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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* 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. Gain of function (GOF) research is a broad area of scientific inquiry involving organisms that gain a new property or have an existing property altered. A key 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 involving enhanced potential pandemic pathogens. Some in the scientific community 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. However, an accident, or deliberate misuse of this 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.

An overlapping set of policies and guidance address aspects of biosafety and biosecurity associated with GOF research with pathogens in the United States—some impose requirements, some provide guidance, some apply only to research with select biological agents, and some policies only apply 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, agency guidance on funding research with potential pandemic pathogens, and the institutions and researchers conducting it.

The general public is at the center of the GOF debate, with experts on each side invoking the public's well-being as reasoning for their positions. Currently there is limited public engagement around GOF research on pathogens and the role the U.S. government has in its funding and oversight.

When weighing options addressing these complex and intertwined policy issues, Congress may have to balance competing and, in some instances, conflicting national and international priorities.

Congress may consider whether policy changes are necessary to minimize risks, maximize benefits, and better incorporate and address public and stakeholder concerns associated with GOF research on pathogens. Congress may continue with current oversight or choose to defer any action until they obtain the recommendations of two reviews of the U.S. biosafety and biosecurity oversight system, one conducted by the Government Accountability Office, and the other by the National Science Advisory Board for Biosecurity, a federal advisory board.

Congress might consider a ban on federally funded GOF research on pathogens. Legislation banning such research in varying capacities has been introduced in both chambers during the 117th Congress. A ban on federal funding of GOF research conducted in China has passed the Senate as S. 1260 and is in conference committee. Congress might consider limiting where such research is permitted based on prescribed standards for how to design, construct, commission, operate or maintain laboratories where such research is conducted. Congress might also support the development of safer alternatives that can still expand scientific understanding of how viruses evolve into potential pandemic pathogens and the ability to monitor and combat them.

Gain of function research is part of a larger life sciences research enterprise that has produced important societal benefits but also has inherent risks. Congress might consider whether increased support for biosafety and biosecurity research is needed. Congress could also consider whether the establishment of a federal biorisk management policy that aligns oversight across federal agencies and provides a consistent review process for research institutions would be more efficient than the current oversight system.

Contents

Figures

Appendixes

Contacts

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 is a research term that covers a broad area of scientific inquiry. The term entered the 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. policy narrowly addressed GOF research as research involving enhanced potential pandemic pathogens (ePPP). The Coronavirus Disease 2019 (COVID-19) pandemic and interest in its origin have refocused attention on GOF. There has been debate in the press and from lawmakers about whether GOF experiments could have produced the SARS CoV-2 virus.[3]

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 in viruses do not necessarily cause an increase in virulence or pathogenesis. One mutation may affect several different traits. The environment in which a virus operates (e.g., inside a human or animal), or is studied (e.g., laboratory conditions), can also impact any mutation that may occur, whether naturally or through experimentation. It could enhance fitness in one environment but not in another.[5] For example, a trait found to be enhanced under laboratory conditions might not be similarly enhanced, or be found to exist at all, outside of the laboratory or in an infected host. The opposite is also true. 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.[6]

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 entails, the history of concerns with such research, the potential benefits and risks of conducting

[1] Amber Dance, "The Truth About Gain of Function Research," *Nature*, vol. 598, no. 7882 (2021), pp. 554-557.

[2] Kelsey Lane Warmbrod, Michael G. Montague, and Gigi Kwik Gronvall, "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).

[3] For one review, see Gigi Kwik Gronvall, "The Contested Origin of SARS-CoV-2," *Survival*, vol. 63, no. 6 (November 2, 2021), pp. 7-36. The SARS-CoV-2 virus is the cause of the COVID-19 pandemic.

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

[5] See Gigi Kwik Gronvall, "The Contested Origin of SARS-CoV-2," *Survival*, vol. 63, no. 6 (November 2, 2021), pp. 7-36.

[6] 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, 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. See https://www.phe.gov/s3/BioriskManagement/biosecurity/Pages/Biosecurity-FAQ.aspx.

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 Gain-of-Function Research

Concern with research involving pathogens and other life sciences is not new. The Subcommittee on Biological Defense Research and Development Committee on Homeland and National Security of the National Science and Technology Council stated that "work with infectious agents in the laboratory always involves risk."[7]

There have been longstanding biosafety/biosecurity concerns involving the use of pathogens and other life-science related research impacts more broadly dating back to historic periods where infectious diseases were recognized as a potential weapon against people and armies.[8] In more recent history, representatives from various Army facilities met together 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.[9] Subsequent concerns arising from biosafety and biosecurity events associated with life sciences research (for a graphical representation of certain events since the 1960s, see **Appendix A**) have prompted subsequent actions to establish oversight mechanisms and address perceived risks.

Concerns over certain types of GOF research—specifically the risk of accidental release of a deadly pathogen and security risks associated with publishing study result—emerged in 2011-2012 around a set of studies funded by NIH on respiratory transmission of the highly pathogenic avian influenza virus H5N1. 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.[10]

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*[11] 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 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*

[7] Subcommittee on Biological Defense Research and Development, Committee on Homeland and National Security, *Fast Track Action Committee Report: Biosafety and Biosecurity*, National Science and Technology Council, 2017, https://obamawhitehouse.archives.gov/sites/default/files/microsites/ostp/NSTC/ftac-bio-report.pdf.

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

[9] See 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*, The Association of Biosafety and Biosecurity, https://absa.org/about/hist01/.

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

[11] Office of Science and Technology Policy, *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, https://www.phe.gov/s3/dualuse/documents/gain-of-function.pdf.

Potential Pandemic Pathogen Care and Oversight (P3CO),[12] 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 it to support GOF research on pathogens of this type. Responding to 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)"[13] in December 2017. HHS appears to be the only agency that has developed and released a GOF review process that addresses the 2017 OSTP GOF guidance, and the only federal agency that has reported GOF research funding involving enhanced potential pandemic pathogens.

A focus of recent concerns over GOF research, particularly in light of the COVID-19 pandemic, has been on a 2014 NIH-funded study by the EcoHealth Alliance. This study, *Understanding the Risk of Bat Coronavirus Emergence*,[14] was conducted at the Wuhan Institute of Virology in China, with results 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 "Framework for Guiding Funding Decisions About Proposed Research Involving Enhanced Potential Pandemic Pathogens (P3CO)" 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.[19]

The virus used in 2014 EcoHealth Alliance study is not genetically close to any known laboratory samples of the SARS-CoV-2 virus that causes COVID-19.[20] A group of scientists have called for investigation into the origins of COVID-19, stating that "We must take hypotheses about both

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

[13] U.S. Department of Health and Human Services, *Framework for Guiding Funding Decisions About Proposed Research Involving Enhanced Potential Pandemic Pathogens (P3CO)*, 2017.

