Stakeholder Engagement Workshop on the USG Policy for Institutional Oversight of Life Sciences Dual Use Research of Concern

National Institutes of Health
Building 10, Lipsett Auditorium
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Welcome and Introduction

Carrie D. Wolinetz, Ph.D.
Associate Director for Science Policy, National Institutes of Health

Dr. Wolinetz welcomed participants in the auditorium and those taking part by webcast.

The problem addressed by the Dual Use Research of Concern (DURC) Institutional Policy ("iDURC policy") is sometimes called the dual use dilemma. Beneficial biological research can sometimes be used for non-benevolent purposes. The dilemma for policy-makers is how to facilitate lifesaving biological research while still mitigating the potential risks of misuse. Equally, they must mitigate the risks of misuse without inhibiting the beneficial value and lifesaving benefits of biological research. Carrying out this delicate balance is the reason for this meeting.

Although the dilemma is often presented as a tension between those favoring biology and those favoring security, the truth is that there is a lot of common ground. Research is important, and it needs to be conducted and communicated responsibly. This commitment to the responsible practice of research includes human subjects protections, animal protections, and all communications. A balance has to be found between the benefits and the potential risks.

Dr. Wolinetz said it will be useful to hear the audience's thoughts on DURC and especially on the iDURC policy of September 24, 2015.

NIH's role in DURC policy includes management of the National Science Advisory Board on Biosecurity (NSABB), which advises the U.S. government on dual use and other biosecurity issues and makes reports and recommendations. Managing DURC is an interagency process

that requires cooperation. Although the policy may be associated with NIH in many people's minds, it is actually a U.S. government policy.

The day's meeting agenda included hearing from the White House Office of Science and Technology Policy about the current DURC policy landscape, discussions with experts on the practical experience of implementing the iDURC policy, an interactive case study on the policy, and discussion of outreach and education with respect to the iDURC policy.

Dr. Wolinetz emphasized that she and policy-makers are eager to hear from stakeholders in the research community. Their experience in actual implementation of the policy makes them experts, and their feedback improves the policy. Policy-makers can be reached at any time by sending an email to durc@ostp.gov. The webcast of this meeting is being archived.

Overview of the USG Policy for Institutional Oversight of Life Science Dual Use Research of Concern

Susan Coller-Monarez, Ph.D.
White House Office of Science and Technology Policy

Dr. Coller-Monarez said that the best policy will come from discussion among government, industry, and academia, with input from international partners. Regular meetings are held to ensure that different parts of the government have the same understanding of policies.

Life sciences research is crucial. It supports biomedical and public health advances; improvements in agriculture, safety, and quality of our food supply; environmental quality; strong national security; and a strong economy. Fear of misuse cannot lead to stopping life sciences research. The benefits of DURC must be considered along with the risks.

Dr. Coller-Monarez offered definitions of two terms to be used throughout the day.

Dual use research (DUR): research conducted for legitimate purposes that generates knowledge, information, technologies, and/or products that can be utilized both for benevolent and harmful purposes.

DURC: 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, material, or national security.

The recognition of DURC has happened gradually over the past decade and a half. Dr. Coller-Monarez reviewed some of the major events that have raised concern.

In 2001, an Australian lab published the results of an experiment in which the interleukin-4 gene was introduced into a mousepox virus. The modified virus was more potent. Concerns were raised that this knowledge could be used for nefarious purposes. That case led to a robust dialogue within the government.

In 2002, a research team published the results of an experiment in which poliovirus was assembled from oligonucleotides.

DURC is not only found in bench science. In 2005, a modeling paper examined the vulnerabilities of the milk supply chain to botulinum toxin contamination. There are many ways to cause harm with biology.

In 2011, two research teams announced results on what mutations can make the H5N1 avian influenza virus spread between animal models. This was important knowledge about virulence of those pathogens. However, the work could also be used by someone whose intention was not to enhance public health and safety. That work led to the federal government's DURC policy, often referred to as the March 29, 2012, policy.

In 2014, vials of smallpox and other pathogens that had not been inactivated for shipment were discovered and were held stored in an insecure place.

The goal of the government's DURC policies is to preserve the benefits of life sciences research while minimizing risk of misuse of knowledge, information, products, or technologies that come from such research. The policies were developed in response to incidents such as those listed. The key is to balance the need for caution and the need for productive life sciences.

Relevant policies include:

- HHS Framework for Highly Pathogenic Avian Influenza Research (2012)
- USG Policy for Oversight of Life Sciences Dual Use Research of Concern (March 29, 2012)
- USG Policy for Institutional Oversight of Life Sciences Dual Use Research of Concern (September 24, 2014) - the policy being discussed at this meeting
- USG Gain-of-Function Policy (under development)

The new policy uses a list of 15 agents identified in the March 29, 2012, policy. All of the agents are known to cause harm to human or animal health. Manipulating them in a variety of ways could lead to a pathogen with enhanced characteristics.

