing certain types of federally funded life sciences research on biological agents and toxins."[62] It addresses oversight of research on biological agents and toxins that, when enhanced, have the potential to pose risks to public health, agriculture, food security, economic security, or national security. The 2024 policy is scheduled to take effect in May 2025 and supersede the 2012 *United States Government Policy for Oversight of Life Sciences Dual Use Research of Concern*,[63] the 2014 *United States Government Policy for Institutional Oversight of Life Sciences Dual Use Research of Concern* (DURC Policy),[64] and the 2017 *Recommended Policy Guidance for Departmental Development of Review Mechanisms for Potential Pandemic Pathogen Care and Oversight (P3CO)* (P3CO Framework).[65] It would also replace the HHS *Framework for Guiding Funding Decisions About Proposed Research Involving Enhanced Potential Pandemic Pathogens*.[66]

The 2024 policy combines what had been two separate policies, the 2014 DURC Policy and 2017 P3CO Framework. It is anticipated that the 2024 policy will create two categories of research—Category 1 and Category 2, respectively (see **Figure 1** and **Figure 2**)—that require certain oversight based on the biological agent or toxin used and the type of research being conducted.

Category 1 research is considered DURC, the meaning of which has been expanded from previous DURC policies. One major change is that all individual agents and toxins listed under FSAP now constitute a criterion to be considered as Category 1, potentially expanding the number of research proposals that meet the qualifications of DURC compared with previous policies. This research is subject to oversight both by research institutions and the federal agency

[61] HHS, *NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules*, April 2024, p. 39, https://osp.od.nih.gov/wp-content/uploads/NIH_Guidelines.pdf.

[62] 2024 policy.

[63] White House, *United States Government Policy for Oversight of Life Sciences Dual Use Research of Concern*, 2012.

[64] White House, *United States Government Policy for Institutional Oversight of Life Sciences Dual Use Research of Concern*, September 24, 2014.

[65] OSTP, *Recommended Policy Guidance for Departmental Development of Review Mechanisms for Potential Pandemic Pathogen Care and Oversight (P3CO)*, January 9, 2017, https://obamawhitehouse.archives.gov/sites/default/files/microsites/ostp/p3co-finalguidancestatement.pdf.

[66] HHS, *Framework for Guiding Funding Decisions About Proposed Research Involving Enhanced Potential Pandemic Pathogens*, 2017.

that issues the funding. Category 2 includes research involving PEPP, which could be interpreted as GOF research. This research involves pathogens with two characteristics:

- Pathogen with pandemic potential (PPP): "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."
- PEPP: "A type of [PPP] resulting from experiments that enhance a pathogen's transmissibility or virulence, or disrupt the effectiveness of pre-existing 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."[67]