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

[15] Vineet D. Menachery, Boyd L. Yount, and Amy C. Sims, et al., "SARS-like WIV1-CoV poised for human emergence," *PNAS*, vol. 113, no. 11 (2016).

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

[17] Kelsey Lane Warmbrod, Michael G. Montague, and Gigi Kwik Gronvall, "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).

[18] Ibid.

[19] Declan Butler, "Engineered Bat Virus Stirs Debate over Risky Research," *Nature*, 2015.

[20] Gigi Kwik Gronvall, "The Contested Origin of SARS-CoV-2," *Survival*, vol. 63, no. 6 (November 2, 2021), pp. 7-36.

natural and laboratory spillovers seriously until we have sufficient data."[21] The debates around the origins of COVID-19 continue to evolve as new information becomes available.[22]

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 based on 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 gain of function 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

> mutations specifically identified by GOF studies allow[s] 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 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 to 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 1.2%.[30] H5N1 did not acquire mammalian transmissibility, and

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[21] Jessee D. Bloom, Yujia Alina Chan, and Ralph S. Baric, et al., "Investigate the Origins of COVID-19," *Science*, vol. 372, no. 6543 (2021).

[22] For additional information on the debates on the origins of COVID-19, see CRS In Focus IF11822, *Origins of the COVID-19 Pandemic*, coordinated by Tiaji Salaam-Blyther.

[23] Medical countermeasures are Food and Drug Administration (FDA)-regulated products that may be used in the event of a potential public health emergency stemming from a terrorist attack with a biological, chemical, or radiological/nuclear material, or a naturally occurring emerging disease. See https://www.fda.gov/emergency-preparedness-and-response/about-mcmi/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 https://www.cdc.gov/flu/about/viruses/change.htm.

[25] Amber Dance, "The Truth About Gain of Function Research," *Nature*, vol. 598, no. 7882 (2021), pp. 554-557.

[26] S. Schultz-Cherry, R.J. Webby, and R.G. Webster, et al., "Influenza Gain-of-Function Experiments: Their Role in Vaccine Virus Recommendation and Pandemic Preparedness," *mBio*, vol. 5, no. 6 (2014).

[27] Ibid.

[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. 413-146.

[29] Michael J. Imperiale, Don Howard, and Arturo Casadevall, "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, see https://coronavirus.jhu.edu/data/

there were no confirmed cases of human-to-human transmission. Proponents of GOF research argue that experiments are needed to understand how a virus like H5N1 was able to move from infecting birds to infecting humans and how or whether it could acquire 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,"[31] potentially causing a pandemic by evading natural immunities or effectiveness of currently available medical countermeasures. Some observers have raised additional concerns that publication of data and information from original GOF research could pose a safety and security threat even if the research is conducted under governmental oversight measures.[32]

Conducting a risk/benefit assessment could aid in determining the potential benefits of any medical countermeasure that may result from GOF research, and the risks associated with a potential laboratory accident or deliberate misuse. However, some have suggested that a risk/benefit assessment is unlikely to determine reliably whether the risks of GOF outweigh the benefits, due, in part, to the absence of data, presumption of future events, and subjectivity in evaluation of risk tolerance.[33] Publicly available data on the number of laboratory incidents associated with life sciences research is 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.[34]

GOF research on potential pandemic pathogens has also been questioned on an ethics basis. Some observers and researchers argue that ethical principles would only allow GOF research on potential pandemic pathogens if public health benefits cannot be achieved by other, safer methods.[35] Some have suggested that safer experimental approaches exist that can enhance surveillance, prevention, and treatment of disease resulting from pandemic pathogens. They cite

mortality.

[31] Marc Lipsitch and Barry R. Bloom, "Rethinking Biosafety in Research on Potential Pandemic Pathogens," *mBio*, vol. 3, no. 5 (2012). Declan Butler, "Engineered Bat Virus Stirs Debate over Risky Research," *Nature*, 2015. Kevin M. Esvelt, "Manipulating Viruses Is Too Dangerous," *Washington Post*, October 7, 2021.

[32] Marc Lipsitch and Alison P. Galvani, "Ethical Alternatives to Experiments with Novel Potential Pandemic Pathogens," *PLOS Medicine*, vol. 11, no. 5 (2014). Arturo Casadevall, Lynn Enquist, and Michael Imperiale, et al., "Redaction of Sensitive Data in Publication of Dual Use Research of Concern," *mBio*, vol. 5 (2013).

[33] Daniel J. Rozell, "Assessing and Managing the Risks of Potential Pandemic Pathogen Research," *mBio*, vol. 6, no. 4 (2015).

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

[35] 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). Marc Lipsitch and Alison P. Galvani, "Ethical Alternatives to Experiments with Novel Potential Pandemic Pathogens," *PLOS Medicine*, vol. 11, no. 5 (2014).

examples including developing universal vaccines, antiviral drugs, and improving technologies and capabilities for rapid vaccine development and manufacturing.[36]

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.[37] In this context, the public consists of all individuals who could become ill or die due to infection with a pathogen of pandemic potential, whether that occurs naturally, accidentally, or by intentional means.[38] 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, the successful outcomes of GOF research that leads to, for example, new medical countermeasures or increased vaccine efficacy provide 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.[39] 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.[40]

Incorporating public input may be hampered by the lack of public engagement. There has been limited public engagement around GOF and the role the U.S. government has in both the funding and oversight of GOF research.[41] Additionally, the use of different terms—GOF, gain of function research of concern, ePPP, 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 polices do and do not cover.

The limited amount of public polling around these issues may reflect the lack of public engagement. CRS identified one poll, conducted during the debate over COVID-19's origins (June 29-30, 2021) and after HHS instituted its P3CO policy that examined the U.S. public's view towards research involving the enhancement of viruses.[42] A separate study examined the U.S. public's awareness, acceptability, and risk perception about infectious disease research and dual-use research of concern (DURC).[43] Although the questions asked could be construed to meet certain definitions of GOF, neither poll used the term GOF specifically. Based on the limited available data it is difficult to assess the U.S. public's views towards GOF research.

[36] Marc Lipsitch and Alison P. Galvani, "Ethical Alternatives to Experiments with Novel Potential Pandemic Pathogens" *PLOS Medicine,* vol. 11, no. 5 (2014).

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

[38] Ibid.

[39] Nicholas G. Evans, Marc Lipsitch, and Meira Levinson, "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.

[40] David Gillum, Rebecca Moritz, and Yong-Bee Lim, et al., "Charting a New Course for Biosafety in a Changing World," *Issues in Science and Technology*, May 23, 2022. Marc Lipsitch and Barry R. Bloom, "Rethinking Biosafety in Research on Potential Pandemic Pathogens," *mBio*, vol. 3, no. 5 (2012).