- Avian influenza virus (highly pathogenic)

- *Bacillus anthracis*
- Botulinum neurotoxin (any quantity)
- *Burkholderia mallei*
- *Burkholderia pseudomallei*
- Ebola virus
- Foot-and-mouth disease virus
- *Francisella tularensis*
- Marburg virus
- Reconstructed 1918 influenza virus
- Rinderpest virus
- Toxin-producing strains of *Clostridium botulinum*
- Variola major virus
- *Yersinia pestis*

The policy also lists seven experimental effects that make research subject to the policy:

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 the policy

The lists of pathogens and experimental effects are set in the policy, but dialogue is still needed on which research is potentially risky. Under the policy, if an institution is working on one of those 15 pathogens and there is a potential to have one of the experimental effects, that is consistent with DURC.

However, there is a third step: determining whether research meets the definition of DURC—whether it can be reasonably anticipated to provide information, products, or technologies that could be directly misapplied. It is important to make sure that all three criteria are properly applied.

If an institution has research that meets all three criteria, the next step is to develop a risk mitigation strategy. There are many potential questions, such as the following: Which risk mitigation strategy is the best for a particular research program? Which will meet the needs of a funding agency? This difficult task requires open dialogue, such as this meeting.

Institutions have responsibilities at many levels. Two key institutional responsibilities are establishing and implementing policies and practices for identifying and overseeing DURC and notifying the funding agencies. Key responsibilities for principal investigators (PIs) include making sure that the work being done on their behalf with federal funding is identified and referred to the Institutional Review Entity (IRE). It is the PI's responsibility to be aware of the situation with DURC and to communicate it to lab members throughout the research process.

The IRE must have at least five members who understand the government policies and have a broad range of expertise. This should include scientists who understand the research. This committee is responsible for verifying that research involves one of the 15 agents and could have one of the seven experimental effects. The committee must also determine whether the research is DURC. If the research is determined to be DURC, the IRE is responsible for developing and reviewing the risk mitigation plan. The Institutional Contact for Dual Use Research (ICDUR) is the person who acts as a liaison between the institution and the funding agency. Dr. Coller-Monarez also reviewed the responsibilities of U.S. government funding agencies, as described in the policy.

Dr. Coller-Monarez directed participants to the information at the Science Safety Security website and encouraged anyone with questions about implementing the policy to use the previously mentioned email address, DURC@ostp.gov.

Case Study

Moderator: Lt. Marcienne Wright, Ph.D.
Office of Planning and Policy, ASPR, HHS

Dr. Wright led an interactive experience based on a case study. The case study involved a fictional scientist, Dr. Jameson, at a fictional institution, Boyle University, which receives funding from several U.S. government agencies, including NIH. Paper copies of the case study, including discussion questions, were handed out in the auditorium. The case study can be found online in pdf form. Throughout the interactive session, Dr. Wright gave participants opportunities to read the narrative and then shared relevant information and answers to the discussion questions.

The objectives of the exercise were to define DURC, to understand the scope of the institutional DURC oversight policy, and to clarify the roles and responsibilities of the institution, PI, IRE, ICDUR, and the government.

Part 1 introduces Dr. Jameson, a tularemia expert who is new to the university. He is interested in a particular pathway of the secretory system of *Francisella tularensis*, which causes tularemia. The institutional biosafety officer approves his use of a particular strain of the organism in BSL-2 conditions. Because the experiment uses an attenuated organism, it is not considered one of the 15 agents listed in the policy.

On page 3 of the case study, Dr. Jameson proposes a new experiment using a non-attenuated, virulent strain. This is on the list of 15 agents. His experiment is not expected to produce any of the seven experimental effects, so it is not DURC, but because it involves one of the agents, it is subject to the policy. At this point, Dr. Greenore, the chair of the university's Institutional Biosafety Committee (IBC), should tell Dr. Jameson about the policy, introduce the ICDUR, and introduce the IRE process.

Dr. Jameson's research was registered with the Federal Select Agent Program at his prior institution, so there are no problems anticipated with getting approval to do the work. However, an attendee pointed out, he does need to register at his current institution.

An attendee suggested requiring anyone who is working at BSL-2 to participate in online training that would include introducing the DURC work. Another attendee suggested adding a few lines about DURC to IBC applications.

In the next section of the case study, Dr. Greenore sends Dr. Jameson to talk with the ICDUR. The group briefly discussed who could function in this role at an institution. It could be a select agent responsible official or a vice president for research, for example. The ICDUR will communicate with the funding agency.

On page 5, Dr. Morrison, the ICDUR, explains the policy and the role of the IRE to Dr. Jameson. The group came up with a brief list of people who might be included on an IRE:

- senior research administration
- science faculty members
- lawyer
- a risk management person from the university
- the IRB's ethicist
- communications/public affairs can be very helpful if they are involved from the beginning
- a representative from the Institutional Animal Care and Use Committee
- a representative from the campus police or department of public safety

The fictional IRE in the case study considers Dr. Jameson's research and concludes that it is not DURC because it is not expected to produce any of the seven experimental effects.

In part 2 of the case study, Dr. Jameson wants to carry out a new experiment with *F. tularensis* that involves modifying a surface protein. Because the research could help the organism evade host immunity, this does now meet the second criterion for DURC. Dr. Jameson should consult the IRE and have the work reviewed and approved before it starts.

Next, the IRE has to determine whether the experiment meets the third criterion, having the potential to be directly misapplied. The outcome of this deliberation must be communicated to the funding agency, whether or not the IRE determines that the research meets the definition of DURC. The IRE has 30 days to notify the funding agency of the outcome of the IRE decision. The ICDUR is responsible for notification. The draft risk mitigation plan must be submitted to the funding agency within 90 days. If there are multiple funding agencies, the ICDUR might contact NIH to triage the evaluation to the appropriate funding source. However, an attendee said, usually each experiment has only one funding agency.

