ABSA INTERNATIONAL
The Association for Biosafety and Biosecurity
1200 Allanson Road • Mundelein, IL 60060-3808 • 866-425-1385 • Fax: 847-566-4580 • E-mail: info@absa.org • Web Site: www.absa.org

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Jasleen K. Modi
Senior Analyst
Health Care
U.S. Government Accountability Office

Dear Ms. Modi,

Thank you for the opportunity to speak with you and your GAO Health Care colleagues for your review of Department of Health and Human Services (HHS) High-Risk Research Oversight (105455). We sincerely appreciate your outreach and invite you to consider ABSA International for future conversations regarding biosafety and biosecurity. Please find below our written comments to the discussion questions you provided to guide our conversation. Do not hesitate to reach out for any clarification needed.

Thank you again for reaching out!

Sincerely,

LouAnn Burnett MS, CBSP(ABSA)
President, ABSA International
louann.burnett@gmail.com

1. **In your opinion, what life sciences research areas involving human pathogens are high-risk?**

   There are diverse areas of concern within the fields encompassing life science research, and it is important to recognize that the research enterprise cannot attain zero risk when conducting research. However, biosafety and biosecurity professionals (B/BSP) collaborate with researchers to reduce the level of risk to as close to zero as possible. B/BSP employ the process of risk assessment, initially and on an on-going basis, to inform the selection of appropriate, layered, site-specific mitigation strategies. That said, research that is novel or of higher risk to the individuals performing the research, the community, and/or the environment (ex. work with risk group 3 or 4 pathogens) usually requires higher levels of risk mitigation measures. Additionally, there are some keywords/phrases and areas of work that currently tend to garner closer examination by a B/BSP. Examples of these include aerosolization, pathogens known to impact the economy, gene editing experiments, novel or emerging human/animal/environmental pathogens, human gene transfer studies, synthetic biology (iGEM), and gene drives.

   The risk assessment process involves, but is not limited to, hazard identification, understanding the experimental manipulations, risk definition (risk of infection, risk of release to the environment, risk of theft, etc.), risk characterization (risk is a function of likelihood of an adverse event and the consequence of that event), and risk evaluation (should the identified risk be accepted as is, controlled, avoided, or transferred?). The B/BSP helps determine what mitigation measures will reduce the risk to an acceptable level. This process relies on trained and experienced B/BSP to help evaluate risk and determine appropriate controls. Resources commonly utilized by B/BSP in the process of risk assessment include scientific literature, the BMBL, NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acids, and the ABSA Risk Group tool, to name a few.

2. **We understand that Dual Use Research of Concern (DURC), Federal Select Agent Program (FSAP), and HHS Framework for Guiding Funding Decisions about Proposed Research Involving Enhanced Potential Pandemic Pathogens (P3CO) are in place to oversee risks associated with biosafety and biosecurity.**

   a. **What are the benefits and drawbacks of having delineated lists of specified agents or experiment types?**

   It is ABSA International's position that relying strictly on a list, or multiple lists, is problematic. It may provide a false sense of security, in that there is a danger that researcher/reviewers will simply take a "checklist" approach to assessing risks and fail to recognize potential hazards because they were not included in a predetermined list. There will also always be an exception to any list, because federally mandated lists cannot be updated at a rate commensurate with changes in technology, techniques, and emerging pathogens. Lists that are not based on a holistic risk assessment may result in unintended consequences, such as chilling research in an area due to overly restrictive mandates (i.e. cost, infrastructure, oversight) or the failure to recognize "dual use" characteristic in agents not selected for the list. However, we recognize that there are advantages to having well-constructed and thoughtfully implemented lists, in that they may serve as a starting point to help identify the resources needed to manage high-risk research as well as to prompt organizational controls and decision-making. We also recognize that not all B/BSP have a depth of knowledge or resources to allow them to focus on characteristics/criteria related to risk rather than specific organisms or procedures, so a well-formed list can be helpful. Finally, ABSA International supports transparency in the development of any lists, such that the

rationale for the list as well as the risks being addressed by the list are clearly communicated to the regulated community.

An example we would like to put forth is our members' experience with botulinum neurotoxin. This toxin is specifically regulated as a Dual Use Agent of Concern for any quantity used, even though botulinum neurotoxin has been widely accepted as an experimental reagent in extremely small quantities and is commercially available. The additional oversight for these very small quantities without clear rationale has burdened B/BSP and IREs with duplicative oversight, caused confusion and mistrust from the regulated community, and prompted researchers to turn away from utilizing this accepted methodology in their research.

Another real-world example is work with *Batrachochytrium salamandrivorans*, or Bsal, a newly emergent fungal pathogen of salamanders and newts. This agent would not appear on the P3CO or BSAT list, but it is currently responsible for the near extinction of fire salamanders in the Netherlands. If an entity was purely focused on human pathogens of consequence, it might miss the opportunity to identify and mitigate the incredible risks to organisms that are vital to an ecosystem here in the United States and globally.

A final example for consideration is the many small colleges that operate without a formal biosafety officer. If an entity does not receive exterior funding (e.g., NIH), or is only performing what is deemed low risk biological research, it may not have the expertise on hand to recognize that the low-risk environmental sampling performed during a microbiology class may be isolating BSAT such as *B. anthracis* or *B. mallei*.

b. Are the research areas covered under each program clear and well understood by researchers, institutions, and its funding agencies?