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

[42] "Poll: Majority of Voters Support Gain of Function Virus Research," *The Hill*, https://thehill.com/hilltv/what-americas-thinking/561078-poll-majority-of-voters-support-gain-of-function-research.

[43] Chandini R. MacIntyre, Dillon C. Adam, et al. "Public Awareness, Acceptability and Risk Perception About Infectious Diseases Dual-Use Research of Concern: A Cross-Sectional Survey," *BMJ Open*, vol. 10, no. 1, (2020).

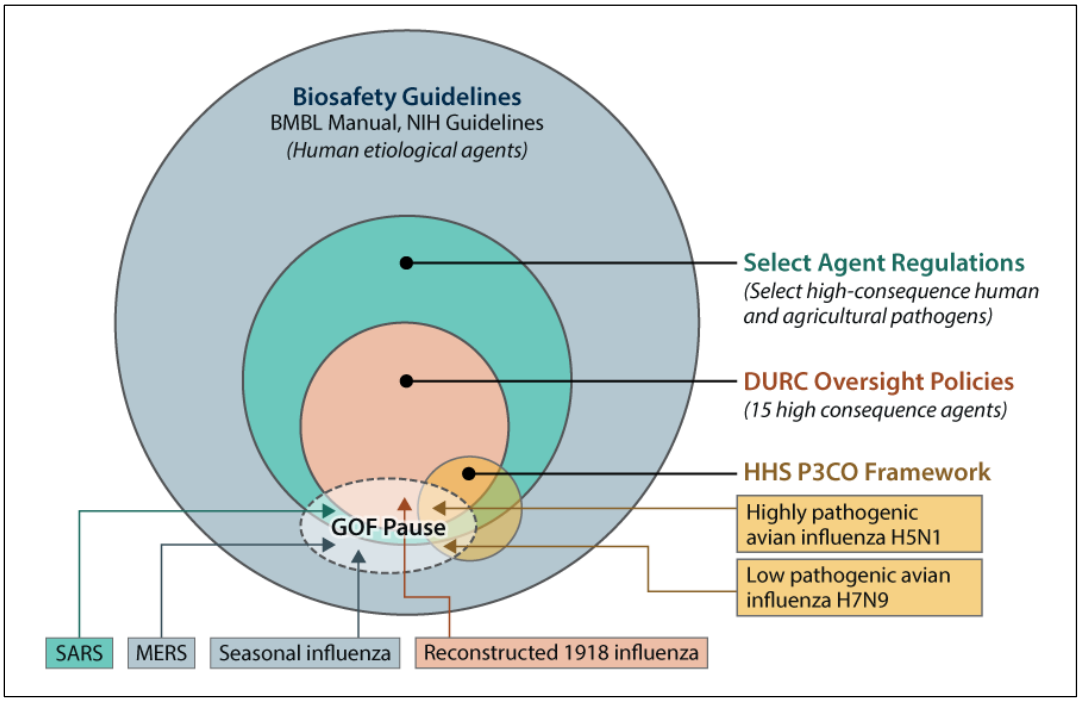
Oversight of Gain of Function Research Involving Pathogens

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 **Appendix A** for a timeline of select events and policy responses). 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. One analysis suggested that the U.S. life sciences research biosafety and biosecurity policymaking process is reactive, leading to inconsistent policies that limit U.S. ability to address emerging threats.[44] This section discusses specific policies and guidance that govern life science research broadly and could impact GOF research specifically, depending on the virus being used and the specific types of experiments being proposed. (See **Appendix B** for brief descriptions of these select U.S. government policies and how they may impact GOF research oversight.)

[44] Diane DiEuliis, Venkat Rao, and Diane Billings, et al., "Biodefense Policy Analysis—A Systems-Based Approach," *Health Security*, vol. 17, no. 2 (2019), pp. 83-99.

Figure 1. Comparison and Overlap of Select Oversight Mechanisms for Life Science Research

Oversight Applies to Specific Agents and/or Types of Experiments



Source: Adapted from National Science Advisory Board for Biosecurity, *Recommendations for The Evaluation and Oversight of Proposed Gain-Of-Function Research*, 2016, p. 28.

Notes: GOF Pause refers to the 2014 *U.S. Government Gain-of-Function Deliberative Process and Research Funding Pause on Selected Gain-of-Function Research Involving Influenza, MERS, and SARS Viruses* issued by the White House Office of Science and Technology Policy (OSTP). BMBL: Biosafety in Microbiological and Biomedical Laboratories; DURC: Dual Use Research of Concern; HHS P3CO: Framework for Guiding Funding Decisions about Proposed Research Involving Enhanced Potential Pandemic Pathogens; SARS: Severe acute respiratory syndrome; MERS: Middle East Respiratory Syndrome.

Biosafety in Microbiological and Biomedical Laboratories (BMBL) Guidelines

The Centers for Disease Control and Prevention (CDC) and the NIH partner together to publish the Biosafety in Microbiological and Biomedical Laboratories (BMBL) guidelines, which serve as 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] Adherence to the BMBL is a term and condition of certain grant awards for recipients of funding from certain federal agencies.

The BMBL describes BSLs, which are designations applied to projects or activities conducted in laboratories, in ascending order of containment based on the degree of the health-related risk

[45] Paul J. Meechan and Jeffrey Potts, *Biosafety in Microbiological and Biomedical Laboratories*, U.S. Department of Health and Human Services, 6th Edition, 2020, https://www.cdc.gov/labs/pdf/SF__19_308133-A_BMBL6_00-BOOK-WEB-final-3.pdf.

associated with the work being conducted.[46] Each biosafety level (BSL 1-4) builds upon the previous level (see **Appendix C** for descriptions of the BSLs). Each level describes a minimum set of safety practices and procedures, required safety equipment, and administrative and engineering controls. 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. In 2020, 190 entities with BSL-3 laboratories and 8 entities with BSL-4 laboratories were registered in the Federal Select Agent Program in the United States, operated by a variety of actors (federal, commercial, academia, and private).[47] Not all of these laboratories are research labs; for example, they could also include clinical laboratories in public health settings that deal with select agents.[48]

Some have raised concerns from an international context that while some BSL-3 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.[49] While the BMBL serves as an "advisory document recommending best practices for the safe conduct of work in biomedical and clinical laboratories,"[50] the Government Accountability Office (GAO) reported in 2013 that there are no national standards for how to design, construct, commission, operate, or maintain a high containment laboratory.[51] Subsequent GAO studies have reviewed individual agency polices and made recommendations on how to improve laboratory safety and oversight.[52]

Federal Select Agent Program

The Federal Select Agent Program (FSAP) is one of the federal regulatory programs addressing biosecurity. The Public Health Security and Bioterrorism Preparedness and Response Act of 2002 (P.L. 107-188) 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 regulate a list of biological agents that have the potential to pose a severe threat to animal health and safety, plant health and safety, or to the safety of animal or plant products. FSAP is managed by the Division of Select Agents and Toxins at the CDC and the Division of Agriculture Select Agents and Toxins at USDA. CDC and USDA share responsibility for some agents because they potentially threaten

[46] Department of Health and Human Services, Science Safety Security, https://www.phe.gov/s3/BioriskManagement/biosafety/Pages/Biosafety-Levels.aspx.