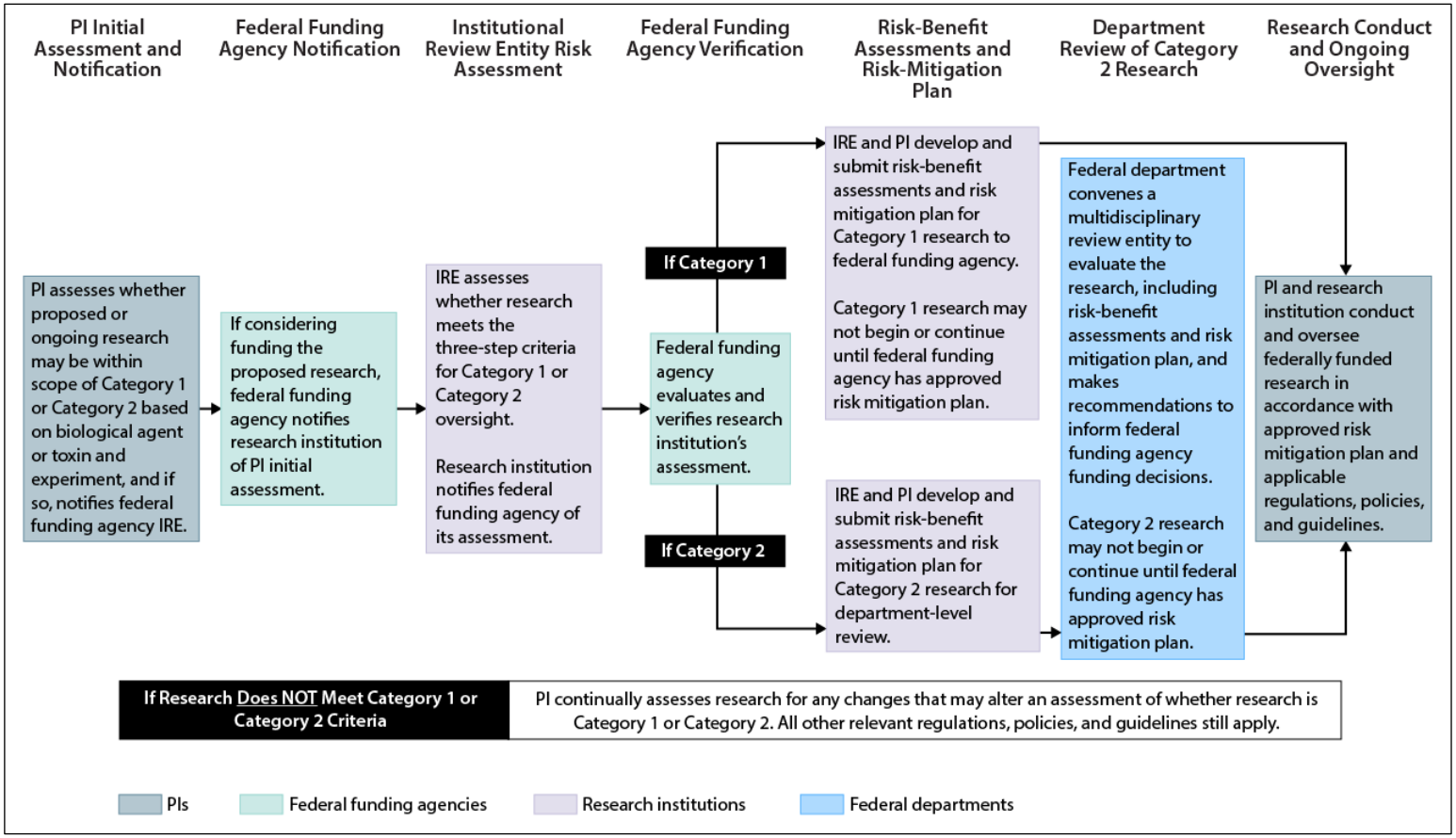
If it is determined that the research involves PEPP, it is subject to oversight by research institutions, federal funding agencies, and their federal department, if applicable, because of heightened potential for biosafety and biosecurity risks. **Figure 2** provides an overview of the entire review process for the two categories of research.

On January 20, 2025, the White House issued a presidential memorandum, "Regulatory Freeze Pending Review," directing executive agencies to consider postponing the effective date for any rules that had been issued but had not taken effect, in order to review "any questions of fact, law, and policy that the rules may raise."[68] Pursuant to the presidential memorandum, until a decision has been made as to whether the 2024 policy will be instituted, the P3CO Framework and associated HHS *Framework for Guiding Funding Decisions About Proposed Research Involving Enhanced Potential Pandemic Pathogens* would still apply to federally funded GOF research.

[67] 2024 policy.

[68] Executive Office of the President, "Regulatory Freeze Pending Review," 90 *Federal Register* 8249, January 20, 2025, https://www.federalregister.gov/documents/2025/01/28/2025-01906/regulatory-freeze-pending-review.

Figure 2. Overview of Review Process for Category 1 and Category 2 Research



Source: White House Office of Science and Technology Policy, *Implementation Guidance for the United States Government Policy for Oversight of Dual Use Research of Concern and Pathogens with Enhanced Pandemic Potential*, May 2024, https://bidenwhitehouse.archives.gov/wp-content/uploads/2024/05/USG-DURC-PEPP-Implementation-Guidance.pdf.

Notes: IRE = institutional review entity; PI = principal investigator.

Considerations for Congress

GOF research is part of a larger life sciences research enterprise that has produced important societal benefits but that also has inherent risks. As discussed above, multiple federal policies provide guidance and oversight for life sciences research, including GOF research, within the United States. While some oversight mechanisms are required by law, others are required only if the research is funded by the U.S. government.

