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Institutional Review of Dual Use Research of Concern to Support a Culture of Responsibility

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Abstract

The National Biodefense Analysis and Countermeasures Center (NBACC) plays a central role in the US Biodefense community, and its unique mission has driven NBACC to make dual use research of concern (DURC) review a focus since inception. Review of research results prior to external release began in 2007 and an institution-level review of all projects that considers DURC was implemented beginning in 2011. The DURC review process at NBACC has evolved through four approaches—each with advantages and disadvantages—that are all consistent with the recently issued U.S. Government Policy for Institutional Oversight of Life Sciences Dual Use Research of Concern. The current NBACC review process emphasizes Principal Investigator (PI) ownership and accountability, builds transparency in DURC review, and is specifically tailored to NBACC in order to reinforce an institutional culture of responsibility. This paper summarizes NBACC's evolutionary process for effective DURC review.

Keywords: DURC; Institutional Oversight; Biodefense; IBC

Introduction

Dual use research of concern (DURC) is defined in the new U.S. Government Policy for Institutional Oversight of Life Sciences Dual Use Research of Concern [1] 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." This definition is nearly identical to the National Science

Advisory Board for Biosecurity (NSABB) DURC criterion proposed in June 2007 [2]. In 2011, the NBACC implemented oversight processes utilizing the NSABB recommended DURC criterion and the 2004 National Academies (Academies) report [3] of seven "experiments of concern" that would:

1. Demonstrate how to render a vaccine ineffective,
2. Confer resistance to therapeutically useful antibiotics or antiviral agents,
3. Enhance the virulence of a pathogen or render a nonpathogen virulent,
4. Increase transmissibility of a pathogen,
5. Alter the host range of a pathogen,
6. Enable the evasion of diagnostic/detection modalities, and
7. Enable the weaponization of a biological agent or toxin.

The report also recommended formation of a group of scientific and security experts to advise the government which was addressed by the 2005 formation of the NSABB [4]. The Academies, NSABB, American Society for Microbiology, and other organizations facilitate continued active dialogue on the importance of a culture of responsibility, reviews of sensitive research before experimentation and communication, assessments of the risks and benefits of DURC research, norms for life science professionals, and expectations from multiple stakeholder perspectives, including the general public.

Recent attention on DURC was catalyzed in 2011-12 by two influenza A/H5N1 manuscripts with a recommendation by NSABB to not fully publish the data and methods [5,6]. Following an NSABB review of the revised manuscripts in 2012 [7], they were published [8,9]. There was a series of government responses to the lessons learned from these two research activities. In brief, the descriptions of the seven experiments of concern were updated and coupled with a focused list of agents and toxins. All government-funded research performing one or more of the designated experiments AND using an agent or toxin from the list would be officially designated DURC and be provided additional oversight by the government and the research institution.

The US government guidance (1) includes a subset of the Biological Select Agents and Toxins (BSAT) that are regulated under Federal law (7 CFR part 331, 9 CFR part 121, and 42 CFR part 73), which are designated as the applicable DURC agents and toxins. These agents and toxins have the potential to pose a severe threat to human, animal, or plant health, or to animal and plant products [10]. An activity is designated DURC if any of the agents or toxins listed in Table 1 are used in an experiment with one or more of the attributes listed in Table 2.

NBACC Culture and Institutional Committees

The US Department of Homeland Security's National Biodefense Analysis and Countermeasures Center (NBACC) was established in 2006 as a national research and development resource in which scientific programs critical to biodefense could be conducted in a safe and secure environment. Since NBACC science commonly involves work with the biological agents listed above, tremendous emphasis has been placed on establishing an institutional culture in which safety and security are core values that reach into every part of the scientific and infrastructure operations. The emphasis on these values extends from

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a)	Avian influenza virus (highly pathogenic)
b)	*Bacillus anthracis*
c)	Botulinum neurotoxin
d)	*Burkholderia mallei*
e)	*Burkholderia pseudomallei*
f)	Ebola virus
g)	Foot-and-mouth disease virus
h)	*Francisella tularensis*
i)	Marburg virus
j)	Reconstructed 1918 Influenza virus
k)	Rinderpest virus
l)	Toxin-producing strains of Clostridium botulinum
m)	Variola major virus
n)	Variola minor virus
o)	*Yersinia pestis*

Table 1: Agents and Toxin Covered by the U.S. Government Policy for Institutional Oversight of Life Sciences Dual Use Research of Concern.