After being notified of the IRE decision, the funding agency has 30 days to respond. However, it emerged in the discussion that it is not clear whether the researcher must wait for a response or approval from the funding agency before beginning the experiment. An attendee suggested that, if nothing in the policy requires waiting, it should be possible to forward.

An attendee asked how the institution can get funding to support the IRE processes and the development of the risk assessment and risk mitigation plan. Dr. Wright said the IRE is an activity the institution undertakes to have a research program.

In part 3 of the case study, the IRE and Dr. Jameson embark on the next step: developing the risk mitigation plan. Risk mitigation possibilities mentioned by attendees include respiration protection, enhanced monitoring of the laboratory with security cameras, and implementing a rule about not lending any *F. tularensis* to other researchers.

Publication is a difficult subject. An attendee suggested a journal of dual use research with limited distribution.

An attendee asked whether some agencies lean toward a policy of moving to classify DURC. An NIH representative said the vast majority of DURC should be openly conducted and openly communicated. However, retroactively classifying research is very difficult, which is why the policy encourages discussion from very early on. Another attendee mentioned that funding agencies should also be having these discussions before providing funding in the first place.

An attendee asked how to make sure, once a decision is made, that all relevant committees are apprised and approve of a decision. Dr. Wright said all committees should be communicating with one another.

An attendee mentioned that IBC meetings are usually public and the committee includes members of the community, so they should be transparent. The IRE's policies and procedures must be publicly available.

Dr. Wright concluded by mentioning that education and training on the policy are an integral part of the project. PIs must provide annual training on the iDURC policy for any individuals conducting research on one or more of the 15 agents. Also, she said, federal government funding agencies have a responsibility to engage in the dialogue.

Panel: Institutional Approaches: Processes for Identifying and Reviewing Research Subject to the Policy

Moderator: Samuel S. Edwin, Ph.D.
Chief, Biosecurity Division, United States Army Medical Research Institute of Infectious Diseases

Dr. Edwin introduced the panelists, and each panelist gave a brief presentation.

Institutional Approaches: Processes for Identifying and Reviewing Research Subject to the DURC Policy

Trevor Ames, D.V.M.
Dean of the College of Veterinary Medicine, University of Minnesota

Collegiate units need to be actively involved in identification of DURC and compliance with the policy, Dr. Ames said. The potential threats of DURC are huge, including human illness and death, catastrophic animal and plant disease, and disruption of the food supply.

In Minnesota, the H5N2 influenza epidemic devastated the poultry industry in the spring of 2015. In the states, the outbreak affected 108 farms, with more than 9 million birds lost and a cost of $650 million. The disease had 90 percent mortality. It appears to have spread by aerosol following wind events. This represents a new biosecurity threat. Dr. Ames speculated about the terrible effects of this outbreak if it had happened because of a lapse in laboratory procedures at the University of Minnesota. It would have led to serious effects for land-grant universities and maybe for federal funding. He emphasized that this was not how the outbreak began but only a hypothetical situation.

The food and agriculture sector has been designated as one of 16 critical infrastructure sectors by the Department of Homeland Security.

The people in charge of institutional oversight must be able to have a nuanced and thoughtful discussion of the risks. Dr. Ames noted that many other research projects could be harmful and are not on the list of 15, such as many plant diseases. Fortunately, he said, universities have a tremendous wealth of human resources available when they assemble these committees.

Dual Use Research of Concern

Robert Ellis, Ph.D., CBSP, SM (ASM), ACVM
University Director of Biosafety, Colorado State University

Dr. Ellis reviewed how his institution is finding possible DURC at the institution. In 2009, they added a question to the Project Approval Request Form that PIs submit to the IBC that asks whether any of the research is DURC. It is a simple "yes" or "no" question that flags relevant research. In 2015, Colorado State University (CSU) added a more detailed question to the form.

At CSU, the IRE will be the same committee as the existing IBC. The ICDUR is the university's vice president for research.

Dr. Ellis identified several issues to be resolved. This includes

- agents that have the potential to be DURC but are not on the list,
- what to do with publications such as the one on botulinum toxin in the milk supply, and
- what to do about research issues such as the Australian mousepox research, with accidental gain of function.

From an ethical standpoint, Dr. Ellis said, the institution should also be considering issues such as these, not only the 15 agents. The timeline should also be considered, he said; if the research is classified as DURC, the waits for notification and enactment of a mitigation plan can constitute an impediment to research.

Dual Use Research of Concern—How We Do Things at St. Jude

Philip Potter, Ph.D.
DURC Sub-Committee Chairman, St. Jude Children's Research Hospital

Dr. Potter noted that St. Jude is best known for cancer research, but it also has a large influenza program funded by the National Institute of Allergy and Infectious Diseases (NIAID) and the World Health Organization. The researchers work with flu samples from around the world. Much of the work is categorization, but they do also insert segments of viruses into other viruses, which means the work qualifies as DURC.