As shown in **Figure 1**, GOF, DURC, and other life sciences research is covered by a patchwork of regulations and guidance. Congress may evaluate the U.S. government's biosafety and biosecurity policies as they apply to life sciences research generally and GOF research specifically. It may consider whether changes to U.S. biosafety and biosecurity policies are necessary to minimize risks, maximize benefits, and better incorporate and address public and stakeholder concerns. In doing so, Congress might consider the following options, among other actions.

Status Quo

Supporters of the status quo argue that based on the small number of explicit GOF projects focusing on potential pandemic pathogens previously reported and currently funded, existing policies are sufficient and provide adequate oversight. Critics of the status quo have suggested that the oversight and reporting mechanisms of current policies are insufficient to address the potential risks of GOF research and that additional oversight mechanisms are needed.[69]

Critics of the status quo also argue that the number and overlap of the current policies creates a burden on the affected institutions, potentially impacting their ability to conduct scientific research effectively. Stakeholders assert that the current regulatory burden is potentially onerous and that efforts to increase biosecurity and biosafety requirements would come at some commensurate cost. These costs would be borne by the research institutions, the research funders (as part of research overhead costs), or the private sector.[70] Such additional oversight costs could also be seen as anticompetitive or innovation inhibiting, potentially leading to research being performed in more permissive oversight environments, such as overseas. Congress may examine what impacts executive orders and presidential memorandums issued during the beginning of the second Trump Administration have on maintaining the status quo.

Impact of "Regulatory Freeze Pending Review" Presidential Memorandum

Policymakers may continue the current oversight framework for GOF and other life sciences research, including the 2024 policy scheduled to take effect in May 2025. However, implementation of the policy may be delayed or canceled by the new Administration.[71] Until a

[69] W. Paul Duprex et al., "Gain-of-Function Experiments: Time for a Real Debate," *Nature Reviews Microbiology*, vol. 13, no. 1 (2015), pp. 58-64, https://doi.org/10.1038/nrmicro3405 (hereinafter Duprex et al., "Gain-of-Function Experiments"); Ryan Ritterson et al., "A Call for a National Agency for Biorisk Management," *Health Security*, vol. 20, no. 2 (2022), https://doi.org/10.1089/hs.2021.0163 (hereinafter Ritterson et al., "A Call for a National Agency for Biorisk Management"); and Lipsitch and Galvani, "Ethical Alternatives."

[70] Ritterson et al., "A Call for a National Agency for Biorisk Management."

[71] Executive Office of the President, "Regulatory Freeze Pending Review," 90 *Federal Register* 8249, January 20, 2025, https://www.federalregister.gov/documents/2025/01/28/2025-01906/regulatory-freeze-pending-review.

decision has been made pursuant to the January 2025 presidential memorandum, previous policies pertaining to GOF studies would still apply to federally funded research. Topics for Congress could include how agencies potentially implement the 2024 policy, its impact on scientific research and risk management generally, and its impacts on U.S. government and industry scientific competitiveness.

Eliminate or Restrict Funding

Policymakers could address concerns regarding GOF research on particular viruses and PEPP through eliminating or restricting federally funded GOF research. During previous Congresses, legislation banning GOF research on particular viruses, pathogens, and potential pandemic pathogens was introduced in both chambers. For example, S. 3012, the Viral Gain of Function Research Moratorium Act, introduced during the 117th Congress, would have banned all federal funding of GOF research that could have been reasonably anticipated to confer attributes to influenza, MERS, or SARS viruses that enhanced pathogenicity or transmissibility in any organism or that involved the enhancement of potential pandemic pathogens or related risky research with potentially dangerous pathogens. This bill was reintroduced as S. 81 in the 118th Congress. A separate but similar bill introduced in the 118th Congress, H.R. 1827, would have prohibited NIH from conducting or supporting GOF research. S. 738, the Dangerous Viral Gain of Function Research Moratorium Act, introduced in the 119th Congress, would institute a moratorium on all federal research grants provided to any institution of higher education or other research institute that is conducting dangerous GOF research, as defined in the bill.

In the 118th Congress, the Senate Committee on Homeland Security and Governmental Affairs reported S. 4667, the Risky Research Review Act, which would have established a life sciences research security board within the executive branch to review proposed federal funding for high-risk life sciences research. After reviewing the research proposal, this board would vote on whether or not the agency in which the proposal was submitted could fund the project. In the 119th Congress, the bill was reintroduced in the Senate (S. 854), and a similar bill was 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 they all take effect. For example, could the federal department-level review prescribed in the 2024 policy, which is slated to take effect May 2025 (see **Figure 2**), be replaced with the research security board prescribed in S. 854 and H.R. 1864, which specify that such a board serve as an additional level of review with final decisionmaking authority?