1.	Enhances the harmful consequences of the agent or toxin
2.	Disrupts immunity or the effectiveness of an immunization against the agent or toxin without clinical and/or agricultural justification
3.	Confers to the agent or toxin resistance to clinically and/or agriculturally useful prophylactic or therapeutic interventions against that agent or toxin or facilitates their ability to evade detection methodologies
4.	Increases the stability, transmissibility, or the ability to disseminate the agent or toxin
5.	Alters the host range or tropism of the agent or toxin
6.	Enhances the susceptibility of a host population to the agent or toxin
7.	Generates or reconstitutes an eradicated or extinct agent or toxin listed in Table 1

Table 2: Attributes of Dual Use Research of Concern experiments.

basic training programs in biological safety and operational security to more advanced mentoring tailored to the individual and their job, including BSL-3 and BSL-4 operations. The NBACC is also a CDC Tier 1 registered laboratory, and all employees with access to Tier 1 BSAT must enroll in a personnel reliability program (PRP) in which medical and psychological fitness are evaluated regularly to create an operational environment where work with BSAT is conducted in a safe, secure, and reliable manner [11].

The emphasis on staff training is combined with a robust framework for project planning and oversight in which all scientific projects are 1) evaluated to ensure appropriate safety and security measures are in place, and 2) reviewed to ensure full compliance with the Biological Weapons Convention (BWC) of 1975 [12]. In addition, projects are reviewed by the Institutional Animal Care and Use Committee (IACUC) and the Institutional Biosafety Committee (IBC) to ensure compliance with animal welfare rules and regulations and/or guidelines for research involving recombinant or synthetic nucleic acid molecules, as appropriate. Finally, scientific results are communicated by presentation or publication only after being reviewed by technical experts for any information that would undermine the biodefense mission. This model for planning and oversight, combined with the existing safety culture, produces an environment that guided and facilitated our DURC review implementation.

Implementation of DURC Oversight at NBACC

NBACC's first approach to institutional oversight of projects began in 2007, when all research projects received 1) an external compliance review conducted by the Department of Homeland Security (DHS), and 2) a formal sensitivity review of all external communications to ensure compliance with dual-use guidelines provided by the NSABB (3). The following year, a high level review for internal regulatory compliance was conducted prior to the start of project execution. This review was conducted by a small committee that included a scientist and the Health and Safety Manager. It was intended to ensure that all research projects at NBACC received appropriate institutional committee reviews—e.g., IACUC or IBC, and included an opportunity for comments on "other concerns," so the project's stakeholders could ensure all the appropriate safety and security measures were in place before the project began.

This initial approach to DURC oversight evolved into a formal project compliance and dual use screening process in 2011, when a subcommittee was formed under the Institutional Safety and Biosecurity Committee (ISBC). This subcommittee included subject matter experts from all relevant scientific fields, chairs of institutional committees, in addition to representatives from the Program Management and Health and Safety groups. A completed review was required prior to the initiation of any laboratory work. Transferring the screening function to this subcommittee allowed.

NBACC to Establish a More Structured Framework For Regulatory Review And DURC Oversight

A year later, the screening subcommittee was moved from the ISBC to the IBC because the DURC screening function seemed to align more closely with the IBC's function. The ISBC provides a forum for general safety concerns, whereas the IBC is more regulatory in nature. NBACC presumed that if the DURC review process were to become more formalized, it would be a straightforward transition to move the functions from the screening subcommittee to the full IBC, since the IBC had members with broad scientific expertise and the IBC already performed regulatory reviews. The process of screening did not change with this shift to the IBC.