[47] 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.

[48] This is a subset of the total number of BSL-3/4 laboratories in operation; laboratories which do not work with select agents would not need to register under the Select Agent Program. Therefore, the total number of BSL-3/4 laboratories may be higher.

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

[50] See Biosafety in Microbiological and Biomedical Laboratories (BMBL) 6th Edition; https://www.cdc.gov/labs/BMBL.html.

[51] U.S. Government Accountability Office (GAO), *High-Containment Laboratories: Assessment of the Nation's Need Is Missing*, 2013.

[52] U.S. Government Accountability Office, *High-Containment Laboratories: Comprehensive and Up-to-Date Policies and Stronger Oversight Mechanisms Needed to Improve Safety*, GAO-16-305, 2016, https://www.gao.gov/products/gao-16-305. U.S. Government Accountability Office, *High-Containment Laboratories: Coordinated Actions Needed to Enhance the Select Agent Program's Oversight of Hazardous Pathogens*, GAO-18-145, 2017, https://www.gao.gov/products/gao-18-145. U.S. Government Accountability Office, *Laboratory Safety: FDA Should Strengthen Efforts to Provide Effective Oversight*, GAO-20-594, 2020, https://www.gao.gov/products/gao-20-594.

both humans and animals. 42 U.S.C. §262a and 7 U.S.C. §8401 require CDC and USDA to review and republish the lists of select agents and toxins on at least a biennial basis.[53] Whether FSAP would apply to GOF research depends upon the virus or agent being used in such experiments. If the pathogen does not appear on the HHS or USDA lists, the research would not be subject to FSAP; however, it may be captured by other policies (see **Figure 1**).

FSAP focuses on both the people who have access to select agents and the facilities where select agents are used and stored. Entities possessing select agents are required under 42 U.S.C. §262a and 7 U.S.C. §8401 to develop explicit biosecurity and biosafety plans and procedures which are reviewed and certified by FSAP.[54] Some have argued that a list-based approach "assumes that we already know what to worry about" and is not able to keep pace with emerging threats that may not yet appear on such a list.[55]

Dual Use Research of Concern (DURC)

The U.S. Government Policy for the Institutional Oversight of Life Sciences Dual Use Research of Concern went into effect on September 24, 2015. The policy articulates the practices and procedures required to ensure that dual use research of concern is identified at the institutional level and risk mitigation measures are implemented as necessary.[56] It defines dual use research of concern as

> life sciences research that, based on current understanding, can be reasonably anticipated to provide knowledge, information, products, or technologies that could be directly misapplied to pose a significant threat with broad potential consequences to public health and safety, agricultural crops and other plants, animals, the environment, materiel, or national security.

It covers research that uses one or more of the 15 agents or toxins listed within the policy and 7 categories of experiments. The policy applies to:

1. All U.S. government departments and agencies that fund or conduct life sciences research.
2. Institutions within the United States that both:
   a. Receive U.S. government funds to conduct or sponsor life sciences research; and
   b. Conduct or sponsor research that involves one or more of the 15 agents or toxins listed within the DURC policy, even if the research is not supported by U.S. government funds.

Certain GOF experiments could be captured by the DURC policy depending on the agent being used and the specific types of experiments being proposed. However, institutions or private companies that do not receive U.S. government funding are not subject to the DURC policy. The

[53] Federal Select Agent Program, https://www.selectagents.gov/sat/index.htm.

[54] An entity is defined as any government agency (federal, state, or local), academic institution, corporation, company, partnership, society, association, firm, sole proprietorship, or other legal entity. 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] Sam Weiss Evans, Jacob Beal, and Kavita Berger, et al., "Embrace Experimentation in Biosecurity Governance," *Science*, vol. 368, no. 6487 (2020).

[56] The United States Government, *United States Government Policy for Institutional Oversight of Life Sciences Dual Use Research of Concern*, September 25, 2015, https://www.phe.gov/s3/dualuse/Documents/durc-policy.pdf.

terms biosafety and biosecurity are used differently in various international regulations and frameworks. Global consensus around what DURC should consist of or what the appropriate safety levels for DURC experiments should be is lacking, except that these types of experiments should be conducted under the safest conditions practicable.[57] Some have argued that instead of developing DURC policies that prohibit or limit certain types of experiments, the focus should be on reviewing the scientific questions proposed.[58]

In January 2020 and again in February 2022, the Secretary of HHS charged the National Science Advisory Board for Biosecurity (NSABB),[59] a federal advisory committee that addresses issues related to biosecurity and dual use research, with reviewing and providing recommendations on the DURC policies. The NSABB is expected to complete its review and provide recommendations in December 2022.

Framework for Guiding Funding Decisions About Proposed Research Involving Enhanced Potential Pandemic Pathogens (P3CO)

In January 2017, OSTP released *Recommended Policy Guidance for Departmental Development of Review Mechanisms for Potential Pandemic Pathogen Care and Oversight (P3CO)*,[60] 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 research on potential pandemic pathogens. Responding to the OSTP guidance, HHS released "Framework for Guiding Funding Decisions About Proposed Research Involving Enhanced Potential Pandemic Pathogens (P3CO)"[61] in December 2017.

Sections III and IV of the HHS P3CO framework establishes an additional review process for HHS-sponsored 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 ePPPs. An ePPP is defined as a potential pandemic pathogen resulting from the enhancement of the transmissibility and/or virulence of a pathogen; which can occur via GOF-type research. To be subject to this extra scrutiny, an ePPP 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 HHS P3CO review process examines both what is being experimented on (a PPP) and what the experiment will produce (an enhanced PPP). If a research proposal meets these criteria, it may

[57] Michael J. Imperiale and Arturo Casadevall, "A New Approach to Evaluating the Risk-Benefit Equation for Dual-Use and Gain-of-Function Research of Concern," *Frontiers in Bioengineering and Biotechnology*, vol. 6 (2018).

[58] Ibid.

[59] See https://osp.od.nih.gov/biotechnology/national-science-advisory-board-for-biosecurity-nsabb/#about.

