SANDIA REPORT

SAND2016-12706
Unlimited Release
December 2016

Biological Select Agents and Toxins: Risk-Based Assessment, Management, and Oversight

LouAnn Crawford Burnett, Lisa Astuto Gribble, Andrew W. Nelson, Mika Shigematsu, Laurie D. Wallis, and Julie Wilder

Prepared by
Sandia National Laboratories
Albuquerque, New Mexico 87185 and Livermore, California 94550

Sandia National Laboratories is a multi-program laboratory managed and operated by Sandia Corporation, a wholly owned subsidiary of Lockheed Martin Corporation, for the U.S. Department of Energy's National Nuclear Security Administration under contract DE-AC04-94AL85000.

Issued by Sandia National Laboratories, operated for the United States Department of Energy by Sandia Corporation.

Available to DOE and DOE contractors from
U.S. Department of Energy
Office of Scientific and Technical Information
P.O. Box 62
Oak Ridge, TN 37831

Telephone: (865) 576-8401
Facsimile: (865) 576-5728
E-Mail: reports@osti.gov
Online ordering: http://www.osti.gov/scitech

Available to the public from
U.S. Department of Commerce
National Technical Information Service
5301 Shawnee Rd
Alexandria, VA 22312

Telephone: (800) 553-6847
Facsimile: (703) 605-6900
E-Mail: orders@ntis.gov
Online order: http://www.ntis.gov/search

SAND2016-12706
Unlimited Release
December 2016

Biological Select Agents and Toxins: Risk-Based Assessment, Management, and Oversight

LouAnn Crawford Burnett
Lisa Astuto Gribble
Andrew W. Nelson
Mika Shigematsu
Laurie D. Wallis
Julie Wilder

International Biological and Chemical Threat Reduction
Sandia National Laboratories
P.O. Box 5800
Albuquerque, New Mexico 87185-1323

Abstract

Sandia National Laboratories' International Biological and Chemical Threat Reduction (SNL/IBCTR) conducted, on behalf of the Federal Select Agent Program (FSAP), a review of risk assessment in modern select agent laboratories. This review and analysis consisted of literature review, interviews of FSAP staff, entities regulated by FSAP, and deliberations of an expert panel. Additionally, SNL/IBCTR reviewed oversight mechanisms used by industries, US agencies, and other countries for high-consequence risks (e.g, nuclear, chemical, or biological materials, aviation, off-shore drilling, etc.) to determine if alternate oversight mechanisms existed that might be applicable to FSAP oversight of biological select agents and toxins. This report contains five findings, based on these reviews and analyses, with recommendations and suggested actions for FSAP to consider.

ACKNOWLEDGMENTS

This study was a collaborative effort and could not have been completed without the significant efforts, expertise, time, and patience of the following:

Expert Panel: Rocco Casagrande, Patrick Condreay, Barry Ezell, Diane Fleming, Julie Fruetel, David Hill, Tom Inglesby, and Todd Klessman

Division of Select Agents and Toxins (CDC DSAT): Daniel Sosin, Cecelia Sanders, Maria Bruner, Mark Hemphill, Lori Bane, and several other members of the DSAT staff who took time out of their schedules to provide expertise, experience, and perspective.

Agriculture Select Agent Services (APHIS AgSAS): Freeda Isaac and Caroline Laverriere

U.S. Health and Human Services: James Holt

The many **representatives of regulated entities** who took time, on short notice, to provide invaluable information via webinars

Sandia National Laboratories International Biological and Chemical Threat Reduction: Benjamin Brodsky, Jennifer Gaudioso, Terry Wilson, Elias Marquez, Monear Makvandi, Susan Caskey, Krystal Aldridge, Peter Hotchkiss, and Janet Montoya

CONTENTS

FIGURES

TABLES

List of Abbreviations and Acronyms

AgSAS	Agriculture Select Agent Services
ANSI/AHIA	American National Standards Institute/Association for Healthcare Internal Auditors
APHIS	Animal and Plant Health Inspection Service
ATCC	American Type Culture Collection
BSAT	Biological Select Agents and Toxins
BMBL	Biosafety in Microbiological and Biomedical Laboratories
BSEE	Bureau of Safety and Environmental Enforcement
CDC	Centers for Disease Control and Prevention
CEN	European Committee for Standardization
CFATS	Chemical Facility Anti-Terrorism Standards
COS	Center for Offshore Safety
CWA	CEN Workshop Agreement
DHHS	Department of Health and Human Services
DHS	Department of Homeland Security
DSAT	Division of Select Agents and Toxins
FBI	Federal Bureau of Investigation
FSAP	Federal Select Agent Program
FTAC	Fast-Track Action Committee
HHS	Department of Health and Human Services (also DHHS)
IBC	Institutional Biosafety Committee
IBCTR	International Biological and Chemical Threat Reduction
IFBA	International Federation of Biosafety Associations
INPO	Institute of Nuclear Power Operation
IRGC	International Risk Governance Council
ISATTAC	Intragovernmental Select Agents and Toxins Technical Advisory Committee
ISO	International Organization for Standardization
MMWR	Morbidity and Mortality Weekly Report
NIH	National Institutes of Health
OCS	Outer Continental Shelf
OSHA	Occupational Safety and Health Administration

PDCA	Plan-Do-Check-Act
SAR	Select Agent Regulations
SEMS	Safety and Environmental Management System
SMS	Safety Management Systems
SNL	Sandia National Laboratories
SOP	Standard Operating Procedures
TRB	Transportation Research Board (National Academies)
USDA	United States Department of Agriculture
USA PATRIOT Act	Uniting and Strengthening America by Providing Appropriate Tools Required to Intercept and Obstruct Terrorism Act

EXECUTIVE SUMMARY

Background

In the wake of incidents where biological select agents and toxins (BSAT) were released, unintentionally, from U.S. Centers for Disease Control and Prevention (CDC) and other federal laboratories, CDC conducted an internal 90-day review of the Federal Select Agent Program (FSAP) and made recommendations to improve CDC's responsibilities within FSAP.

