October 13, 2023

Submitted Electronically to: https://www.regulations.gov

RE: Response to Request for Information on Potential Changes to the Policies for Oversight of Dual Use Research of Concern (DURC) and the Potential Pandemic Pathogen Care and Oversight (P3CO) Policy Framework

To Whom It May Concern:

We write to offer comments in response to the Office of Science and Technology Policy's (OSTP) request for information on *Potential Changes to the Policies for Oversight of Dual Use Research of Concern (DURC) and the Potential Pandemic Pathogen Care and Oversight (P3CO) Policy Framework*[1] (RFI) that were published in the Federal Register on September 1, 2023. COGR is an association of over 200 public and private U.S. research universities and affiliated academic medical centers and research institutes. We focus on the impact of federal regulations, policies, and practices on the performance of research conducted at our member institutions, and we advocate for sound, efficient, and effective regulation that safeguards research and minimizes administrative and cost burdens.

COGR and its member institutions recognize the importance of conducting research involving the use of pathogens and toxins ("Regulated Materials") in a safe and secure manner, and we support the need for federal requirements aimed at achieving this goal. We support OSTP's solicitation of public input on potential changes to the policy framework governing Dual Use Research of Concern (DURC) and research using enhanced potential pandemic pathogens (ePPPs), and we appreciate the opportunity to provide comments.

We begin with general comments regarding the RFI's proposal to merge the three federal policies that currently govern DURC and ePPPs and to move from a list-based to a risk-based approach. We then provide comments on specific questions included in the RFI. Note that we have included the text of questions to which we have responded, but excluded references cited therein.

General Comments

Presently, DURC is regulated under the following two complementary policies: United States Government Policy for Oversight of Life Sciences Dual Use Research of Concern ("USG Agency

[1] 88 FR 60513

DURC Policy) and the United States Government Policy for Institutional Oversight of Life Sciences Dual Use Research of Concern ("Institutional DURC Policy"). The Institutional DURC Policy sets forth the responsibilities of non-governmental research institutions that receive federal funding in support of life sciences. Under this policy, an institution must establish an Institutional Review Entity (IRE) to which principal investigators (PIs) must refer for review any potential DURC, which encompasses research using a non-attenuated form of one of 15 agents listed in the policy that "produces, aims to produce, or is reasonably anticipated to produce" one or more of seven listed experimental effects. The IRE must develop a risk mitigation plan (RMP) for any research that meets the DURC definition, and the RMP must be approved by the federal funding agency[2] and overseen by the IRE.

The RFI proposes moving away from this "list-based" approach to determining whether research constitutes DURC. Instead, the RFI proposes an approach that defines DURC as research that involves "***any*** human, animal, or plant pathogen, toxin, or agent" that "is reasonably anticipated to result in one or more of the seven experimental effects." [***Emphasis added***]. COGR and its member institutions are deeply concerned that such an approach would place an untenable burden on PIs and IREs to conduct risk assessments of an unlimited number of pathogens and toxins. Further, we are apprehensive about the inter-institutional inconsistency that may result from this approach as to the risks presented by certain pathogens/toxins/agents.

Similarly, the proposed changes to the regulation of ePPPs, also place significant new burdens on institutional biosafety review processes by making institutions responsible for reviews that are currently carried out by federal agencies. Presently, ePPP research is regulated in accordance with the Recommended Policy Guidance for Departmental Development of Review Mechanisms for Potential Pandemic Pathogen Care and Oversight (P3CO) ("P3CO Policy"). This policy requires federal agencies funding ePPP research to develop review mechanisms to determine if the research should be conducted,[3] and if so, appropriate risk mitigation, oversight, and reporting requirements. The RFI proposes combining the USG and Institutional DURC Policies with the P3CO Policy. Although combining these policies has the appeal of potentially reducing duplicate reviews for DURC/ePPP, we are concerned that institutions may not have the bandwidth and/or subject matter expertise necessary to perform the required risk assessments for "***any*** human, animal, or plant pathogen, toxin" under the DURC and P3CO criteria.