If Congress were to consider banning or restricting GOF research on particular pathogens, defining GOF would likely become an important consideration. As discussed previously, "gain of function" is a research term that covers a broad area of scientific inquiry. A broad definition may impact research that does not raise biosafety and biosecurity concerns, while a narrow definition may, by intention, have limited effect. Another consideration is how the definition might be interpreted, because the definition could be manipulated in a way that enables research to continue outside a particular policy.

While other oversight mechanisms might apply to privately funded research (e.g., FSAP), the current GOF policy and the proposed 2024 policy are applicable only to federally funded grants and contracts. To address GOF experiments that may be taking place outside the 2024 policy, one legislative option could be to specifically cover GOF research not funded by the U.S. government.

Depending on how GOF is defined, eliminating funding for GOF research on pathogens, or limiting where GOF research is allowed in the United States, could encourage GOF researchers to

move such research to countries with fewer restrictions or, in the absence of legislation covering private companies, to institutions outside the reach of federal oversight. Such a shift could have implications both for biosafety and biosecurity and for U.S. competitiveness. In addition, a broad definition could inadvertently capture GOF experiments that are not part of the current debate on GOF involving pathogens. Such a prohibition might disrupt research in multiple areas, such as health, bioenergy, remediation, and others.

Laboratory Design and Oversight Standards

In 2020, 190 entities with BSL-3 laboratories and 8 entities with BSL-4 laboratories were registered in FSAP in the United States, operated by a variety of actors (federal, commercial, academic, and private).[72] As discussed in "Biosafety in Microbiological and Biomedical Laboratories (BMBL) Guidelines," there are no national standards for how to design, construct, commission, operate, or maintain a high-containment laboratory,[73] although recommendations are provided in the BMBL. Congress could consider specifying in what laboratories GOF research on pathogens is permitted based on prescribed laboratory standards.

However, such standards may create financial and administrative burdens for affected research institutions, especially if new standards are more stringent than previous recommendations. Such a situation might require additional investment by affected institutions in order to meet any more stringent standard. Restricting GOF research on pathogens to laboratories that meet specific requirements might limit the number of investigators able to conduct such research. Congressional considerations might include weighing the biosafety and biosecurity advantages of limiting where such research can be conducted against the impacts of limiting who can conduct such research, including whether those researchers operate outside the United States.

Increased Support for Research Programs That Focus on Alternatives to GOF Research on Pathogens

Some of the debates around GOF research focus on the safety and security of experiments that attempt to clarify whether and how viruses become transmissible to humans. Other debates are on virulence and the chimeric nature[74] of the experiments. Some stakeholders suggest that approaches exist to studying pathogenesis and transmission that are safer than GOF research on potential pandemic pathogens.[75] Congress could support the development of safer approaches to expanding scientific understanding of how viruses evolve into potential pandemic pathogens and the ability to monitor and combat them.

Researchers have proposed alternatives to GOF research on potential pandemic pathogens, for example, by inactivating mutations and manipulating key functional domains in attenuated

[72] Federal Select Agent Program, *2020 Annual Report of the Federal Select Agent Program*, 2020, https://www.selectagents.gov/resources/publications/docs/FSAP_Annual_Report_2020_508.pdf. This is a subset of the total number of BSL-3 and BSL-4 laboratories in operation; laboratories that do not work with select agents would not need to register under the Select Agent Program. Therefore, the total number of BSL-3 and BSL-4 laboratories may be higher.

[73] U.S. GAO, *High-Containment Laboratories: Assessment of the Nation's Need Is Missing*, GAO-13-466R, February 25, 2013, https://www.gao.gov/products/gao-13-466r.

[74] Josephine Johnston et al., "Clarifying the Ethics and Oversight of Chimeric Research," *Hastings Center Report*, vol. 52, no. 2 (2022).