The review recommendations included:

> *Recommendation 3: Review and implement options for standardized risk assessment.*
>
> > *CDC, in collaboration, with APHIS, shall convene an independent scientific body to review the science and practice of risk assessment in the modern select agent laboratory and provide recommendations that improve the timeliness and effectiveness of the inspection process.*

Sandia National Laboratories' International Biological and Chemical Threat Reduction program (SNL/IBCTR) coordinated, on behalf of FSAP, an independent review of risk assessment in the modern select agent laboratory.

The CDC internal 90-day review also included this additional recommendation:

> *Observation E: Enforcement options for [the Division of Select Agents and Toxins] DSAT are limited and difficult to scale to the range of safety and security findings on inspections. Most compliance issues and violations are resolved through negotiated corrective action plans.*
>
> > *Recommendation 6: DSAT shall produce a report on other approaches to increasing compliance with regulations (e.g., consultative services and incentives) based on review of other regulatory programs (e.g., nuclear research, aviation safety).*

SNL/IBCTR concurrently reviewed other regulatory programs for potential oversight and enforcement options to benefit BSAT oversight and enforcement.

SNL/IBCTR conducted literature review and analyses on risk assessment and risk management processes in general and the use of these processes across other industries with high-consequence risks, on biorisk assessment and management, and on the response of other industries to potentially high consequence incidents. SNL/IBCTR interviewed FSAP staff, representatives from regulated entities, and experts in activities involving BSAT, biosafety, biosecurity, risk assessment, and risk management. Many of the experts participated in expert panel discussions and deliberations to craft the recommendations detailed in this report. This study benefitted immensely from open and transparent dialogue with FSAP during the entirety of the project.

The study team (SNL/IBCTR and the expert panel) concurs with CDC's internal review conclusion that no standard method of risk assessment is used by regulated entities. The team also agrees that FSAP could benefit by considering alternate oversight and enforcement options used by other industries; however, the FSAP regulated community is extremely diverse and unique among high-consequence risk industries, which limits the direct applicability and relevance of existing alternate oversight mechanisms.

Summary of Findings and Recommendations

Table 11 of the report describes, in whole, the findings and recommendations of the study. The summary below highlights key conclusions and some suggested actions.

Finding 1. *The Select Agent regulations, FSAP regulators, and regulated entities are imprecise and inconsistent in the use of terminology and processes to manage risks deriving from BSAT. In addition, well-accepted publications on risk assessment and risk management of biological agents and toxins (regardless of Select Agent status) differ in their use of terminology and processes. Dialogue on risks from and risk management of BSAT would benefit from common terminology and understanding.*

The study team determined that much of the misunderstanding of what risk assessment and risk management comprise could be improved by more precise definition and use of terminology. The primary difference between various risk assessment and risk management frameworks is the use of different terminology to label the same actions. FSAP should adopt and provide guidance on standard terminology and a standard framework for risk management (which includes risk assessment) and should expect regulated entity literacy and implementation using the terminology and framework for site-specific BSAT risk management plans, that consolidates safety and security plans.

Suggested actions include:

- Establish a standardized, harmonized BSAT risk management method with precise terminology and steps.
- Require that an entity-developed BSAT risk management plan serve as the primary discussion guide and basis for evaluation during reviews and inspections.
- Require BSAT-involved entity personnel to be familiar with and literate about the BSAT risk management plan and how the risk control measures function to reduce identified risks.

Finding 2. *Entities possessing BSAT may be similar only in the fact that they each have a regulated agent. Given this diversity, the use of risk assessment can, in a site-specific manner, tease out and focus control measures on the agents and situations that present the highest risk(s) in that setting. The focus of risk management should lead to the control of these identified risk(s) in addition to compliance with regulations. However, the diversity of settings and the broad universe of valid and effective risk control measures could make oversight more difficult and resource-intensive.*

The community regulated by FSAP is small, extremely diverse, and ever-evolving. Site-specific risk assessment and risk management can, and must, identify and address BSAT and activities that present the highest risk at that site. While entities have an obligation to prevent occupational exposures for their workers, FSAP should focus the limited resources of both entities and regulators on risks with the greatest potential to harm the community beyond the laboratory boundary. Critical control points are those that prevent or interrupt intentional or unintentional release beyond the laboratory boundary.

Entities must be literate on what risks are present or probable and on how the controls chosen will function to reduce those risks. Despite the diverse community, sharing best practices and lessons-learned between peers and to and from the regulators is essential to

educating and equipping the entire BSAT community with relevant and reliable information for BSAT risk management. Inclusion of peer audits or a peer assist program could increase the fidelity of BSAT risk management plans and build an environment of learning between entities. Improved and well-executed BSAT management plans can, in turn, reduce inspection time or allow inspection focus and interaction on critical control measures.