The St. Jude system is similar to that described for CSU, in that it includes an online submission form for IBC protocols and amendments. The form lists the seven questions; a "yes" answer to anything triggers review. Any member of the IBC can suggest review of a protocol for DURC potential. St. Jude reviews all the highly pathogenic avian influenza (HPAI) research to consider the possibility of DURC, even if the scientist answers "no" to all the questions.

The St. Jude DURC subcommittee includes

- Dr. Potter.
- 2–4 faculty experts in the proposed research area.
- Biological safety officer (BSO).
- Director of Environmental Health & Safety.
- IRB coordinator.
- Staff from scientific editing because at some point this information is likely to be published. Communications and public relations staff are not involved until later.
- Legal counsel.

The PI delivers a detailed proposal in advance; at the meeting, he or she presents the research and discusses it with the committee members.

Dr. Potter described two areas of difficulty:

1. The wording of the fifth of the seven experimental effects captures all research in which the host range or tropism of the agent or toxin is altered. The problem is the word "altered." This means they spend a lot of time reviewing protocols in which researchers are making viruses *less* pathogenic. If the policy said "increases" instead of "alters," these studies could be ignored.

2. H7N9 is not on the list of 15 agents, but the committee is worried about it. They created a new category called "durc," in lowercase, but having a new category creates new problems.

Q&A

An attendee asked if this process creates a bottleneck for research.

Dr. Potter answered that the committee has reviewed only about a half-dozen protocols since it started operating in 2012. People who work on influenza know that this will happen, he said, and many are directing their research away from potential DURC. Also, the vast majority of the work at St. Jude is surveillance. Very little research will potentially be DURC. An institution with more protocols to review could find this to be a much more time-consuming process.

An attendee asked Dr. Ellis the same question.

Since 2009, Dr. Ellis said only three people have checked “yes” to the question about whether the research could possibly be DURC. They were dealing with pathogenicity, and someone would have had to take several steps to twist the research to be DURC. With eight of the agents in active protocols, he said, he expects to have more to look at. He said he is not concerned about a bottleneck at CSU, but rather a delay in responses from funding agencies.

An attendee asked about clinical research at a large medical institution in which a researcher is using Botox but off label. Botox is FDA approved, so under the select agent standard, it is theoretically exempt. However, if it is being used off label, it is technically not approved for that particular use.

Dr. Edwin answered that, if the work is classified as research, it has the potential to be considered DURC.

The questioner expressed dismay.

Dr. Ellis mentioned using Botox for tumor destruction. Even though it is well under the limit, it is still necessary to make sure that no one is collecting Botox in amounts under the threshold and combining them. CSU has a mechanism for keeping track of every microgram of botulinum toxin.

Dr. Potter asked how a new agent might be identified and added to the list.

Dr. Edwin mentioned Middle East Respiratory Syndrome (MERS) and H7N9. He noted that a PI is often focused on their specific research question and does not think about ways the results could be misused. U.S. Army Medical Research Institute of Infectious Diseases has a large select agent program, so a team reviews every research protocol at the inception and again at the end for operational security.

An attendee asked whether researchers are censoring themselves.

Dr. Edwin said he has a good relationship with all of the investigators. Committees that are reviewing the research maintain close communication to keep the process moving. The primary goal is not to make the policy restrictive but to follow the regulations. The PI must feel included, with no negativity attached to the process.

Dr. Potter says St. Jude has struggled with that problem. While there are probably viruses circulating in the environment that are worse than what researchers are using in the lab, the public perception is that flu research is dangerous, he said. That can make scientists want to avoid doing key experiments that could have major benefits for public health.

An attendee asked what resources and training university leadership has provided for this activity.

Dr. Ames said DURC work has been handled under the existing support for the IBC. Dr. Ellis said the vice president for research at CSU is supportive, but there has been no financial support for this work, which will mean more responsibilities and longer meetings for the IBC and possibly more frequent meetings. He does not know yet how they will handle the increased workload. The goal is not to impede the research, he said. Dr. Potter said St. Jude has employed two new people in the last four years: a manager and a person who handles paperwork for the IBC.

An attendee asked whether the information from the IRE is freely available for projects that might be considered DURC.

Dr. Ellis said this comes back to how to publish scientific research so that it is useful but not usable as a pattern on how to do bad things. Dr. Potter said the minutes from subcommittee meetings include important information but not all the details.

Panel: Institutional Approaches: Developing Risk Mitigation Plans

Moderators:
Dennis Dixon, Ph.D.
Chief, Bacteriology and Mycology Branch, NIAID, NIH

Joe Kozlovac, M.S., RBP, CBSP
Biological Safety Officer, ARS-USDA

Dr. Dixon briefly introduced the panel and his own history of working with select agents. Many of the bacterial select agent pathogens are handled through his branch at NIAID. He served on federal committees that helped frame the first two select agent rules. Each panelist gave a brief presentation.

Untitled Presentation

Joseph Kanabrocki, Ph.D., CBSP
Associate Vice President for Research Safety, University of Chicago

Dr. Kanabrocki explained the organization at the University of Chicago. Governance structures play a large role in mitigation of risk. He is concerned with the Ricketts Laboratory, a state-of-the-art biocontainment lab built with funding from NIAID on the campus of Argonne National Laboratories. The location means it has many layers of security. It is on a closed campus with

security guards at the entrance. It also has security at the level of the facility and at individual laboratories. The select agent program is entirely at the Ricketts Lab. Researchers with the lab also work with other pathogens that are not select agents.