[75] Simon Wain-Hobson, "Gain-of-Function Research Can't Deliver Pandemic Predictions: Are There Alternatives?," *Bulletin of the Atomic Scientists*, June 27, 2022; and Lipsitch and Galvani, "Ethical Alternatives."

genetic backgrounds[76] or by modifying an animal to reproduce the human disease of interest.[77] However, proponents of GOF research have argued that while other types of experiments could demonstrate the potential for a pathogen to alter its host range or experience enhanced transmissibility or virulence, only GOF research can conclusively prove that a wild-type virus can acquire the potential to cause a human pandemic.[78]

Advances in artificial intelligence and its use within the biological sciences could also provide alternatives to GOF research. For additional details on the convergence of artificial intelligence and the biological sciences, see CRS Report R47849, *Artificial Intelligence in the Biological Sciences: Uses, Safety, Security, and Oversight*, by Todd Kuiken.

Address Transparency and Public Engagement

Part of the scientific method involves confidential peer review, which occurs at different stages, including a merit review of the research proposal and of publications that may result from the research. The extent to which federal oversight of GOF research should be transparent and open to public engagement is an area of policy debate, as is whether GOF research is sufficiently different from traditional life sciences research to necessitate differential treatment more generally.

Some stakeholders have called for increased transparency of the review process for GOF research.[79] In the current P3CO policy, HHS stated that it intended to link to information about projects approved under the P3CO review process and publicly identify individual projects approved under the P3CO policy; however, the website that formerly contained this information is no longer active. It did not make available the assessments conducted by the advisory body for P3CO. HHS did not publicly release data on how many projects, if any, were referred for P3CO review but were subsequently retracted. It also did not make public any pre-funding review information for specific proposals. This is also the policy of other federal agencies sponsoring research. According to HHS, this preserves confidentiality and allows for candid critique and discussion of individual proposals.[80] It is not clear what information agencies might provide that is publicly related to the 2024 policy review process.

One legislative option would be to specify that information on projects that may be reviewed under Category 2 of the 2024 policy (if it takes effect), including the results of the risk-benefit assessment, should be made publicly available to help policymakers and the public understand why certain projects have been approved. Providing this type of transparency could improve public engagement and trust around how GOF work is approved. However, disclosing this type of information could present information hazards by publicly disclosing research methods that have been determined to raise biosafety/biosecurity risks. In addition, public disclosure of information about research proposals could potentially create reputational and intellectual property risks for

[76] Duprex et al., "Gain-of-Function Experiments."

[77] Duprex et al., "Gain-of-Function Experiments."

[78] Nicholas G. Evans, "Ethical and Philosophical Considerations for Gain-of-Function Policy: The Importance of Alternate Experiments," *Frontiers in Bioengineering and Biotechnology*, vol. 6 (2018); Warmbrod et al, "COVID-19 and the Gain of Function Debates"; and Arturo Casadevall et al., "An Epistemological Perspective on the Value of Gain-of-Function Experiments Involving Pathogens with Pandemic Potential," *mBio*, vol. 5, no. 5 (2014), https://doi.org/10.1128/mbio.01875-14.

[79] Michael J. Imperiale and Arturo Casadevall, "Rethinking Gain-of-Function Experiments in the Context of the COVID-19 Pandemic," *mBio*, vol. 11, no. 4 (2020).

[80] See NIH, "NIH Commitment to Transparency on Research Involving Potential Pandemic Pathogens," March 5, 2019, https://www.nih.gov/about-nih/who-we-are/nih-director/statements/nih-commitment-transparency-research-involving-potential-pandemic-pathogens.

proposers. Research proposals describe new ideas and potential outcomes; if this information is released, other researchers could use it when making claims about future scientific discoveries. Further, publicly disclosing proposals that have been rejected could reflect poorly on a researcher's perceived expertise or research capabilities. If Congress were to contemplate public disclosure of the review process and results, it may consider both transparency and these concerns.

Support for a Coordinated Biorisk Management Framework

Oversight of life sciences research is governed by multiple regulations, policies, and guidance, many of which are implemented at the institutional level and compulsory only when grantees receive federal funding or contracts. To ensure compliance, many research institutions use a biorisk management approach. *Biorisk management* is a system designed to minimize biosafety and biosecurity risks associated with research involving biological agents and toxins.[81] The approach can include at least three review mechanisms for determining which regulations and federal guidance may apply to proposed research:[82]

1. The knowledge and expertise of the researcher and laboratory personnel.
2. A formal review of the proposed research by a trained biosafety professional.
3. A committee review by fellow researchers evaluating the research on behalf of the institution.