[60] Office of Science and Technology Policy, *Recommended Policy Guidance for Potential Pandemic Pathogen Care and Oversight (P3CO)*, 2017, https://obamawhitehouse.archives.gov/sites/default/files/microsites/ostp/p3co-finalguidancestatement.pdf.

[61] U.S. Department of Health and Human Services, *Framework for Guiding Funding Decisions about Proposed Research Involving Enhanced Potential Pandemic Pathogens (P3CO)*, 2017.

be required 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;
- the 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 (e.g., 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 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.[62] 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 was approved by the P3CO review process with additional risk mitigation measures. However, the grant sponsoring agency, which has the final decisionmaking authority for approval of grants, decided to redirect all funds under the award to support alternative approaches that do not involve enhanced potential pandemic pathogen research.[63]

In January 2020 and again in February 2022, the Secretary of HHS charged the NSABB,[64] a federal advisory committee that addresses issues related to biosecurity and dual use research, with reviewing and providing recommendations on the P3CO guidance. The NSABB is expected to complete its review and provide recommendations in December 2022.

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 creating and handling recombinant and synthetic nucleic acid molecules, and organisms and viruses containing such molecules.[65] Compliance with the NIH Guidelines is a term and condition of grant awards for recipients of funding from the NIH and certain other federal agencies. The guidelines are

[62] For a description of the projects see https://www.phe.gov/s3/dualuse/Pages/ResearchReview-PPP.aspx.

[63] See Research Review Under the HHS P3CO Framework: https://www.phe.gov/s3/dualuse/Pages/ResearchReview-PPP.aspx.

[64] See https://osp.od.nih.gov/biotechnology/national-science-advisory-board-for-biosecurity-nsabb/#about.

[65] Department of Health and Human Services, *NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules*, 2019, https://osp.od.nih.gov/wp-content/uploads/NIH_Guidelines.pdf.

structured in a manner that can apply to an entire research institution, even if a particular research project/experiment was not funded by NIH. The NIH Guidelines describe and designate the responsibilities of institutions, investigators, and its Institutional Biosafety Committees. The guidelines classify organisms into four risk groups based on their pathogenicity towards humans:

1. Risk Group 1 agents are not associated with disease in healthy adult humans.
2. Risk Group 2 agents are associated with human disease which is rarely serious and for which preventive or therapeutic interventions are often available.
3. Risk Group 3 agents are associated with serious or lethal human disease for which preventive or therapeutic interventions may be available.
4. Risk Group 4 agents are likely to cause serious or lethal human disease for which preventive or therapeutic interventions are not usually available.[66]

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

Considerations for Congress

Gain of function research is part of a larger life sciences research enterprise that has produced important societal benefits but also has inherent risks. As discussed above, the United States has multiple policies that provide guidance and oversight for life sciences research within the United States, including GOF research. 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 and ePPP 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.

Status Quo

Policymakers may decide to continue the current oversight system for GOF and ePPP research. Supporters of the status quo might argue that based on the small number of explicit GOF projects focusing on potential pandemic pathogens previously and currently funded, existing policies are sufficient and provide adequate oversight. Other critics have suggested that the oversight and reporting mechanisms of current policies are insufficient to address the potential risks of GOF research on potential pandemic pathogens, and additional oversight mechanisms are needed.[67]

Critics of the status quo might 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 could assert that the current regulatory burden is potentially

[66] Ibid.

[67] Paul W. Duprex, Ron A.M. Fouchier, and Michael J. Imperiale, et al., "Gain-of-Function Experiments: Time for a Real Debate," *Nature Reviews. Microbiology*, vol. 13, no. 1 (2015), pp. 58-64. Ryan Ritterson, Linette Kingston, and Adam E. J. Fleming, et al., "A Call for a National Agency for Biorisk Management," *Health Security*, vol. 20, no. 2 (2022). Marc Lipsitch and Alison P. Galvani, "Ethical Alternatives to Experiments with Novel Potential Pandemic Pathogens" *PLOS Medicine,* vol. 11, no. 5 (2014).

onerous and efforts to increase biosecurity and biosafety requirements would come at some commensurate cost. These costs would either be borne by the research institutions, the research funders (as part of research overhead costs), or the private sector. Additionally, those in favor of maintaining the status quo might perceive additional oversight costs as anticompetitive or inhibiting innovation, potentially leading to research being performed in more permissive oversight environments, such as overseas.

Await Recommendations

Policymakers might choose to obtain a better understanding of the current oversight system and the recommendations of two forthcoming reviews of the U.S. biosafety and biosecurity oversight system, including the P3CO policy.

The NSABB,[68] a federal advisory committee that addresses issues related to biosecurity and dual use research, was charged by the Secretary of HHS in January 2020 with reviewing and providing recommendations on DURC policies and the P3CO guidance.[69] NSABB was to review and provide recommendations to HHS regarding the balance between security and public transparency when sharing information about PPP research and on whether or how to incorporate the P3CO policy into DURC policies. The COVID-19 pandemic disrupted NSABB activities. It reconvened in February 2022 when it was given an updated charge to review both P3CO and DURC policies. [70] The updated charge is similar to the one given in January 2020, with additions in regards to the P3CO policy: (1) considerations for funding international research involving PPP and (2) the policy's effectiveness in terms of preserving benefits of ePPP research while minimizing potential biosafety and biosecurity risks. The NSABB is anticipated to deliver its recommendations by December 2022.

The GAO is currently conducting a review of high-risk research oversight at HHS, including the NIH and the CDC. This study is to examine what constitutes high-risk life sciences research and the extent to which HHS oversight addresses biosafety and biosecurity risks through DURC, FSAP, and P3CO.[71]

Eliminate or Restrict Funding

Policymakers could address concerns regarding GOF research on particular viruses and enhanced potential pandemic pathogens through eliminating or restricting federally funded GOF and ePPP research. Legislation banning GOF research on particular viruses, pathogens, and potential pandemic pathogens has been introduced in both chambers during the 117th Congress. S. 3012 (Viral Gain of Function Research Moratorium Act) would ban all federal funding of GOF research that may be reasonably anticipated to confer attributes to influenza, MERS, or SARS viruses such that the virus would have enhanced pathogenicity or transmissibility in any organism or involves the enhancement of potential pandemic pathogens or related risky research with potentially dangerous pathogens. H.R. 3593 (Department of Energy Science for the Future Act) and S. 3699 (Department of Energy Science for the Future Act of 2022) would ban the

[68] For more information about the NSABB, see https://osp.od.nih.gov/biotechnology/national-science-advisory-board-for-biosecurity-nsabb/#about.

[69] For more information about this charge, see NSABB January 2020 Meeting Slides: https://osp.od.nih.gov/biotechnology/national-science-advisory-board-for-biosecurity-nsabb/#meetings.