The chair of the Ricketts Lab select agent committee is also a member of the dual use task force. The task force also has representation from the veterinary staff, an attorney, and the chairs of both IBCs. The task force reports to the IBCs, but the deliberations of the task force are not part of IBC minutes.

The task force carries out an initial review of the grants before they are submitted and a continuing review synchronized with the annual progress report process usually required by funding agencies. They also review the manuscript in collaboration with the funding agency.

When the PIs write progress reports, they are supposed to report to the task force. A set of questions are added to the IBC's standard electronic process, which PIs go through when they register their work. In the review, the task force asks questions about the seven experimental effects and adds an eighth question that is triggered by a "yes" to any of the questions about the seven experimental effects: Does this potential outcome have an immediate threat to public health and security? This question eliminates a lot of work related to altered tropism.

Their evaluation of biosafety risks includes the potential for the strain of concern to evolve naturally. They also consider the susceptibility to antimicrobial therapy and make sure that the occupational health, medicine, and surveillance program are robust. They have also developed profiles of the pathogens to instruct a clinician on how it should be treated.

Their process for management of inventories is rigid. Close attention is also paid to staff. Members of the research staff must sign a code of conduct document every year.

The benefits side of the DURC risk–benefit analysis needs to be more clearly articulated, Dr. Kanabrocki said. This research has benefits to society and public health. The benefits need to be explained to the public, along with the steps to take to mitigate the risk. Institutions also need to make the argument that *not* doing the research poses a risk to public health. The loss in public confidence poses a risk and has a negative impact on the industry, Dr. Kanabrocki said, as some investigators leave the field and students choose not to enter it.

DURC Review and Development of Risk Mitigation Plans

Rebecca Moritz, M.S., CBSP, SM (NRCM)
Select Agent Program Manager, University of Wisconsin

At the University of Wisconsin, the IRE is a subcommittee of the IBC. Ms. Moritz is the ICDUR. The subcommittee includes an associate professor of virology, an associate professor of medicine, an infectious disease physician, and others. Each member of the subcommittee reviews materials and comes to the meeting with an opinion. They have sometimes decided that work is technically DURC but is still worth doing.

Research is also reviewed by a biosecurity task force. This is a diverse group, including associate deans for research, representatives from university communications, the director of information security, and the police department, among others. Everyone in the group has a stake in the safety, security, and risk mitigation of research with pathogens at the university.

Questions asked of researchers include:

- Is there anything unique about your facility?
- What biosafety level do you work at?
- Is it higher than you need?
- Are vaccines available? If so, have relevant personnel received it?

Because the University of Wisconsin is a public institution, research is not considered complete until it is appropriately communicated. Questions to be considered include the risks and benefits of publication, the value of the research to science and to the public, what biosafety and biosecurity measures have been used, and any media talking points or press releases that should accompany publication.

DURC Review at ISM-MS

Philip Hauck, M.S., M.S.H.S., CIH, CBSP, SM (NRCM)
Institutional Biosafety Officer and Responsible Official, Icahn School of Medicine at Mt. Sinai (ISM-MS)

Mr. Hauck went through the example of a review from 2012 with a group studying host-specific functions of H5N1 polymerase. The group indicated on the forms that they were working with a virus on the list of agents and decreasing its virulence. They were able to study the question using an attenuated version of the virus. The research team also explained the potential benefits of the work. Reviewers agreed that the work was important and that it was not DURC. The work has since been published.

Q&A

An attendee asked the panelists how they intend to address information technology security.

Ms. Moritz said the University of Wisconsin began considering vulnerabilities in this area in 2011–2012. There are building controls to make sure the university meets the requirements of the select agent program. The university is in the process of giving researchers encrypted laptops, which is expensive and particularly difficult under the funding constraints in Wisconsin.

An attendee mentioned the issue of public trust and how it relates to transparency and the need to better communicate about the process of risk assessment. She asked whether there are parts of the process that can be made publicly available, or if they could be released after some time has elapsed, so the public can see how the process works.

Dr. Kanabrocki said that articulating the risks and benefits requires hard data and he thinks the public will be interested in that.

An attendee asked about the appropriate time frame to produce a risk mitigation plan.

Dr. Kanabrocki said the process at the University of Chicago begins with the PI's assessment. PIs are motivated and complete this promptly. The task force tries to finish within two weeks. Funding agencies have responded quickly. Ms. Moritz agreed and noted that it depends on when the PI's notification falls in the cycle of meetings. They will have to wait until the meetings unless there is a hard deadline for a funding agency, in which case the committee can adjust. Mr. Hauck said PIs reach out to him and the relevant committee chairs before the grant process begins and they move quickly.

Dr. Dixon asked how the institutions identify potential DURC and whether they are dependent solely on the PI to self-identify.

Ms. Moritz said her IBC has also identified potential DURC in IBC protocols and sent them to the DURC subcommittee. They have also looked at a handful of agents that are not one of the 15 agents. Dr. Kanabrocki is aware of which PIs may be doing this kind of research. Mr. Hauck is on multiple committees, so very little potential DURC escapes him.