Specific Comments

Question 1(b) - What are the anticipated benefits and challenges of investigators and institutions having primary responsibility for identification of both DURC and ePPP research?

[2] Federal agencies may also designate research as DURC and develop an associated RMP. An institution's IRE does not need to review and develop a RMP for agency-designated DURC, but it must provide oversight for this research.
[3] For example, in response to the P3CO Policy, the Department of Health and Human Services (HHS) has implemented its Framework for Guiding Funding Decisions about Proposed Research Involving Enhanced Potential Pandemic Pathogens, which calls for funding agency and HHS review/consideration of such research.

Comments

Giving institutions the primary responsibility for identification of both DURC and ePPP research has the potential advantage of combing the current separate review paths for DURC and ePPP into one. However, this potential benefit is outweighed by the significant burdens that institutions would face from being required to perform risk assessments for an unlimited range of agents and making both DURC and ePPP determinations.

Question 1(c) - What types of resources or tools would be useful for researchers and institutions to determine if their research falls into a revised policy scope that is risk-based rather than list-based, and adequately conduct risk assessment to identify DURC and ePPP research?

Comments

Should OSTP decide to abandon the current list-based approach to DURC review **and** place the burden of ePPP review on institutions, OSTP and/or federal agencies that support DURC research must provide clear, detailed guidance to institutions and researchers as to what must be reviewed and how expected risk assessments must be conducted. In this vein, OSTP should require federal agencies that support DURC to provide extensive training to IREs on the conduct of reviews and provide detailed decision trees that they can employ. Also, OSTP should require each such agency to establish a dedicated office that is readily available to provide detailed and specific guidance regarding reviews, development of RMPs, as well as answer institutional questions.

Question 2(a) - Currently, the scope of the DURC policies is research that uses one or more of 15 listed agents or toxins and that produces, or is anticipated to produce, any of seven listed experimental effects. The NSABB recommended that the scope of research requiring review for potential DURC should include research that directly involves* any *human, animal, or plant pathogen, toxin, or agent that is reasonably anticipated to result in one or more of the seven experimental effects outlined in the DURC policy (Recommendation 10.1).

Considering the diversity of federally-funded research settings and portfolios, how would adoption of NSABB's Recommendation 10.1 affect policy implementation and research programs at the institutional level?

Comments

As noted, Recommendation 10.1 will result in a tremendous expansion of institutional duties that will lead to delays in the initiation and progress of important research projects. This could ultimately result in some institutions curtailing or ceasing work in microbial research. Although, institutions with complex and mature biosafety review processes and access to extensive subject matter experts, with adequate federal support, may be able to adapt to these new processes, institutions that lack such resources (e.g., smaller institutions, emerging research institutions) may be unable to conduct DURC or ePPP research.

Question 2(b) - Rather than including* any *pathogen within the scope of DURC review, one possible modification of Recommendation 10.1 would be to include DURC experiments that

utilize:

i. HHS and Overlap Biological Select Agent and Toxins (BSAT) List[l] and/or
ii. Pathogen risk group (RG) classification of 3 or 4 and/or
iii. Any pathogen where the conduct of work (e.g., one of the DURC experimental categories) would require biosafety level 3 or 4 containment.

Would a modification of Recommendation 10.1, in line with the outlined scope of pathogens above, be useful for policy implementation? What specific benefits, challenges, and/or are gaps anticipated by this revised scope?

Comments

COGR supports the current list-based approach to DURC review because of the clarity it provides to researchers and institutions as to what research may be considered DURC. If the current 15 agent list is abandoned, however, we strongly recommend that Recommendation 10.1 be modified to clearly define the agents that require DURC review. In this regard, we believe that subsections 2.b.i and 2.b.ii. assist in providing such clarity, but 2.b.iii. does not, and therefore, should be eliminated.