[70] For more information about this charge, see NSABB February 2022 Meeting Slides: https://osp.od.nih.gov/biotechnology/national-science-advisory-board-for-biosecurity-nsabb/#meetings.

[71] CRS communication with GAO, March 2022.

Department of Energy's Office of Science from funding GOF research with the potential to generate pathogens with high transmissibility and high virulence in humans. H.R. 4071 (Foreign Gain-of-Function Research Prevention Act of 2021) would prohibit the use of federal funds to conduct or support certain GOF research by a foreign adversary to include China, Russia, Iran, North Korea, and any other country the Secretary of State, in consultation with the Secretary of Defense, the Director of National Intelligence, or any other appropriate federal official, determines to be a foreign adversary for the purposes of this section. Four bills—H.R. 5988, (Fairness and Accountability in Underwriting Chinese Institutions Act" or the "FAUCI Act"), S. 3159 (Fairness and Accountability in Underwriting Chinese Institutions Act" or the "FAUCI Act"), S. 3463 (Coronavirus Origin Validation, Investigation, and Determination Act of 2022" or the "COVID Act of 2022"), and S. 1260 (United States Innovation and Competition Act of 2021)—would prohibit funding of GOF research on certain viruses and research involving the enhancement of potential pandemic pathogens in China. These bills would also prohibit researchers and institutions based in the United States that receive federal funding from engaging in collaborative projects involving GOF research on certain viruses and research involving the enhancement of potential pandemic pathogens with individuals or institutions based in China. S. 1260 has passed the Senate and a conference committee is resolving differences. On May 4, 2022, the Senate agreed by voice vote to instruct the Senate conferees to insist on the inclusion of provisions that would prohibit the use of federal funds for "gain-of-function" research in China.

Gain-of-Function (GOF) refers to any genetic mutation in an organism that confers a new or enhanced ability.[72] It's a research term that covers a broad area of scientific inquiry. As noted above, legislation introduced in the 117th Congress defines GOF research in different contexts; from identifying research on specific viruses (e.g., MERS) to generalizing research involving potential pandemic pathogens. Legislation banning or restricting GOF research may consider how GOF research is defined in terms of the organisms and attributes being studied to avoid inadvertently capturing research that does not raise concern or may be needed for national security or public health purposes.

Ban or Restrict GOF Research

If Congress were to consider banning or restricting GOF research on particular pathogens, defining it 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 which does not raise biosafety and biosecurity concerns; while a narrow definition may have limited intended effect. How the definition is interpreted may also be considered to avoid definitional manipulation which could enable research to continue outside a particular policy. Since 2017, the P3CO policy has reported three experiments that it has reviewed and approved since the policy went into effect.

Currently, oversight of GOF research involving enhanced potential pandemic pathogens, as defined by the P3CO policy, is limited to federally funded research projects. While other oversight mechanisms might apply to privately funded research (e.g., Select Agent program); the P3CO review process is only applicable to federally funded grants/contracts. To address GOF experiments that may be taking place outside the P3CO policy, policymakers could consider legislation banning or restricting 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 researchers performing GOF research to move such research to countries with fewer restrictions or, in the

[72] Amber Dance, "The Truth About Gain of Function Research," *Nature,* vol. 598, no. 7882 (2021), pp. 554-557.

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 easily capture gain of function experiments that are not part of the current debate on GOF involving pathogens. Such a prohibition might disrupt multiple areas of research, such as into 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 the Federal Select Agent Program in the United States, operated by a variety of actors (federal, commercial, academia, and private).[73] 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,[74] although recommendations are provided in the BMBL. Congress could consider limiting in what laboratories GOF research on pathogens is permitted based on prescribed standards for how to design, construct, commission, operate or maintain laboratories where GOF research on pathogens is conducted. 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. Congress might therefore consider weighing the biosafety and biosecurity advantages of limiting where such research can be conducted against the potential loss of scope, researchers, and research outcomes.

Increase 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 understand whether and how viruses become transmissible to humans. Other debates are on virulence and the chimeric nature 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 seek to 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

[73] 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-3/4 laboratories in operation; laboratories which do not work with select agents would not need to register under the Select Agent Program. Therefore, the total number of BSL-3/4 laboratories may be higher.

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

[75] Marc Lipsitch and Alison P. Galvani, "Ethical Alternatives to Experiments with Novel Potential Pandemic Pathogens," *PLoS Medicine*, vol. 11, no. 5 (2014).

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]

Address Transparency and Public Engagement

Part of the scientific method is based on confidential peer-review which occurs at different stages; including a merit review of the research proposal and publications that may result from the research. Prior GOF research involving H5N1 had been reviewed by the NSABB before publication of the results. Since 2017, the P3CO process relies on an additional review by subject area experts before a project can be funded. The extent to which these processes should be transparent and open to public engagement is an area of policy debate, as is whether GOF research on ePPP is sufficiently different than 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] HHS has stated that it intends to link to information about projects approved under the P3CO review process on their Science, Safety, Security website "to further demonstrate our commitment to transparency."[80] HHS identifies publicly individual projects approved under the P3CO policy.[81] It does not make the assessments conducted by the advisory body for P3CO available. It also does not make pre-funding review information for specific proposals public. This is also the policy of other federal agencies sponsoring research. According to HHS, this is in order to preserve confidentiality and to allow for candid critique and discussion of individual proposals.[82] HHS does not publicly release data on how many projects, if any, have been referred for P3CO review but subsequently retracted.

Congress could decide that information on how many projects are referred to the P3CO review process and the results of the risk/benefit assessment of those reviews should be made publicly

[76] Paul W. Duprex, Ron A.M. Fouchier, and Michael J. Imperiale, et al., "Gain-of-function experiments: time for a real debate," *Nature Reviews. Microbiology*, vol. 13, no. 1 (2015), pp. 58-64.

[77] Paul W. Duprex, Ron A.M. Fouchier, and Michael J. Imperiale, et al., "Gain-of-Function Experiments: Time for a Real Debate," *Nature Reviews. Microbiology*, vol. 13, no. 1 (2015), pp. 58-64.

[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). Kelsey Lane Warmbrod, Michael G. Montague, and Gigi Kwik Gronvall, "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). A. Casadevall, D. Howard, and M. Imperiale, "An epistemological perspective on the value of gain-of-function experiments involving pathogens with pandemic potential," *mBio*, vol. 5 (2014).

[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] National Institute of Health, "NIH Commitment to Transparency on Research Involving Potential Pandemic Pathogens," https://www.nih.gov/about-nih/who-we-are/nih-director/statements/nih-commitment-transparency-research-involving-potential-pandemic-pathogens.