These review processes are designed to meet the obligations of the institution under federal regulations and guidance and to determine whether experiments can be performed at an acceptable level of safety and security by utilizing risk-mitigation measures.[83] However, programs of this type vary widely depending on each institution's expertise, resources, and biosafety/biosecurity cultural norms.

One legislative option could be to require the establishment of an overarching federal biorisk management policy that unites all of the recommendations, guidance, and policies discussed previously into a single comprehensive framework of protocols and procedures. This could better align oversight of life sciences research across federal agencies and provide a consistent review process for research institutions.

If Congress were to require development of an overarching federal biorisk management policy, factors likely to be considered are

- determining which body should develop the policy—a single agency, such as HHS, or an interagency body, such as the National Science and Technology Council (NSTC);[84]
- providing guidance to the body tasked with developing the policy to design it to anticipate emerging science and novel public health threats, so that the policy

[81] Sabrina Brizee et al., "Development of a Biosecurity Checklist for Laboratory Assessment and Monitoring," *Applied Biosafety*, vol. 24, no. 2 (2019), pp. 83-89. Jennifer Gaudioso et al., "Developing a Risk Assessment and Management Approach to Laboratory Biosecurity," *Applied Biosafety*, vol. 11, no. 1 (2006), pp. 24-31.

[82] Rebecca L. Moritz and David R. Gillum, "Adaptation of Research Infrastructure to Meet the Priorities of Global Public Health," *Frontiers in Bioengineering and Biotechnology*, vol. 8 (2020).

[83] David Gillum and Rebecca Moritz, "Why Gain-of-Function Research Matters," *The Conversation: Science + Technology*, June 21, 2021.

[84] National Science and Technology Council, https://www.whitehouse.gov/ostp/nstc/.

could cover timely research and avoid needing to be reactively revised when science advances or each time an event occurs; and

- determining whether a new regulatory oversight body, independent from agencies funding research, is necessary to coordinate and enforce the policy, as suggested by some experts.[85]

A new oversight body could be tasked with addressing real or perceived conflicts of interest, such as when funding agencies perform risk assessments and reviews of their own or funded research. For example, under the 2024 policy, HHS would review research proposals that have been recommended for funding by its own proposal review panels. Some scholars suggest that "the risk assessment process should be directed by those without a clear personal stake in the outcome, just as peer review of science is performed by those without a direct interest in the outcome," to bolster the credibility of any assessment.[86]

While some oversight mechanisms are required by law, others are required only if the research is funded by the U.S. government. The threat of withholding future funding can serve as an incentive for institutions that receive such funding, but that approach is likely to be less effective for other institutions. Congress may consider whether a biorisk management policy should be expanded to cover private research labs that do not receive federal research funding or contracts. If expanded, such a biorisk management framework may include an enforcement mechanism that goes beyond the withholding of future government grants or contracts. This may require the granted authority to conduct laboratory inspections and audits to determine what type of research is being conducted and whether a particularly laboratory has violated any restrictions defined in the policy.

Creating a single common framework could result in a "one size fits all" solution that may have differing and detrimental effects on research institutions or clinical laboratories depending on their size. Potential disadvantages of these approaches include direct financial costs to research institutions arising from new oversight requirements; indirect costs arising from administrative burdens, such as staff time to develop and implement oversight policies and training programs; and impacts on research programs, such as the potential for research to not be taken up or conducted because of the increased oversight.

Current research and regulatory requirements of agencies and their different research portfolios would likely need to be harmonized under such a system, potentially creating conflict between agencies. This could raise various questions, including what the scope of such harmonized regulations should be, what entity would be responsible for compliance across the different agencies, and who would bear the costs.

Federal Support for Biosafety and Biosecurity Research

GOF research involving viruses and potential pandemic pathogens falls within the broader life sciences and associated biosafety and biosecurity risks. Some experts have called for biosafety and biosecurity to become its own field of research to help inform risk mitigation across the life sciences.[87] There currently is limited funding for programs that study applied biosafety and biosecurity. Options for Congress could include

[85] Ritterson et al., "A Call for a National Agency for Biorisk Management."

[86] Marc Lipsitch and Thomas V. Inglesby, "Moratorium on Research Intended to Create Novel Potential Pandemic Pathogens," *mBio*, vol. 5, no. 6 (2014), https://doi.org/10.1128/mbio.02366-14.

[87] Warmbrod et al., "COVID-19 and the Gain of Function Debates."