In February of 2013, the White House Office of Science and Technology released the proposed policy on Institutional Oversight of Dual Use Research of Concern. This proposed policy formalized the oversight of life sciences dual use research by delineating roles and responsibilities of research institutions and life scientists in addition to establishing requirements and performance standards for review of research. It also identified categories of research that may have dual use potential and proposed strategies for the development and implementation of risk mitigation measures for DURC. NBACC was already meeting most of the requirements laid out in the proposed policy; however the screening subcommittee processes were not as structured as those suggested by the new policy. Given the new guidance, NBACC reexamined its process and determined that implementing DURC review under the IBC would be less than ideal, and that screening and DURC review would be done best within a committee dedicated to those specific functions. This was partly because the IBC is chartered to address research involving recombinant technologies and the DURC oversight was viewed as a dilution of this focus. Another contributing reason was the increased time commitment that DURC review of all research projects would put on the NIH-mandated community members of the IBC.

Given these facts, NBACC formed the Institutional Review Committee (IRC) in the summer of 2013, and it became fully functional by October 2013. Its purpose and scope are to review all NBACC scientific projects for DURC and identify any regulatory reviews (e.g., IACUC, IBC) that must be completed prior to project initiation. The committee was kept to a small size to maintain flexibility, and includes the chairs of the other institutional committees, a Health and Safety representative, a project management representative, a non-scientist, and an alternate. One of the keys to accomplishing a thorough but efficient DURC review of all projects with a small committee is engaging the research staff, particularly the PIs, and that was a primary goal as the IRC and its basic operating procedures were established.

The committee also implemented a training program for the NBACC research staff to ensure that both fundamental DURC concepts and the regulatory processes being implemented were fully understood by the scientists performing the projects.

The IRC's review process begins when the PI submits a project plan and a completed IRC DURC and Regulatory Screening Form. In addition to any required institutional committee reviews or approvals, this form guides the PI through a self-assessment in which the potential for DURC is identified. Projects and their assessments are reviewed along with any proposed risk mitigation strategies at a meeting of the IRC, and a majority vote is required for committee approval. If necessary, the IRC assists the PI to ensure appropriate risk mitigation plans are implemented prior to approval. The IRC Chair provides the results to the PI, and the form and meeting minutes serve as a record of the meeting's decisions and actions.

At NBACC, a risk mitigation plan is developed for each DURC project as a separate document that outlines the reason for protecting information associated with a project and the strategy that will be used to protect the experimental design, methods, and data. Risk mitigation strategies may include classification and other restrictions on dissemination of information associated with the project, requirement of additional reviews before project information is released, and/or additional laboratory physical security if necessary. Once a project is approved, the PI has the primary responsibility for ensuring implementation of the risk mitigation plan and informing the IRC of any significant updates to the project plan. The current review process has been very successful because it facilitates staff engagement and awareness in protecting the information associated with DURC projects throughout their life-cycle.

Conclusions and Guiding Principles

Which is the best approach for DURC review? Although there are obvious benefits and challenges to each of the approaches used at NBACC, several guiding principles have emerged:

- DURC review is complex and deciding whether a project has DURC potential often requires thoughtful review by key scientific subject matter experts as well as safety and security professionals.
- The primary responsibility for DURC review should lie with the PI since he/she plans the work, knows its impact on biodefense, and is in the best position to judge its risks. Placing responsibility and accountability on the PI ensures that DURC review continues throughout the project, and that staff on a given project are kept aware of the goals and risks.
- Engagement of the research staff including the IRC members requires simple and defined processes for submitting research proposals, conducting the review, and mitigating the risks associated with DURC. Training on these processes and the fundamentals of DURC must be done regularly by the IRC to ensure institutional compliance and to demystify the issues that DURC presents as well as the ways that the concerns are addressed.
- Implementation of DURC review is specific to the circumstances of each institution and should take into consideration the scope and volume of research performed. According to the US Policy on DURC, it can be done as a component of existing institutional committees' reviews or by a committee set up explicitly for DURC review. Regardless, a formal DURC review process performed by an institutional committee reinforces an awareness of risks and benefits in research and provides a framework for sponsor-required documentation.

The NBACC IRC and its processes, which include required reporting to the funding agencies, provide a successful model for DURC review in the US. While NBACC is a very specialized institution, the overarching conclusions and guiding principles identified here will be valuable to other life science research institutions where the implementation of DURC review and compliance is a relatively new challenge.

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