The group briefly discussed botulinum toxin again. Research use of botulinum toxin happens primarily among gastroenterologists and neurologists.

An attendee asked whether any of the panelists had examined various risk mitigation measures and concluded that the only option is to either significantly alter the experiment or to not do it at all.

Dr. Kanabrocki said that had not happened. He noted that the risks are not limited to those 15 agents. His group has been trying to cast a wider net and educate the research community about DURC even if they are not working with one of the 15 pathogens. Some of the classic cases do not involve any on the list of 15 agents.

Outreach and Education on Dual Use Research Issues: Activities of the National Institutes of Health and the U.S. Government

Ryan Bayha
Senior Analyst for Biosecurity and Biosafety Policy, NIH

Mr. Bayha presented information on the array of DURC outreach and education resources that have been developed by the U.S. government for institutions and investigators. The general public is very interested in these issues, and they might be less worried if they knew how many talented people are working on keeping them safe, he said.

The goals of outreach and education efforts, including promoting awareness of the dual use issue, keeping the research community up to date on the status federal policy-making, promoting input from stakeholders, and sustaining a culture of responsibility.

One of the ways this is accomplished is through exhibits and posters at major scientific meetings. They have a colorful, eye-catching booth that gets a lot of attention. They have also offered posters on NSABB and Dual Use Research in the Life Sciences.

The new educational poster uses colorful design and graphics to reach investigators who may be working with one of the agents and instructs them to contact the ICDUR. A video from about 2008 provides a conceptual introduction to the dual use issue. More than 5,000 copies of a brochure about dual use in general have been distributed to institutions. NIH also offers a brochure that is specifically for PIs who work with one of the agents.

Dr. Bayha and his colleagues also make many presentations on the dual use issue, NSABB activities, federal policy-making, and related issues. Their slides are on the Science Safety Security (S3) website, http://www.phe.gov/s3/dualuse/Pages/default.aspx. There are about 50 slides, with the idea that only the useful slides can be selected for any particular talk.

NIH's course offerings on IBCs are primarily about IBC operations but also provide information about DURC and the dual use issue.

To keep the research community current on the status of the federal policy-making process, including the activities of NSABB, the Office of Biotechnology Activities offers a biosecurity

website with information on the NSABB, its meetings, and its work products. The website also offers an email address for public queries. The website is also a place to find work products from NSABB and information about their activities. The NSABB FAQ provides information on DURC and other topics. The FAQ is a living document; more will probably be added after this meeting, Mr. Bayha said.

The Office of Science Policy also has a policy blog and public meetings. The comments provided by attendees at this and other meetings help form the policies.

The iDURC policy was issued September 24, 2014, and institutions and federal agencies were given one year (until September 24, 2015) to put the policy in place, to leave enough time for training and planning. The Companion Guide that was distributed at the meeting is a very important resource for implementing the policy. While the policy is only 13 pages long, the companion guide is 86 pages. It can answer most general questions about the policy. It includes templates that institutions can use, if they wish, in fulfilling the policy requirements.

The website also offers case studies that provide a range of examples of research subject to the policy. The interactive case study from the morning session is a good training exercise for IREs, because it is interactive and engaging. It can be amended to fit a particular committee's procedures.

Future outreach and education plans include a webinar for ICDURS and others and a continued presence at key society and association meetings.

DURC is a global issue, so international engagement is also part of the outreach and education plan. The objectives include raising awareness of DUR internationally and getting global perspectives on DUR and DURC. Mr. Bayha and his colleagues have identified individuals, countries, and organizations that are active globally on issues related to DUR.

Mr. Bayha recommends the S3 website for additional information on the iDURC policy.

An attendee asked how compliance will be monitored.

Mr. Bayha said the policy depends on trust. When researchers accept an award, they sign a statement saying they are complying with many guidelines and policies. The office will have to decide on a case-by-case basis what to do about noncompliance. He said that noncompliance is usually caused by a misunderstanding or lack of awareness. The first approach is to reeducate about the policy and then to work with the institution to make sure it is in compliance in the future. The approach is to handle it as a partnership, Mr. Bayha said.

Panel: Institutional Approaches: Raising Awareness and Educating About DURC

Moderator:
Cheryl Doerr
Compliance Assurance Program Manager
Department of Homeland Security

Each panelist gave a brief presentation.

Institutional Approaches: Raising Awareness and Educating About DURC

Stephen Higgs, Ph.D.
Associate Vice President for Research
Director, Biosecurity Research Institute, Kansas State University

Dr. Higgs described how Kansas State University (KSU) has been handling DURC but noted that the procedures will change somewhat with the new regulations. For all research on biological agents and toxins, PIs are required to submit a registration document to the University Research Compliance Office (URCO). All staff involved in the research must complete training. Different online training modules are assigned, depending on the particulars of the research. Participation is tracked through staff logins. The training is based on NIH training programs. All researchers at KSU will be required to have training on DURC every three years.

Dr. Higgs noted that the PI is the person with ultimate responsibility for biosecurity in their lab. At KSU, the PI is supposed to inform the ICDUR and the URCO about all research with the potential for DURC. In the IRE meeting, the group discusses whether the research is DURC. The PI can ask for an appeal if the IRE determines their work is DURC.