Suggested actions:

- Consider tiering entities based on relative risk to community rather than a focus on occupational risks
- Prioritize controls that prevent intentional or unintentional release of BSAT beyond the laboratory boundary
- Increase transparency, collaboration, and data-sharing between and among regulators and regulated entities.

Finding 3. *Even with a standardized, harmonized, ideal risk assessment process, risk assessment is only as good as the input. Likewise, decisions on risk control measures are only as good as the understanding of the risk derived from a fully-informed risk assessment. Using data that is relevant, reliable, and current, regulated entities could prepare more consistent and effective risk assessments and risk management plans. FSAP could then more consistently evaluate those documents.*

Like the terminology and framework discussed above, there are few standardized or vetted sources from which entities can derive data to feed into the risk assessment and risk management process. While a site-specific risk assessment and BSAT risk management plan is imperative for managing BSAT risks, site-specific terminology, frameworks, and data can muddy an already complex regulatory environment. If regulators and regulated entities utilized, to the extent feasible given site-specific differences, the same data sources for input into risk assessment and risk control, communication could focus on actual gaps in risk reduction rather than on gaps created by the use of disparate methods and data and the resulting miscommunication. The entire FSAP community, regulated and regulators alike, must be able and encouraged to contribute to data sources to assure that information is relevant, reliable, and current.

Additionally, the life sciences are evolving quickly and traditional data or nomenclature may not be sufficient to fully characterize anticipated risks. Genetic modifications could create an agent of concern literally overnight. Augmenting current taxonomic descriptions with information on the phenotype that defines the agent characteristic(s) of concern should, at a minimum, provide additional input into the risk assessment process, and perhaps even help investigators realize when they may be moving towards a genetic modification, regardless of taxonomy, that warrants consideration of additional risk control.

As was continually highlighted during this study, the diversity of entities, agents, activities, and missions makes site-specific risk assessment and risk management plans essential. While the current regulations require an entity to conduct site-specific risk assessments, both inspectors and regulated entities report that these assessments are rarely used during the inspection process. Instead, other documents, like inspection

checklists, tend to guide the inspection and subsequent enforcement actions, if required. Where possible, FSAP should focus on supporting this site-specific process rather than on prescribing pre-determined control measures. Entities must be articulate and accountable for the risk controls they choose. Site-specific BSAT risk management plans must document and justify these choices in terms of expected impact on risk reduction rather than just cross-referencing regulations or regulator-provided guidance. Peer review of BSAT risk management plans could increase the quality of these plans prior to submission to FSAP.

Suggested actions:

- Utilize phenotypic descriptions of listed agents to benefit understanding of risk posed by the nature of the agent
- Increase access to, availability of, and quality of data sources needed to conduct well-informed risk assessments and risk control decisions.
- Support and expect entities to develop site-specific BSAT risk management plans that clearly articulate why and how the risk control measures chosen will reduce identified or anticipated risks, rather than prescribing control measures.
- Support the development of formal or informal peer assist activities where BSAT risk management plans can be reviewed and refined prior to submission to FSAP.

Finding 4. Lessons-learned from a wide variety of high-risk industries addressing catastrophic or critical incidents increasingly identify failures at the top management and organizational level as key precursors to the incidents. The focus on applying additional technology to avoid incidents has evolved, across many industries, to a focus on the organizational system and culture. As an example, many industries noted that additional prescriptive measures were less beneficial to risk management than increased training and mentoring designed to improve critical thinking.

The outcome of investigations into catastrophic incidents across many industries highlight that in order for technical- and systems-approaches to succeed, the organizational culture must model safety and security as imperative to its mission. The most publicized incidents have resulted in safety or environmental impacts; however, investigations of security incidents, albeit fewer in open-source literature, also point to organizational culture as key to preventing future incidents. FSAP should require entities to include and demonstrate top management engagement and other system-wide activities as part of BSAT risk control. A site-specific BSAT risk management plan must include mechanisms to collect and evaluate evidence that risk control measures, including these system-level activities, are functioning and continually improving to reduce identified risk and entities must be prepared to provide FSAP inspectors with this evidence.

Personnel involved with BSAT must know that top management will not compromise safety and security in pursuit of production and expediency, where those goals conflict. A written commitment statement is important, but not enough. Personnel perceive that leaders care more about areas that are well-financed and highlighted in organizational communication.

Entities must inform and equip their personnel, at all levels, with the knowledge and skills necessary to understand and implement the BSAT risk management plan and to make appropriate risk-based decisions in the face of unanticipated events or emerging situations. Awareness training is not enough for most personnel. Critical thinking skills are required. Training and mentoring programs must be designed to elicit and reinforce educated and informed responses to routine and unanticipated activities involving BSAT.

Suggested actions:

- Include organizational activities and top management engagement as key risk control measures in the site-specific BSAT risk management plan.
- Utilize performance indicators for, at a minimum, controls that prevent intentional or unintentional release of BSAT beyond the laboratory boundary. Review data collected and evaluations made for these indicators during inspections.
- Support training and mentoring programs for BSAT-involved personnel that enhances the literacy of personnel with risk assessment and risk management plan and the acquisition of critical thinking that will benefit risk-based decision making in the face of unanticipated events.