Stated more broadly, in lieu of the proposed wide-scope definition, any modification to the current DURC policy should incorporate a mechanism that refines the agents subject to DURC review. Potential mechanisms could include reference to other existing frameworks to identify risk such as definition of risk group 3 or 4, provision of an indicative list, or utilization of more pertinent agent characteristics (e.g., high morbidity and/or mortality, high likelihood of person-to-person spread, existence of preventative or therapeutic measures, high risk to healthcare personnel, etc.). Additionally, we recommend excluding diagnostic clinical laboratories from this research oversight to avoid hampering their crucial efforts to respond to pandemics in a timely manner.

Question 3(a) - A PPP is currently defined in the P3CO policy framework as: "a pathogen that satisfies both of the following: 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 NSABB recommended that the definition of PPP be modified to: (1) Likely moderately or highly transmissible and likely capable of wide and uncontrollable spread in human populations; and/or (2) Likely moderately or highly virulent and likely to cause significant morbidity and/or mortality in humans; and, in addition (3) Likely to pose a severe threat to public health, the capacity of public health systems to function, or national security" (Recommendation 2).

(a) How would the change in the definition of PPP affect the overall scope of a Revised Policy and its subsequent implementation?

Comments

This definition of a PPP adds yet more uncertainty and vagary to the determination of what requires regulation under the P3CO Policy, making the proposed new policy even more difficult for

institutions to implement. Further, we note that the definition is internally inconsistent, i.e., how is an item that is "likely moderately" transmissible also "likely capable of wide and uncontrollable spread in human populations."

Question 3(c) - Do you have additional suggestions to modify the PPP definition to mitigate the most significant risks not currently addressed and enhance effective implementation, while limiting negative or unintended consequences and burden on researchers, institutions, and the Federal government?

Comments

We recommend incorporating into the PPP definition limitations on items that may be considered PPPs. For example, the development and production of prophylactic and/or therapeutic treatments in response to a public health crisis such as a pandemic or epidemic.

Question 4(a) - A Government Accountability Office (GAO) report from January 2023recommended that the Department of Health and Human Services funding agencies should develop and document a standard to define "reasonably anticipated" to ensure consistency in identifying research that falls within scope of a Revised Policy. One possible definition of "reasonably anticipated" is:

> ***"'Reasonably anticipated' describes an assessment of an outcome that an individual with scientific expertise relevant to the research in question would expect this outcome to occur with a non-trivial likelihood. It does not require high confidence that the outcome will definitely occur and excludes experiments in which an expert would anticipate the outcome to be technically possible, but highly unlikely."***

(a) Does this definition of "reasonably anticipated" provide additional clarity to ensure greater consistency in identifying research that falls within scope of the Revised Policy? What modifications to this definition (if any) would be most helpful?

Comments

Institutions already struggle in applying the term "reasonably anticipated" under the current DURC review process (i.e., determining when one of the 15 listed agents "produces, aims to produce, or is reasonably anticipated to produce" one or more of seven listed experimental effects). We support the development of a clear definition of "reasonably anticipated" to assist institutions in their reviews. For the proposed definition to be helpful, however, the terms "non-trivial likelihood" and "technically possible, should be replaced with more quantitative measures.

Question 5 - NSABB recommends the removal of blanket exclusions for research activities associated with surveillance and vaccine development or production for research with ePPPs (Recommendation 3).

(a) Should exemptions for certain activities be included in a Revised Policy?

Comments

Section II.C of current P3CO Policy contains an exemption from the definition of ePPPs for certain types of research involving surveillance activities and vaccine development and production:

> To the extent that transmissibility and/or virulence of PPPs are modified in the following categories of studies, the resulting pathogens are not considered to be enhanced PPPs for the purposes of this Framework.
>
> 1. Surveillance activities, including sampling and sequencing; and
> 2. Activities associated with developing and producing vaccines, such as generation of high growth strains. [Footnote from original omitted.]

The recent COVID-19 pandemic illustrated the acute need for the ability to quickly stand-up research on surveillance and vaccine development. To this end, we urge OSTP to retain exemptions for surveillance (including diagnostic assay development) and vaccine development and production in any new P3CO policy. To do otherwise, would imprudently hamper such research in circumstances in which facilitating its conduct is vital to public health.