Training at Duke University on the USG Policy for Institutional Oversight

Richard Frothingham, M.D., CBSP
Director, NIAID Regional Biocontainment Laboratory at Duke Medicine

Dr. Frothingham is co-chair of the Duke IBC and IRE. Duke has been reviewing dual use research since 2003. They reviewed many kinds of protocols and published on their experiences in the journal *Science* in 2007.

Most biological research has some dual use potential, Dr. Frothingham noted. When the university began asking PIs, most did not understand the concept, so they could not review their own research for it.

Often the committee was able to agree that the research was not a problem. Sometimes the Duke IBC members could not reach consensus on the classification of dual use potential for specific protocols. This was before DURC had been defined. However, the committee could still agree on management strategies. These strategies include education, contingency plans, and changing the research plan to avoid the dual use potential.

All researchers working with any of the 15 agents are required to have training. This is straightforward and happens as part of the select agent training each year. They plan to train all Duke personnel who conduct research with botulinum toxin but have not identified any. He said that research labs have given up studying botulinum toxin.

Different groups need different amounts of information. Gatekeepers such as the people who review grants contact Duke's Biological Safety Officer, who is also the ICDUR, if research involves any of the select agents or any botulinum toxin. Researchers receive training on iDURC. IRE members need broader training.

Dr. Frothingham concluded with another example of dual use technology that is misused many times each month with fatal consequences: the automobile. We need the technology and are not going to give up automobiles. However, they can also be used as car bombs. This risk can be managed with vehicle barriers, checkpoints, mirrors, or an open-chassis design.

Institutional Approaches: Raising Awareness and Educating About DURC

Patricia Olinger, RBP
Assistant Vice President, Office of Research Administration
Executive Director, Environmental Health and Safety Office
Emory University

Ms. Olinger introduced the Emory Biorisk Management Program. All investigators at Emory are required to submit a notice of intent that describes the research they plan to conduct. Even before that, Emory labs are all required to be registered with the research safety group. As they come into the university, researchers are asked whether they are going to be working with biological agents. They are required to update their answer each year. If they click "yes" they are given the list of 15 agents.

Currently, the IBC reviews all applications with recombinant DNA work. All other applications are reviewed by the Research Health and Safety Committee (RHSC). The protocol will not be reviewed unless the laboratory is up to date on inspections and training.

Emory currently is not a Select Agent Approved site. Emory is part of a center of excellence for influenza research, in collaboration with the University of Georgia. UGA is responsible for the

select agents portion of that work. Researchers at Emory use some low pathogenic influenza strains.

The issue of training is complicated. Researchers find it frustrating to have requirements for more training. The experience with Ebola has shown that training is often not effective. A person might check the box to indicate that they knew about personal protective equipment. However, it is very difficult to put this equipment on correctly. The people who enforce these policies need to think about the effectiveness of training and whether it is achieving its goals. With some of the PIs carrying out higher-risk research, staff meet individually to talk about what needs to be done and how they can help.

Support staff members who need training include those on the biosafety and research safety staff and the IBC-RHSC staff. People who work with grants and contracts also need training, Ms. Olinger said.

Ms. Olinger said her staff is working in a collaborative team with research staff. The goal is to understand one another's needs and to establish relationships. While she expects all of the requirements to be met by September 24, 2015, she thinks she will still have a lot of work to do.

An attendee asked Dr. Higgs how an appeals process will affect reporting to the funding agency. Will it delay reporting?

Dr. Higgs said they do not know yet. He expects the review process to be rapid.

Gerald Epstein, Ph.D., Department of Homeland Security, thanked the speakers for sharing their experiences. He was interested in the Duke experience that even committee members who could not agree on whether something had potential for misuse could agree on a management plan. He also mentioned that having a clear process for reviewing research makes it much easier to defend the institutions to the public.

An attendee asked about research funded by non–U.S. government sources.

Dr. Frothingham said Duke has some collaborations with Novartis that could potentially involve high-path avian influenza. Because Duke receives NIH research funds, everything is covered by the NIH guidelines on recombinant DNA, he said, and if high-path avian influenza is involved, he plans to contact Mr. Bayha for advice.

Open Forum for Stakeholder Input/Future Directions

Moderators:
Dr. Coller-Monarez

Frank Schaefer
Microbiologist, U.S. Environmental Protection Agency

Dr. Epstein
U.S. Department of Homeland Security

Mr. Kozlovac

Mr. Edwin

Mr. Bayha

Dr. Coller-Monarez asked the audience for any questions they would like to ask these federal representatives.

Kimberly Orr, D.V.M., Ph.D., Department of Commerce, told the attendees about two federal register notices related to the issue of publication restrictions. June 3, 2015, was for the EAR and ITAR definitions and June 17, 2015, is category XIV, which involves biological research. Both can be seen on the Department of Commerce website or at the federal register. There is still time to comment on both.

Dr. Coller-Monarez commented that the issue of post-manuscript and prepublication development has been a topic of much discussion. How can the DURC sensitivities be appropriately communicated?

Rebecca Ryan Caruso, Harvard Medical School, shared that her IBC has been challenged by what to do with research that does not involve one of the 15 agents. She asked whether originally harmless bacteria that are engineered to produce federally regulated substances, such as harmless *E. coli* altered to produce a drug, be considered DURC?