In many circumstances the answer is no. ABSA International believes there is a range of awareness related to each of these areas. All institutions do not have the same research portfolios, and researchers and B/BSP have specific areas of experience and expertise. As such, the level of understanding related to each of these policies is expected to vary and be related to institutional past and present engagement with each of these programs. Institutions, researchers, and biosafety professional who have experience with P3CO and/or DURC will have more robust program awareness. It is our current understanding that the P3CO nomenclature is not broadly used or understood among research communities that are not actively performing P3CO research.

c. Do you think the oversight provided by these programs adequately cover all high-risk research with human pathogens?

Please see answer 2a.

d. In our earlier interview, you noted that the P3CO framework was duplicative of DURC. Please elaborate on how the framework is duplicative of DURC.

ABSA International acknowledges that DURC and P3CO are two separate governmental policies, but notes that at an institutional level, operationally, they are often addressed using the same infrastructure. While it is institution specific, our current understanding is that some institutions go above and beyond the requirements and do not focus on one list at a time. Minus DURC and/or P3CO, entities take a more holistic, streamlined approach when reviewing research, considering all regulations or guidance that may apply. Separate reviews are not performed for bloodborne pathogens, recombinant nucleic acids, infectious agents, respiratory protection program, state/local waste disposal processes, etc. Instead, the research as a whole is reviewed against these various regulatory frameworks that are familiar to a B/BSP and mitigation strategies are developed in coordination with each other. This is why it is so essential that the B/BSP be well versed in all these areas, receive clear communication from regulatory agencies, and be provided access to relevant continuing education opportunities.

e. What are other ways that risks could be characterized and captured in an oversight scheme?

ABSA International believes that a centralized and harmonized approach to biological research oversight would involve using well-developed, informed criteria to review all biological research. We envision an overarching entity focused on Biosafety and Biosecurity of life sciences, separate from conflicting funding sources, tasked with such high-level review, oversight, and education of risks and mitigations involved in high-risk research. This entity would be designed from ground up with mechanisms that would allow it to be agile in responding to changes in technology and threats. Additionally, the entity would be adept at bringing together stakeholders from various cross-sections of the life sciences landscape to promote dialogue, create awareness, break down silos, and ultimately become a nimble and credible authority focused on real risks and mitigations instead of perceived risks.

3. What is your perspective on HHS agencies', such as NIH or CDC, ability to identify and flag proposed high-risk research studies?

a. What improvements, if any, could these agencies make to their ability to identify, review, fund, and provide ongoing oversight for high-risk research?

First, awareness and transparency are key. An oversight agency's ability to identify and perform reviews of high-risk research depends primarily on the funded PI's awareness of such risks and the existing policies in place, either from the oversight agency or from their institution, to mitigate them. Additionally, the PI must be willing to continually assess and reveal such risks as research progresses. It is imperative that such disclosures do not result in "punishments" (real or perceived) either for the PI or their institution; this will be counterproductive to the agency's efforts.

Next, the review of research to identify potential high-risk studies can be done at multiple points in the research life cycle, from study section to progress reports. Funding agencies can ensure that those reviewing research proposals and progress reports as well as program officers are trained to identify high risk studies. Additional training to identify and evaluate high-risk research should be provided to other stakeholders involved in review process. This includes but is not limited to, members of the Scientific Review Group (mainly external experts), members of the Advisory Councils or Boards within the agencies, final authorities approving the funding, study section administrators, grant administrator and program officers. Currently, the level of quality, expertise, experience, and training varies widely among the various stakeholders and can impact their ability to discern and identify higher risk research. Expertise in biological risk assessment and mitigation should be required for these roles. Additionally, subject matter experts, such as B/BSP, could be included in the review process.

Finally, to better identify high-risk research, funding agencies could explore funding multi-disciplinary research that identifies and mitigates potential DURC in research programs as a whole. The entire life cycle of identifying, mitigating and communicating high-risk research has several domains that could benefit from additional research. Additionally, such funded research could produce tools that make the review process more efficient. Machine learning, automation, artificial intelligence, and advanced language screening tools could be used to flag grant proposals, annual reports and manuscript drafts for high-risk research in near real-time. These flagged studies could then be reviewed by a network of trained biosafety and biosecurity professionals. Agencies could implement a clear and effective processes to screen and identify high-risk research. The process should be transparent and include ways to collaboratively find solutions for allowing research to continue while still mitigating the high-risk consequences. Finally, we could envision the creation of a centralized initial and on-going DURC training "academy" for a variety of different recipients tailored to their roles in the review process. This

could be a multi-sector approach with input from various stakeholders and housed within the centralized oversight entity discussed in response 2e.

4. **We understand that biosafety and biosecurity are important considerations for researchers, and most institutions have biosafety committees that help review and facilitate research. How does the work of biosafety committees align with DURC, FSAP, and P3CO reviews?**

   Please refer to answer 2d.

   Institutional Biosafety Committees (IBCs) provide important institutional oversight. However, no two IBCs are exactly the same. They have access to and knowledge of institution-specific research aims, local requirements, and resources. We believe the variety among IBC structure and function is a success story for providing criteria and allowing institutions to develop institution-specific means to meet the criteria. Many organizations have expanded the role of the IBC as needed to address more than the duties assigned by the NIH Guidelines, and this includes BSAT oversight and serving as the IRE for DURCP3CO reviews, among others. While there is no standardized approach, many institutions could serve as models for a harmonized process (e.g. those which have a clear, written charge for the IBC and/or other institutional committees specifically established for additional oversight.).