- providing funding to agencies for additional staff or existing programs and
- establishing new agency programs to support extramural biosafety and biosecurity research at universities or other outside institutions, identify and study best practices for effective biosafety and biosecurity, or explore novel solutions for biosafety and biosecurity concerns.

Providing additional funding for agency staff and programs may present a conflict of priorities with the Trump Administration's goal of reducing the overall size of the federal government.

Concluding Observations

GOF research is a broad field of scientific inquiry within an even broader context of life sciences research that poses biosafety and biosecurity concerns. Certain research that poses biosafety and biosecurity risks undergo risk assessments at various stages, from the initial proposal to eventual product development. Risk science, ethics, and values underlie those risk assessments. Predicting whether an incident (intentional or accidental) could lead to an outbreak, epidemic, or pandemic is extremely difficult, as is predicting potential scientific benefits.[88] The benefits of most research may not be realized, or sometimes even imagined, until years after the work has been completed. Risks, both real and potential, may never be realized, occur during experiments, or occur immediately after their completion.[89] The weight placed on a particular data point, the questions asked, or even who is asking the questions can shift the perception of risk and outcome of assessments. Increasing the transparency of risk assessment processes, and, if desired, enabling broader public input might clarify, legitimize, or even inform the choice of benefit and risk parameters and how they are evaluated. Alternatively, narrowing the risk assessment process to those who are most expert in specified areas may increase the quality of the risk assessment around a particular set of parameters.

U.S. policies address multiple aspects of biosafety and biosecurity—some impose requirements, some provide guidance, some policies overlap, some apply only to research with select biological agents, and some policies apply only to federally funded research and may not cover certain research institutions or private companies. Discussion of these issues sometimes focuses on defining the scope of GOF research, distinguishing it from other related categorizations, identifying the types of experiments that are of concern, or listing specific biological agents to be addressed in particular ways. This patchwork of biosafety and biosecurity policies can be reactionary as new biological threats emerge and lag relative to rapid developments in science and technology.

[88] Talha Burki, "Ban on Gain-of-Function Studies Ends," *The Lancet Infectious Diseases*, vol. 18, no. 2 (2018), pp. 148-149.

[89] Michael J. Imperiale et al., "The Silver Lining in Gain-of-Function Experiments with Pathogens of Pandemic Potential," *Methods in Molecular Biology*, vol. 1836 (2018), pp. 575-587.

Appendix. Biosafety Levels and Events

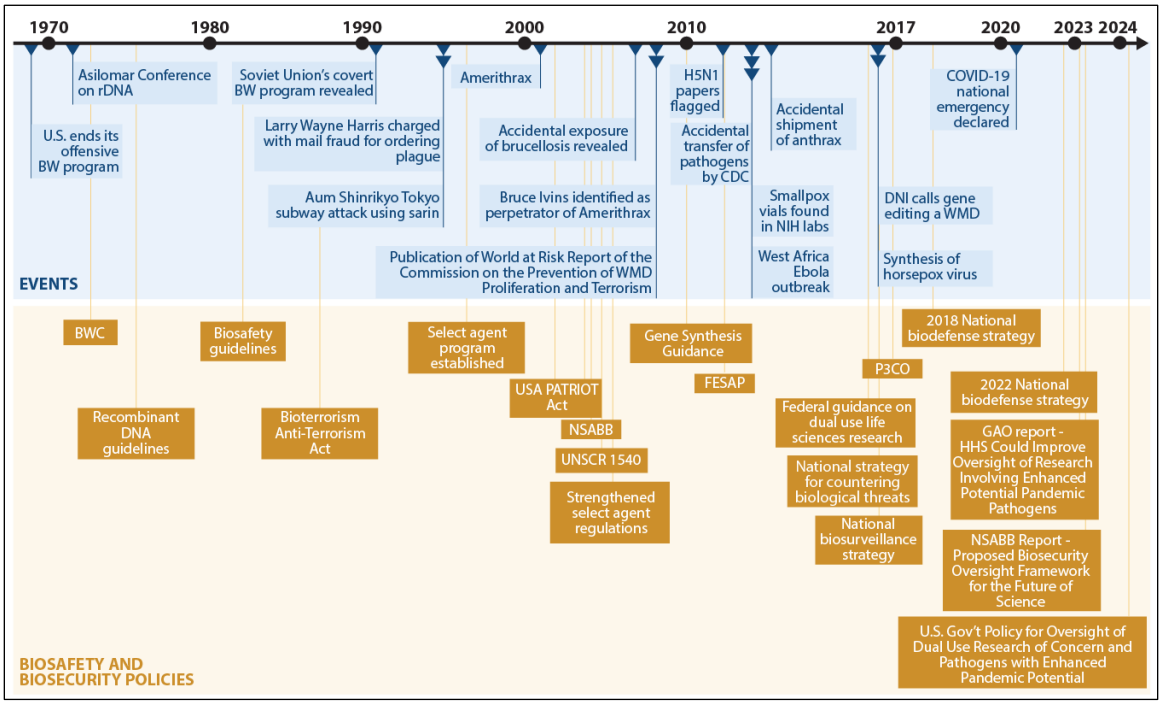
Table A-1. Laboratory Biosafety Levels (BSLs)