Mr. Bayha said research is not subject to the policy unless it involves one of the 15 agents on the list. However, he encourages institutions to contact the program officer or funding agency in case they have any recommendations. The policy recognizes that there may be many other projects that are DURC but do not include one of those 15 agents. For now, it is limited to those 15 agents so policy-makers can see what implementation is like.

Dr. Epstein seconded the suggestion to contact the funding official. It is important for them to know the other things outside the formal policy that are raising questions. This helps them evaluate the policy.

Dr. Schaefer said that both the 2012 and 2014 policies are about a culture of responsibility, and institutions should also be considering the dual use potential of research that is not covered by this policy.

Dr. Edwin mentioned the example of monitoring synthetic genes. Whenever institutions identify something with potential for dual use, there should be a plan.

An attendee asked whether citing or referencing previously published material that could be DURC is a problem or about a situation in which publishing a new piece of information on a previous project could complete the picture and make it possible to apply that research in a negative way. He asked for guidance on how to treat things that have already been brought.

Dr. Coller-Monarez called this the "DURC by compilation" issue. She said the question is how to evaluate, if three pieces of the puzzle have been published, what should be done about the fourth piece.

Dr. Epstein said the policy does not apply retroactively to research that has already been published. Part of the risk–benefit assessment for new research covered by the policy should involve considering it in the context of previously published research.

Mr. Bayha noted that the fear of redaction and classification is a common theme through the day. The government's default position is free and open communication, he said. In limited circumstances, it might be necessary to restrict something, but that should not be normal. The task is to avoid stigmatizing this kind of research to the point that researchers avoid it. Only a small subset of projects will be determined to be DURC.

Dr. Epstein said the government, in many cases, has no legal authority to prevent publication. Instead, researchers and institutions would make decisions not to publish.

The same attendee asked, if research is done in collaboration with a lab outside of the United States, whether being listed as an author on a paper with DUR would be a problem.

Mr. Bayha said it is the funding that matters, not the paper.

Sherry Bohn, Ph.D., University of Maryland, described some of the problems with implementing the policy. For example, finding members for a new committee without funding is very difficult. She asked for advice on post-approval monitoring.

Mr. Bayha agreed that post-approval monitoring is a problem. If researchers think of a new experiment, they are unlikely to contact their IBC or IRE. Instead, you need to go to the investigator and ask whether anything has changed, Mr. Bayha said. Mr. Edwin encouraged institutions to review researchers' progress reports; that will show changes in the procedure. Also, combining chores can help, for example, talking with the PI during lab inspections. Mr. Bayha suggested engaging deans, whose emails are more difficult to ignore than an email from someone involved with biosafety.

Patrice Binder, French National Institute of Health and Medical Research, said France has a similar approach to the United States. France does not have a strong policy on dual use research, but there has been discussion. Three years ago the Pasteur Institute was contacted to organize a follow-up on dual use potential of large programs, including research on influenza. The research involved 17 labs. Each year there is a review for ethical problems, including animal and human research and dual use. They use a similar questionnaire with nine questions instead of seven. In the beginning, the researchers objected to the questions. After three years, response is good and researchers have been educated. Mr. Binder thanked the participants for their reflections on the process of dialogue with researchers and said this will be useful in deciding how to handle the process in France.

Meg Lauren Flanagan, Ph.D., Department of State, noted that the State Department leads the U.S. participation in the Biological Weapons Convention. Dual use issues have been discussed for a long time in that arena. Different countries are using different measures to deal with dual use issues. For example, Germany is using some of its current regulation with regard to genetically modified organisms to try to address some disease research issues. Each country is using the mechanisms that are available, and the landscape of what different countries are doing is quite varied.

Nicholas G. Evans, Ph.D., University of Pennsylvania, asked what types of evidence are needed for benefits and risks. He also asked about compliance. He described "a bit of a public relations disaster" for biosafety in the last year.

Mr. Bayha reiterated that this is a relationship of trust. When researchers accept funding, they agree to certain terms and conditions. Noncompliance can take many forms, from forgetting to submit notification within 30 days to not having a required committee. Actions would have to be tailored to the type of noncompliance. There are penalties for willful noncompliance, such as loss of funds, limitation of funds, or being barred from applying for funding.

Closing Remarks

Dr. Coller-Monarez

Dr. Coller-Monarez emphasized that this is the first opportunity to implement a new policy, and some growing pains are anticipated. Institutions can help by providing data.

Any policy, when it is implemented, seems like it will be resource intensive, Dr. Coller-Monarez said. However, it is unclear whether this policy will be so different from the IBCs and other mechanisms that are already in place that it will demand additional resources beyond what is already available for safety. If so, it will be important to know the actual costs of implementation.

The second item on which data would be useful is the concerns about scientists or students avoiding a research area because of the DURC policies. A quantifiable decrease in, for example, the number of students recruited to these labs would be very useful to know about. Policy-makers do not want to impede science.

Also, policy-makers will want to track issues related to the implementation of the policy, including noncompliance, how institutions deal with the subjective question of whether research meets the definition of DURC, and how IREs deliberate.

Anecdotes are very informative, but they are less persuasive in terms of modifying a policy than systematic data.

This is a partnership, Dr. Coller-Monarez said. The government and life sciences researchers are all in this together and all have the same goal. Meetings like this are very useful. The policy will be updated as appropriate.