[81] For a list of research projects approved under the P3CO policy, see https://www.phe.gov/s3/dualuse/Pages/ResearchReview-PPP.aspx. All projects funded by NIH, including those approved under P3CO, are listed in the NIH RePORTER database, https://reporter.nih.gov/.

[82] To read the NIH commitment to transparency on research involving potential pandemic pathogens see https://www.nih.gov/about-nih/who-we-are/nih-director/statements/nih-commitment-transparency-research-involving-potential-pandemic-pathogens.

available to help policymakers and the public understand why certain projects have been approved and whether, or how many, research projects are referred for P3CO review and do not go forward due to the requirements of the P3CO policy. 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 proposers. Research proposals describe new ideas and potential outcomes; releasing this information could be used by other researchers potentially impacting claims to 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, they may consider how to balance transparency against 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 receiving 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.[83] The approach can include at least three different review mechanisms for determining which regulations and federal guidance may apply to proposed research:[84]

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.[85] However, programs of this type vary widely between institutions based on each institution's expertise, resources, and biosafety/biosecurity cultural norms.

Congress could consider mandating the establishment of an overarching federal biorisk management policy that brings together the recommendations, guidance, and policies shown in **Figure 1** and **Appendix B** into a single common framework of protocols and procedures. This could better align oversight of life science research across federal agencies and provide a consistent review process for research institutions.

[83] Sabrina Brizee, Mark W. J. van Passel, and Linda M. van den Berg, et al., "Development of a Biosecurity Checklist for Laboratory Assessment and Monitoring," *Applied Biosafety*, vol. 24, no. 2 (2019), pp. 83-89. Jennifer Gaudioso, Reynolds M. Salerno, and Natalie Barnett, "Developing a Risk Assessment and Management Approach to Laboratory Biosecurity," *Applied Biosafety*, vol. 11, no. 1 (2006), pp. 24-31.

[84] 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).

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

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

- which body should develop the policy—a single agency, such as HHS, or through an interagency body such as the National Science and Technology Council (NSTC),[86]
- 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 can cover timely research and avoid needing to be reactively revised when science advances or each time an event occurs, and
- whether a new regulatory oversight body, independent from agencies funding research, is necessary to coordinate and enforce the policy, as suggested by some experts.[87]

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 current P3CO policy, HHS reviews research proposals that have been recommended for funding by its own proposal review panels. Some scholars suggest that the risk assessment process should be conducted 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.[88]

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 may 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 due to 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. Such harmonization might include what the scope of such regulations should be, what entity would be responsible for compliance across the different agencies, and who would bear the costs.

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

[87] Ryan Ritterson, Linette Kingston, and Adam E. J. Fleming, et al., "A Call for a National Agency for Biorisk Management," *Health Security*, vol. 20, no. 2 (2022).

[88] Marc Lipsitch and Thomas V. Inglesby, "Moratorium on Research Intended to Create Novel Potential Pandemic Pathogens," *mBio*, vol. 5, no. 6 (2014).

Increased 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.[89] There currently is limited funding for programs that study applied biosafety and biosecurity. Congress could consider providing funding to agencies for additional staff or existing programs; or establish 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.

Conclusion

Gain-of-function 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.[90] 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.[91] 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 of expertise may increase the quality of the risk assessment around a particular set of parameters.

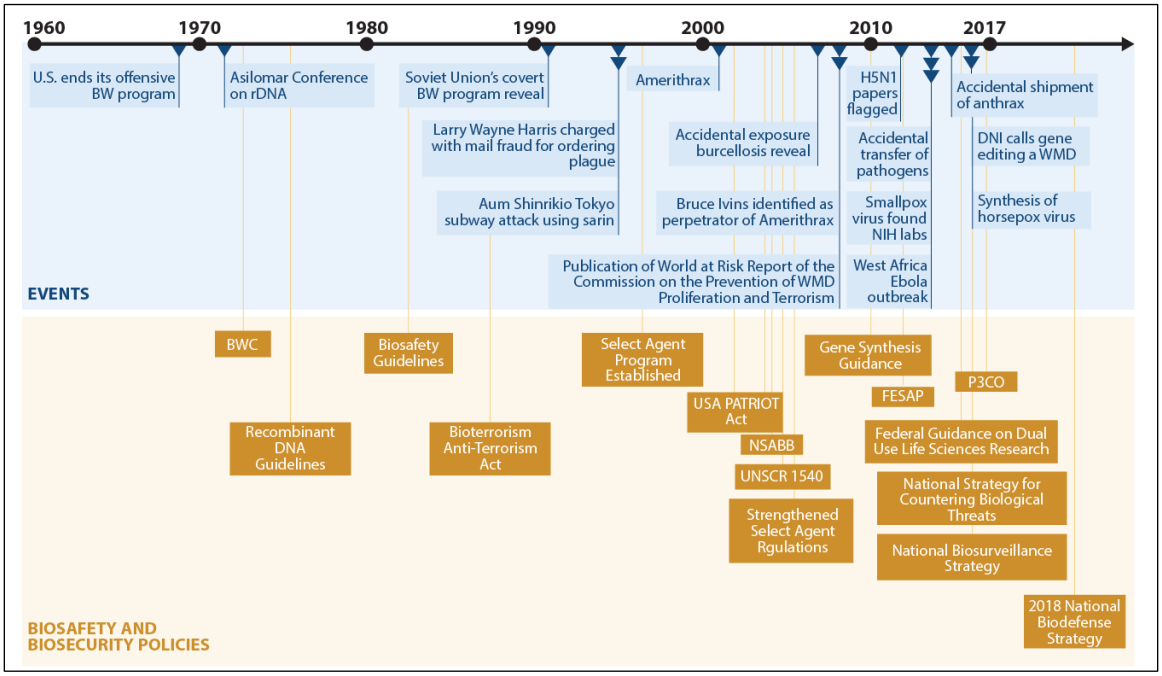
U.S. policies address multiple aspects of biosafety and biosecurity—some impose requirements, some provide guidance, some policies overlap, some apply only to research with select biological agents, and some policies only apply to federally funded research and may not cover certain research institutions 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, issues the NSABB and GAO are both currently examining.

[89] Kelsey Lane Warmbrod, Michael G. Montague, and Gigi Kwik Gronvall, "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).

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

[91] Michael J. Imperiale, Don Howard, and Arturo Casadevall, "The Silver Lining in Gain-of-Function Experiments with Pathogens of Pandemic Potential," *Methods in Molecular Biology*, vol. 1836 (2018), pp. 575-587.

Appendix A. Select Biosafety/Security Events and Associated U.S. Policy Implementation Through 2018



Source: Adapted from Diane DiEuliis, Venkat Rao, and Emily A. Billings, et al., "Biodefense Policy Analysis—A Systems-Based Approach," *Health Security,* vol. 17, no. 2 (2019).