Question 6 - NSABB recommends that continued assessment of the risks and benefits associated with advances and applications of bioinformatics, modeling, and other in silico experimental approaches and research involving genes from or encoding pathogens, toxins, or other agents must inform future evaluations of the scope of research oversight policies to help ensure that associated risks are appropriately identified and managed. (Recommendation 10.2). This type of research is not currently included in the DURC and ePPP oversight policies.

(a) Is there a subset of such in silico research that should require risk assessment and review in a Revised Policy, and if so, how should this research be defined so that the Policy captures the appropriate research without hampering activities with limited biosecurity risks?

(b) One possible way to define this category of in silico research within a Revised Policy would be to include experiments that are reasonably anticipated to:

> ***"(i) Develop in silico models that directly enable the predictive design of an enhanced potential pandemic pathogen or novel pathogen or toxin covered under a Revised Policy that could be constructed via genomic editing or de novo synthesis; and/or***
> ***(ii) Develop a dataset(s) connecting nucleic acid or amino acid sequences with experimentally-determined pathogenic functions in a manner sufficient to enable the development of in silico models described in (i)."***

If a new category of research, similar to the examples provided above, were to require risk assessment and review in a Revised Policy, what would be the benefits and challenges with implementation?

The DURC and P3CO policies are designed to specifically address the enhancement of pathogens of concern through research activities. By expanding review responsibilities to cover *in silico*

research activities, the proposed policy will put a new burden on research entities to monitor bioinformatics research. Although *in silico* research is a helpful tool in predicting certain research outcomes without *in vivo* verification, all *in silico* research is ultimately just predictive. Further, when predictions from *in silico* research are tested with *in vitro* and/or *in vivo* assays, this subsequent testing is covered under DURC and ePPP oversight mechanisms.

Moreover, *in silico* research regulation would require dataset publication monitoring to determine whether the information could be used to enhance a pathogen. If so, use and publication restrictions would need to be considered, but such restrictions would significantly impede the conduct of collaborative research necessary to address public health emergencies. For example, if the availability of the sequence of the SARS-CoV-2 had been restricted during the recent pandemic, the development of treatments and vaccines would have been significantly hampered and/or delayed. Although we appreciate the concern voiced by the National Science Advisory Board for Biosecurity (NSABB) that access to such datasets may be used to produce pathogens with pandemic potential, we believe that this potential for harm is significantly outweighed by the benefit that broad access to datasets provides in facilitating research efforts to combat emerging pathogens.

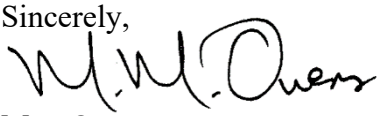
Conclusion

COGR and its member institutions acknowledge the difficulties inherent in developing requirements governing research on continually evolving pathogens and other agents that have the potential for great harm to public health. We also appreciate the need for agencies to periodically examine existing policies to determine if they address risks that have emerged since they were originally adopted. To be effective, any changes to such policies must be abundantly clear as to what research they encompass and the specifics of any required reviews.

The RFI proposes to substantially alter not only the scope of DURC and ePPP research, but also the allocation of responsibilities regarding its review. As our comments note, requirements in this area must be concrete and explicit, so that researchers and institutions can understand and carry out their responsibilities. We are concerned, however, that the RFI takes the opposite approach and introduces more uncertainty in this regulatory sphere. Finally, whatever changes are made to these policies, we urge OSTP to retain the current exemption for surveillance activities and vaccine development and production, and to ensure that institutions will have adequate time to implement any policy changes.

COGR and its member institutions appreciate the opportunity to comment on the RFI and appreciate OSTP's consideration of our comments for its improvement. Should you have any questions regarding these comments, please contact me or Kristin West, COGR's Director of Research Ethics and Compliance at kwest@cogr.edu.

Sincerely,



Matt Owens
President