BSL	Description
BSL 1	Biosafety Level 1 (BSL-1) is suitable for work involving well-characterized agents not known to consistently cause disease in immunocompetent adult humans and that present minimal potential hazards to laboratory personnel and the environment. Work is typically conducted on open benchtops using standard microbiological practices. Special containment equipment or facility design is not generally required but may be used as determined by appropriate risk assessment. Laboratory personnel receive specific training in the procedures conducted in the laboratory and are supervised by a scientist with training in microbiology or a related science.
BSL 2	Biosafety Level 2 (BSL-2) is suitable for work with agents associated with human disease and [that] pose moderate hazards to personnel and the environment. BSL-2 differs from BSL-1 primarily because 1) laboratory personnel receive specific training in handling pathogenic agents and are supervised by scientists competent in handling infectious agents and associated procedures; 2) access to the laboratory is restricted when work is being conducted; and 3) all procedures in which infectious aerosols or splashes may be created are conducted in [biosafety cabinets] or other physical containment equipment.
BSL 3	Biosafety Level 3 (BSL-3) is suitable for work with indigenous or exotic agents that may cause serious or potentially lethal disease through the inhalation route of exposure. Laboratory personnel receive specific training in handling pathogenic and potentially lethal agents, and they are supervised by scientists competent in handling infectious agents and associated procedures. A BSL-3 laboratory has special engineering and design features.
BSL 4	Biosafety Level 4 (BSL-4) is required for work with dangerous and exotic agents that pose a high individual risk of aerosol-transmitted laboratory infections and life-threatening diseases that are frequently fatal, agents for which there are no vaccines or treatments, or work with a related agent with unknown risk of transmission. Laboratory staff receive specific and thorough training in handling extremely hazardous infectious agents. ... The laboratory supervisor controls access to the laboratory in accordance with institutional policies.

Source: Paul J. Meechan and Jeffrey Potts, *Biosafety in Microbiological and Biomedical Laboratories*, 6th ed. (Washington, DC: U.S. Department of Health and Human Services, 2020), https://www.cdc.gov/labs/pdf/SF__19_308133-A_BMBL6_00-BOOK-WEB-final-3.pdf.

Notes: Each BSL describes standard practices, safety equipment, and facility specifications that are generally appropriate for the organism(s) being worked on.

Figure A-1. Timeline of Selected Biosafety and Biosecurity Events and Associated U.S. Policy Implementation 1960-2024



Source: CRS, adapted from Diane DiEuliis et al., "Biodefense Policy Analysis—A Systems-Based Approach," *Health Security*, vol. 17, no. 2 (2019), pp. 83–99, https://doi.org/10.1089/hs.2018.0082.

Notes: Figure represents a selection of major events and should not be interpreted as comprehensive. BW = bioweapons; BWC = UN Bioweapons Convention; CDC = Centers for Disease Control and Prevention; DNI = Director of National Intelligence; FESAP = Federal Experts Security Advisory Panel; GAO = Government Accountability Office; HHS = Department of Health and Human Services; H5N1 = a strain of a highly pathogenic avian influenza virus; NIH = National Institutes of Health; NSABB = National Science Advisory Board for Biosecurity; P3CO = *Recommended Policy Guidance for Departmental Development of Review Mechanisms for Potential Pandemic Pathogen Care and Oversight*; rDNA = recombinant DNA; UNSCR = UN Security Council Resolution; WMD = weapon of mass destruction.

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