Finding 5. *An examination of the risk management methods and strategies developed for other industries reveals that oversight of regulated industries involves utilizing a management system approach in essentially three ways: 1) supplemental validation using industry standards (e.g., accreditation, certification, etc.), 2) performance-based regulation, or 3) a blend of both. Supplementing these mechanisms with tools that increase technical depth, peer assistance, entity accountability, and critical thinking provide options for consideration in strengthening risk reduction without undue burden to the regulated community.*

SNL/IBCTR reviewed open-source literature and documents available from a variety of industries with high-consequence risks. Most of the industries reviewed have suffered incidents with catastrophic outcomes and have conducted, or been the subject of, investigations and studies seeking to avoid additional incidents. As mentioned above, this investigation and introspection ultimately focused on the necessity of a systems-approach, supported by an organizational culture committed to safety and security.

No other industry, nor the regulatory oversight applied, is directly comparable with the community overseen by FSAP. Likewise, open-source review revealed no other country with an oversight program for agents and toxins of concern with the same focus and intent as the U.S. FSAP. The community is unique; the regulatory approach is unique.

That said, there are tools developed and utilized by other industries that, with strategic modification, may facilitate and promote entity accountability, consistency, and documented BSAT risk reduction. Chief among these is the use of a management system requiring demonstrable engagement and accountability at all levels of an organization and the documentation of ongoing performance checks to assure that the system is in place and is not degraded or degrading.

Suggested actions:

- Identify key components for a systems-approach to support BSAT risk management. Highlight those components to be considered and addressed in a site-specific BSAT risk management plan.
- Consider using tools identified and developed by other industries – examples include peer assist or audit, self-audit, performance indicators, etc. - to promote and support entity accountability for BSAT risk management.

Conclusion

The study team commends FSAP for its work to address the risks posed by biological select agents and toxins. Open dialogue with FSAP during this study demonstrated FSAP's intent and desire for continual improvement in oversight and communication with the regulated community.

The community regulated by FSAP is extremely diverse - oversight requires a complex approach that cannot (and should not) be a one-size-fits-most concept. Although incidents involving BSAT have been documented and publicized, none of these incidents resulted in a catastrophic impact, although each held that potential. FSAP can learn from industries that have suffered through high-consequence incidents.

Streamlining and fine-tuning the terminology, methodology, and inputs for BSAT risk assessment and risk management should make the controls applied for risk reduction, even across the diverse community, more consistent and comparable. Assuring that best practices and lessons-learned are accessible, available, and are, as much as possible, peer-reviewed will provide much-needed information and context to both the regulators and regulated community. Applying a management system approach where top management must be articulate and engaged and performance must be checked and documented will require the organization to pay attention and to be accountable for the work conducted within its walls. The study team acknowledges that few of these recommendations can be accomplished in the near term and that considerable thought and effort will be required should FSAP choose to implement even some of these measures. Due to the long-term nature of planning and implementation, and at FSAP request, suggested scope-of-work for addressing some of these suggested actions are included in the appendices of the report.

1. INTRODUCTION

The Federal Select Agent Program (FSAP) oversees the possession, use, and transfer of biological select agents and toxins (BSAT), which have the potential to pose a severe threat to public, animal, or plant health, or to animal or plant products.

Following high-profile laboratory incidents involving unintentional releases of select agents and toxins that occurred in 2014 at regulated entities, the Centers for Disease Control and Prevention (CDC) initiated an examination of the biosafety and biosecurity practices involved in the conduct and oversight of this critical work. One examination comprised an internal 90-day review of CDC's select agent and toxin regulatory program. A CDC Internal Review Workgroup examined the FSAP and made recommendations to improve CDC's responsibilities within FSAP.

The Workgroup developed three broad categories of recommendations: 1) inspections, 2) incident reporting, and 3) transparency to improve the CDC select agent and toxin regulatory program.

Two recommendations are relevant to this study (the entire report can be viewed at: http://www.cdc.gov/phpr/dsat/full-report.htm):

> *Observation C: Select agent laboratories do not currently implement a standardized risk assessment process to identify the highest risks.*
>
> > *Recommendation 3: Review and implement options for standardized risk assessment.*
> >
> > > *CDC, in collaboration, with APHIS* [Animal and Plant Health Inspection Service] *, shall convene an independent scientific body to review the science and practice of risk assessment in the modern select agent laboratory and provide recommendations that improve the timeliness and effectiveness of the inspection process*
>
> *Observation E: Enforcement options for DSAT* [Division of Select Agents and Toxins] *are limited and difficult to scale to the range of safety and security findings on inspections. Most compliance issues and violations are resolved through negotiated corrective action plans.*
>
> > *Recommendation 6: DSAT shall produce a report on other approaches to increasing compliance with regulations (e.g., consultative services and incentives) based on review of other regulatory programs (e.g., nuclear research, aviation safety).*

Study Description

In response to the observations and recommendations noted above, FSAP contracted Sandia National Laboratories' International Biological and Chemical Threat Reduction (SNL/IBCTR) program to support FSAP in evaluating and strengthening the biorisk assessment[1] process employed in regulated facilities in order to:

[1] Although the term "risk assessment" was utilized in contract documents, one of the outcomes of this study was a determination that "risk management" is a more encompassing and appropriate term for the process to be studied and strengthened. All subsequent references in this report where "risk assessment" was originally used have been changed to "risk management" except where "risk assessment" is indeed the correct term. Definitions will be provided upon the first use of the

- Reduce biosafety and biosecurity risks associated with biological select agents and toxins within regulated facilities,
- Enhance effectiveness of inspection processes to identify safety and security vulnerabilities,
- Enable FSAP to identify common vulnerabilities across multiple regulated entities that warrant prioritization for broad improvement.