Notes: Figure represents a selection of major events and should not be interpreted as a comprehensive list. Acronyms: Bio weapons (BW); U.N. Bioweapons Convention (BWC); National Science Advisory Board for Biosecurity (NSABB); U.N. Security Council Resolution (UNSCR); Federal Experts Security Advisory Panel (FESAP); Recommended Policy Guidance for Departmental Development of Review Mechanisms for Potential Pandemic Pathogen Care and Oversight (P3CO); Director of National Intelligence (DNI); Weapon of Mass Destruction (WMD).

Appendix B. Select U.S. Policies for Biosafety and Biosecurity Oversight

Oversight Measures	Risks Addressed	Description of Oversight	Analysis/Applicability to GOF Studies Involving Pathogens
Biosafety in Microbiological and Biomedical Laboratories (BMBL), 6th Edition (June 2020) https://www.cdc.gov/labs/pdf/SF__19_308133-A_BMBL6_00-BOOK-WEB-final-3.pdf	Biosafety risks	Applies to: Life sciences research involving infectious microorganisms or hazardous biological materials. Description: General biosafety practices and biological containment for various classifications (risk groups) of microorganisms and etiological agents.	BMBL is applicable to those studies even though it doesn't address them expressly. BMBL is a guidance document and generally considered the authoritative reference for laboratory biosafety. While it is not a regulatory document, adherence to the BMBL is a term and condition of grant awards for recipients of funding from certain federal agencies.

Oversight Measures	Risks Addressed	Description of Oversight	Analysis/Applicability to GOF Studies Involving Pathogens
NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules (November 2013) http://osp.od.nih.gov/office-biotechnology-activities/biosafety/nih-guidelines	Biosafety risks	Applies to: Basic or clinical life sciences research that involves recombinant or synthetic nucleic acid molecules and is conducted at an institution receiving NIH funding for any such research. Description: Describes roles and responsibilities of institutions and investigators in safely conducting research. 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. Advised by: NIH Recombinant DNA Advisory Committee (RAC).	The NIH Guidelines have been amended to include additional guidance for work with Risk Group 3 influenza viruses (1918 H1N1, H2N2, highly pathogenic avian influenza [HPAI] H5N1) to specify enhancements to biosafety level 3 containment, practices, and occupational health requirements. NIH Guidelines were amended again to require further enhancements to facilities, biosafety equipment and practices, including occupational health practices, for research involving HPAI H5N1 strains transmissible among mammals by respiratory droplets. NIH Guidelines are often used as a model of biosafety guidance by the broader scientific community. Compliance is required of institutions receiving funding from the NIH. The scope is also limited to research involving recombinant or synthetic nucleic acids. Some Institutional Biosafety Committees (IBCs) also review and approve nonrecombinant pathogen research; however, not all institutions require their IBCs to do so.

Oversight Measures	Risks Addressed	Description of Oversight	Analysis/Applicability to GOF Studies Involving Pathogens
HHS and USDA Select Agent Program (as of July 2014) http://www.selectagents.gov/	Biosecurity (physical and personnel) and biosafety risks	Applies to: Specified biological agents and toxins deemed by HHS or USDA to pose a severe threat to public health and safety, based on a set of criteria. Description: Regulates the possession, use, and transfer of select agents and toxins. Overseen by the Federal Select Agent Program (FSAP). Requires registration of individuals and entities; federal background investigations; federal review of restricted experiments; training; institutional compliance; etc. Advised by: Intragovernmental Select Agents and Toxins Technical Advisory Committee.	Studies that could be considered GOF studies, which involve pathogens on the select agent list, are subject to oversight by the FSAP. Researchers and institutions performing such studies must receive favorable security risk assessments by the Federal Bureau of Investigation, register with the FSAP, receive training on the proper procedures and practices for handling such agents, and abide by other aspects of the regulations. SARS-CoV, HPAI H5N1 influenza, and 1918 influenza viruses are select agents and GOF studies involving these pathogens are subject to oversight by the FSAP.

Oversight Measures	Risks Addressed	Description of Oversight	Analysis/Applicability to GOF Studies Involving Pathogens
U.S. Government (USG) Policy for Federal Oversight of DURC (March 2012) http://www.phe.gov/s3/dualuse/Pages/USGOversightPolicy.aspx and USG Policy for Institutional Oversight of DURC (September 2014) http://www.phe.gov/s3/dualuse/Pages/InstitutionalOversight.aspx	Biosecurity risks; and knowledge, information, products, or technologies that could be directly misapplied to pose a significant threat with broad potential consequences to public health and safety, agricultural crops, and other plants, animals, the environment, materiel, or national security	Applies to: Life sciences research conducted at an institution receiving U.S. government funding that involves any of the specified 15 pathogens and toxins deemed to pose the greatest risk of deliberate misuse with most significant potential for mass casualties or devastating effects to the economy.	The federal DURC policy requires federal funding agencies to identify and oversee certain pathogen research involving 7 experimental types, some of which can be described as GOF experiments (e.g., enhancing the harmful consequences of an agent; increasing transmissibility; altering host range). The institutional DURC policy requires federally funded institutions to implement the federal DURC policy by establishing a system for the identification and oversight of certain pathogen research involving the same 7 experimental types. DURC policies only apply to research involving 15 pathogens and toxins. Institutions may review other studies for DURC potential but are not required to do so. Certain GOF studies that involve other agents would not be subject to DURC oversight under the policies.
HHS Framework for Guiding Funding Decisions about Proposed Research Involving Potential Pandemic Pathogens (2017) https://www.phe.gov/s3/dualuse/Documents/P3CO.pdf	Biosafety and biosecurity risks associated with experiments that are reasonably anticipated to create, transfer, or use enhanced potential pandemic pathogens	Applies to: Gain-of-function studies that are reasonably anticipated to develop enhanced potential pandemic pathogens resulting from the enhancement of the transmissibility and/or virulence of a pathogen. Description: Describes an HHS Department-level review and approval process for certain GOF studies, which can result in funding, not funding, or funding with certain conditions and ongoing oversight.	Focused on specific studies that 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.

Source: Adapted from National Science Advisory Board for Biosecurity, *Recommendations for The Evaluation and Oversight of Proposed Gain-Of-Function Research*, 2016, pp. 57-58.

Appendix C. Laboratory Biosafety Levels

BSL Level	Description
Biosafety Level 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 hazard 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.
Biosafety Level 2	Biosafety Level 2 (BSL-2) builds upon BSL-1. BSL-2 is suitable for work with agents associated with human disease and 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.
Biosafety Level 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.
Biosafety Level 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: Adapted from *Biosafety in Microbiological and Biomedical Laboratories*, 6th Edition, 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.

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