In addition, FSAP asked SNL/IBCTR to identify additional enforcement and compliance options (including incentives) that could lead to more effective biorisk management without excessive burden on regulated entities, using lessons drawn from other established industries subject to regulation in order to reduce safety and security risks.

Based on the FSAP request, SNL/IBCTR constructed the following statement of purpose for this study:

Desired End State:

- Regulators and regulated community will utilize risk management in a consistent way to:
  - Improve (targeting of) safety and security at the individual entity level,
  - Contribute to lessons-learned for the FSAP community, and
  - Support options for oversight and enforcement that enhance safety and security without excessively burdening the regulated community.
- Models used in other industries successfully to mitigate risk will inform regulatory oversight and enforcement.

Study Outcome:

- Gain an understanding of current status of FSAP relative to desired end state. Make informed recommendations to move the program from current state to the above desired end state.

Appendix A contains a list of research questions utilized to guide the study.

Research and Analysis Methods

SNL/IBCTR performed an extensive literature review on the basic principles and models for risk management, the use of risk management for biorisks, risk management in other industries, and risk-based oversight models in other industries, especially those with regulatory oversight. SNL/IBCTR met with FSAP staff to determine how they conduct and/or utilize risk assessment.[2] A series of webinar forums was held with representatives of regulated entities to gather information on how the entities conduct and/or utilize risk assessments and risk management and to determine their general perception of the program, regarding risk assessment (Table 1;

---

term and, for consistency, have been drawn from the 2015 DHS Lexicon (and are excerpted in Appendix D). For example, "risk management" is defined as the "process of identifying, analyzing, and communicating risk and accepting, avoiding, transferring or controlling it to an acceptable level considering associated costs and benefits of any actions taken."

[2] "risk assessment" = "product or process evaluating information based on a set of criteria and assigning values to risks for the purpose of informing priorities, developing or comparing courses of action and informing decision-making."

Appendix B contains an aggregate summary of the data collected from these webinars). These activities were utilized primarily to provide background and context to guide discussions and deliberations with an expert panel (Appendix C contains panel members' biographies) that was convened to review preliminary research results and to offer recommendations designed to move the FSAP program from the current state to the desired end state (above).

Table 1. Composition of Expert Panel

Panelist	Affiliation
Rocco Casagrande	Gryphon Scientific, LLC
Patrick Condreay	pcBiosafety Consulting Services, LLC
Barry Ezell	Innovative Decisions/Old Dominion University
Diane Fleming	Retired biosafety consultant
Julie Fruetel	Sandia National Laboratories (CA)
David Hill	NY State Department of Health Wadsworth Center
Tom Inglesby	UPMC Center for Health Security
Todd Klessman	DHS Infrastructure Security Compliance Division

Terminology

As will be seen in the research and findings, terminology around risk assessment in the regulation of BSAT is imprecise. In fact, this study highlights that the lack of consistent definition significantly contributes to the differences in perception regarding the use and effectiveness of risk assessment and the risk management process. To avoid ongoing confusion in this report and to introduce some needed precision around commonly-used terms, we will use definitions, where available, from the DHS lexicon (U.S. Department of Homeland Security Office of Policy 2015) which contains a "unified controlled vocabulary that DHS and its Components can use when communicating and sharing data." The first use of each term will be defined in a footnote. Appendix D contains definitions related to risk, risk assessment and risk management excerpted from the DHS Lexicon.

Relationship to other documents and activities

Documents published by FSAP (www.selectagents.gov) were utilized by this study to determine the current state of the program only. Several other initiatives reviewing FSAP are concurrently underway – results and recommendations from those initiatives may overlap, duplicate, or conflict with the results of this study. No effort was made to reconcile this report with any other publication or initiative – this report should be viewed as an independent contribution.

Organization of Report

This report is organized into four main areas:

1. Background Research and Initial Findings – description of current select agent program (regulations, regulators, regulated community) relevant to discussions of risk management.
2. Key Research Areas & Analysis – summary of literature review with context from interviews of FSAP staff and representatives from regulated entities; analysis of research relevant to study goal

3. Alternate Oversight Approaches and Applicability to FSAP – review, analysis, and applicability to FSAP of other industries, US agencies, and other countries oversight approaches for high-consequence risks.
4. Findings & Recommendations – results of expert panel deliberations with recommendations for meeting the study goals. Some of the recommendations require additional input and expertise to implement – at FSAP request, suggested scopes of work for these efforts are referred to in the body of the report and inserted as appendices.

2. BACKGROUND RESEARCH AND INITIAL FINDINGS

Federal Select Agent Program

FSAP oversees the possession, use and transfer of BSAT, which have the potential to pose a severe threat to public, animal, or plant health, or to animal or plant products. It was jointly established in 2002 by the Centers for Disease Control and Prevention (CDC)/Division of Select Agents and Toxins and the Animal and Plant Health Inspection Services (APHIS)/ Agriculture Select Agent Services in order to regulate BSAT. The FSAP regulates BSAT by:

- Developing, implementing and enforcing the Select Agent Regulations (SAR):
  - 42 Code of Federal Regulations (CFR) Part 73 (human health); "Select Agents and Toxins"
  - 7 CFR Part 331 (plant health and products); "Possession, Use, and Transfer of Select Agents and Toxins"
  - 9 CFR Part 121 (animal health and products); "Possession, Use, and Transfer of Select Agents and Toxins",
- Maintaining a national database of select agents (Appendix E contains the current list of biological select agents and toxins),
- Inspecting entities that possess, use, or transfer select agents,
- Ensuring that all individuals who have access to select agents undergo a security risk assessment performed by the Federal Bureau of Investigation (FBI),
- Providing guidance to regulated entities on achieving compliance with the SAR,
- Investigating incidents in which non-compliance with the SAR may have occurred.

The SAR mandate that any person that possesses, uses, or transfers BSAT have a program to address a) physical and information security, b) accountability, c) personnel responsibility and reliability (Tier 1), and d) worker and community health and safety. Physical security is generally addressed, at a minimum, with perimeter fencing and building access controls (key cards, personal identification numbers, badges) and locks on individual storage units containing BSAT (such as refrigerators, freezers, and cabinets). Information security refers to maintenance of secure databases of select agent and toxin inventories, whereas accountability refers to the ability of the institute to track and monitor those individuals who have access to the BSAT, and receipt and shipment of the agents. Screenings by the Federal Bureau of Investigation (FBI) identify those individuals who are prohibited from access to BSAT based on categories specified in 18 USC 175b, 42 USC 262a(e)(3), and 7 USC 8401(e)(3). The entity must allow only non-restricted parties access to BSAT. Medical surveillance programs of laboratory personnel, and provision of administrative and engineering controls and personal protective equipment by the institute, are methods by which institutes comply with the mandate to monitor worker and community health and safety.

History of the FSAP

As reviewed by Morse (Morse, 2015), events as early as 1995 led to the issuance of regulations restricting access to dangerous human pathogens and toxins. In that year, American Type Culture Collection (ATCC) shipped three vials of lyophilized *Yersinia pestis*, the causative agent of plague, to the Lancaster, Ohio home of Larry Wayne Harris. Although those at the ATCC knew not to send the vials to anywhere but an established laboratory, Harris, a man with ties to the Aryan Nations, provided the ATCC with fraudulent paperwork that convinced the company that his house was indeed a legitimate laboratory. Harris' impatient behavior, however, prompted the ATCC to contact the CDC about the order, who in turn notified the local health department, eventually leading to notification of the local authorities. Law enforcement recovered the unopened vials from the glovebox of Harris' vehicle.

This highly publicized event led to a review of the Federal regulations governing the possession of dangerous pathogens. Several regulations were identified that restricted possession, transfer, and use of high consequence *plant and animal* pathogens to qualified institutions and scientists; however, no such regulation restricting access to dangerous *human* pathogens were identified. A multi-agency[3] panel was convened to address the issue. The framework for a solution was incorporated into the Antiterrorism and Effective Death Penalty Act of 1996 (Public Law 104 – 132) directing the Department of Health and Human Services (HHS) Secretary to *establish and maintain a list of each biological agent that has the potential to pose a severe threat to public health and safety*. The criteria that were to be considered when placing an agent on this *Select Agent List* included a) the effect on human health from infection with the agent, b) the infectious potential of the agent and the route of infection, and c) the availability and effectiveness of vaccines to prevent the disease and medical countermeasures or therapeutics to treat any illness resulting from infection with the agent.

The scientific community provided further input, and in particular members of the American Society of Microbiology, leading to new regulations requiring that those shipping or receiving BSAT be registered with the CDC. In addition, the law called for regulations that outline safety procedures for agent transfer, training programs for those handling the agent, and requirements for handling agents in laboratories designed to contain and dispose of the agents properly. The "Biosafety in Microbiological and Biomedical Laboratories (BMBL), 3rd Edition," a publication of the CDC/NIH, was originally "incorporated by reference" in the regulation – meaning that entities were required to utilize provisions of the BMBL for compliance with the regulations. Congress specifically stated that the design of the BSAT regulation not limit or obstruct legitimate research and education.

In the fall of 2001, *Bacillus anthracis* spores were disseminated through the U.S. mail resulting in 22 cases of anthrax and five deaths. The FBI requested that CDC's select agent program provide them with a list of all laboratories possessing the Ames strain of the bacteria. However, the list was likely incomplete in that only those laboratories that had shipped or received the bacteria since April of 1997 were registered with the SAP. Thus, another loophole in the regulations was exposed. As a result, Public Law 107- 56 "Uniting and Strengthening America by Providing Appropriate Tools Required to Intercept and Obstruct Terrorism (USA PATRIOT) Act" was signed in October 2001. This law was applicable to those who handle or possess any

[3] Health and Human Services; CDC; Office of Emergency Preparedness; Office of Science and Technology Policy; Executive Office of the President; FBI; Department of Justice (DOJ); Department of Defense (DOD) US. Army Medical Research Institute for Infectious Diseases (USAMRIID); U.S. Department of Agriculture (USDA); Department of Commerce; Environmental Protection Agency (EPA); U.S. Postal Service; National Institutes of Health (NIH); Food and Drug Administration (FDA)

biological agent or toxin by amending the United States criminal code, restricting their possession to those "justified by a prophylactic, protective, bona fide, research, or other peaceful purpose…". Further, regulation of BSAT was impacted by the "Public Health Security and Bioterrorism Preparedness and Response Act of 2002" (PL 107 – 188), which directed the HHS Secretary to a) establish, maintain and review the BSAT list at least biennially; b) regulate the transfer of agents on the list; c) establish and enforce standards and procedures governing their possession and use, d) require registration with the HHS Secretary for possession, use, and transfer of the agents; and e) provide safeguards and security requirements for persons handling the agents. In addition, Congress authorized the HHS Secretary to inspect facilities to insure compliance with the regulations. The requirements to ensure that only legitimate, and otherwise unrestricted, persons were handling the BSAT include the provision for the Attorney General's security risk assessment (SRA) process. The revised SAR were published as 42 C.F.R. Part 73.

As a part of the "Public Health Security and Bioterrorism Preparedness and Response Act of 2002" (PL 107 – 188), the Secretary of the U.S. Department of Agriculture (USDA) was directed to establish and maintain a list of BSAT that has the potential to pose a severe threat to animal or plant health or products. This Act broadened the criteria for placement of animal or plant pathogens on the Select Agent List to include agents causing economic consequences and/or effects on international trade agreements. This is in contrast to the HHS list where the primary factor for inclusion is impact to public health and safety.

Evolution of the FSAP

Changes to the FSAP over time can be tracked primarily through changes to the Select Agent List. The original list of HHS BSAT (1997) contained 42 agents and toxins, and, while some agents were zoonotic, none affected only animals or plants. The Australia Group List of Human and Animal Pathogens and Toxins for Export Control served as the basis for the BSAT list, with input from experts inside and outside of the US government. The primary criteria for placement on the Australia Group list were prior weaponization, effect on human health, infectious dose, degree of contagiousness, route of infection, and the availability of effective medical countermeasures and vaccines. The Select Agent List grew with addition of USDA agents (animal and plant). Select agents and toxins can be added or removed based on new information or better scientific understanding. For example, the reconstructed 1918 influenza virus was added in 2005, SARS-associated coronavirus in 2012, and *Bacillus cereus* Biovar *anthracis* in 2016. The current BSAT list contains 66 agents and toxins, many varying significantly from each other in their pathogenicity and perceived ability to be used for bioterrorism.

The National Science Advisory Board for Biosecurity recognized that the broad application of regulations to agents with significantly different pathogenicity might make the conduct of legitimate research on those of less pathogenicity more cumbersome than necessary. Their 2009 report recommended that the FSAP stratify the BSAT list (National Science Advisory Board for Biosecurity, 2009). In 2012, 13 BSAT posing the greatest risk of deliberate misuse causing mass casualties, or devastating effects to the economy, infrastructure, or public confidence, were designated Tier 1 agents and toxins. Additional security standards for institutions working with Tier 1 agents were mandated (i.e. annual insider threat awareness briefings), as well as changes to occupational health and incident response plans. The FSAP published these changes as Final Rules in the Federal Register on October 5, 2012 as part of the biennial review of the BSAT list.

In order to facilitate legitimate research on BSAT and their surrogates, the FSAP also established procedures by which attenuated or avirulent strains of Select Agents can be excluded from the Select Agent regulations. The FSAP makes exclusions on a case-by-case basis upon request, and based upon consultation with subject matter experts and reviews of both published studies and unpublished data submitted by the requestor(s). The FSAP has excluded 28 such agents from SAR between 2003 and 2013.

Recent incidents involving BSAT raised serious safety and security policy issues. In response, both the Federal Experts Security Advisory Panel (FESAP) and the Fast Track Action Committee on Select Agent Regulations (FTAC) convened to make recommendations to strengthen biosafety and biosecurity practices and the government's system of oversight. The two groups released recommendations in October 2015, concurrent with the CDC 90-day internal review previously mentioned.

FSAP Staff

The FSAP has offices within the CDC Office of Public Health Preparedness and Response – the Division of Select Agents (DSAT)—and the USDA APHIS – Agriculture Select Agent Services (AgSAS). In general, FSAP employees provide services in these areas: program management/administration, operations (inspections), program services (import permits (DSAT), security and response team, etc.), and advisory (biosafety, science, policy, communication, etc.).

FSAP science advisors oversee risk determinations that lead to the listing or delisting of BSAT, exemptions, and exclusions from the list and interpretations for what constitutes a BSAT. This involves the CDC's Intragovernmental Select Agents and Toxins Technical Advisory Committee (ISATTAC) and Agriculture-ISATTAC (Ag-ISATTAC) – scientific advisory committees of experts. Input for these risk determinations can include scientific data, expert opinion, and other U.S government agency input (e.g., FBI), among others.

Operations personnel comprise the teams of inspectors that visit regulated entities to determine the status of regulatory compliance. The FSAP conducted 216 inspections in 2015 – inspections last an average of 3 days (Federal Select Agent Program, 2016). Inspectors do not conduct entity- or laboratory-specific risk assessments themselves but are aware of various risk control[4] measures and required implementation of those control measures under certain circumstances. Inspectors report that they do refer to regulated entity "risk assessments[5]" when more clarity is needed to make a risk-based decision between different risk control measures.

This report will highlight other findings from interviews with FSAP staff in discussions of key research areas below.

Regulated Entities

In 2015, there were 291 entities regulated by FSAP (Federal Select Agent Program, 2016). Figure 1 shows the distribution of these entities across types. Of note, the highest numbers of regulated entities are academic, followed closely by "non-federal government" entities (presumed to be predominately state public health labs). The difference between the two types

[4] "risk control" = "deliberate actions taken to reduce the potential for harm or maintain it at an acceptable level."

[5] In this case, the term "risk assessment" is used as this is the term utilized in the regulations. However, this study identified that regulatory use of the term is more correctly "risk management plan" which encompasses risk assessment, risk evaluation, risk control, and risk management evaluation.

of laboratories is striking (see Table 2). The fact that they comprise greater than 60% of regulated entities underscores the difficulty in providing guidance, equally applicable across all regulated entities, to a diverse laboratory community. Risk is driven largely by specific characteristics of the individual facility, which can render a one-size-fits-all approach less effective.

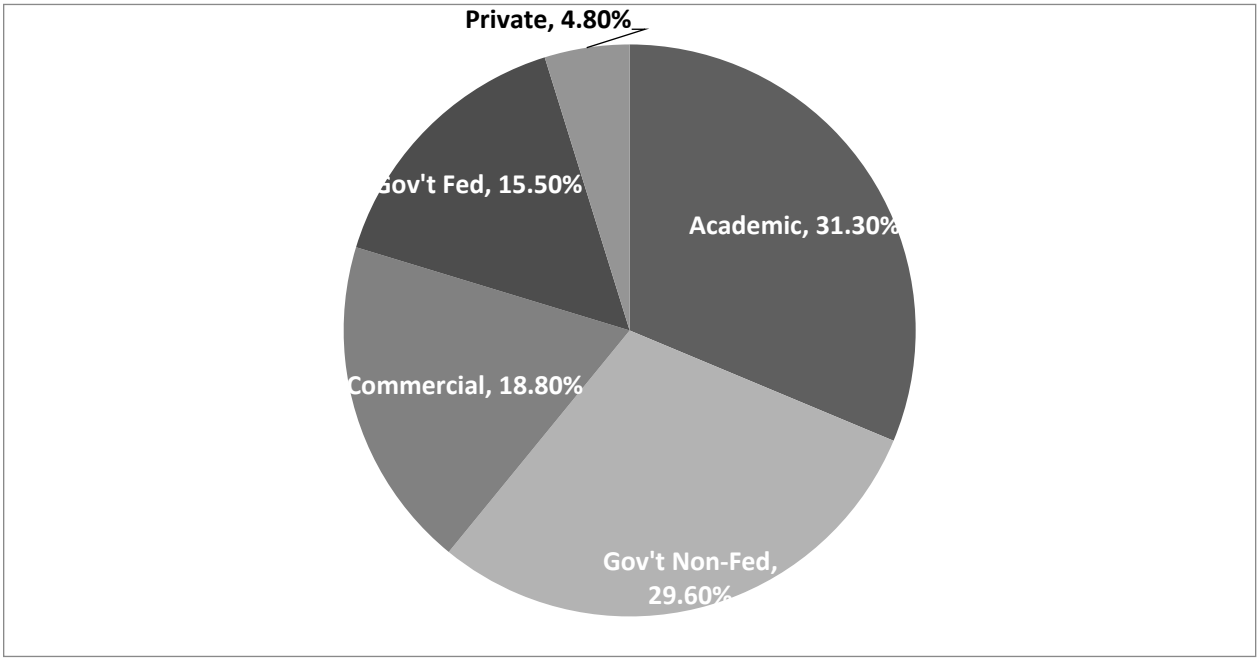


Figure 1. Entities Registered with FSAP in 2015

Table 2. General Comparison of Academic and Public Health Entities

	Academic	Public Health
Leadership	Decentralized –Principal Investigator for individual labs	Centralized – Laboratory Director oversees multiple labs
Laboratory Staff	Transient (graduate students, post-docs)	Stable (professional staff)
Activities	Research	Diagnostics (some targeted research)
Likelihood for Unknown Agents	Limited	High
Ability to Avoid Risk by Avoiding High Risk Agents	High (although certain research could not take place if higher risk agents cannot be used)	Low
Ability to Transfer Risk	Low (except in rare cases, academic research activities are confined to a single investigator's laboratory)	Moderate (depending on lab responsibility)
Likelihood for Modified Agents	High	Low (unless modified agents are circulating in community)
Safety Personnel	Likely to have specialized biosafety staff	Likely to oversee other safety issues, as well as biosafety
Security Personnel	On-site security force (campus police)	Security guards
Responsible and Alternate Responsible Officials	Generally EHS director or biosafety officer.	Generally the Laboratory Director or Principal Investigator responsible for BSAT at the Public Health Laboratory

As mentioned previously, SNL/IBCTR convened four webinar forums for representatives of regulated entities to comment on risk management practices with BSAT (Appendix B). One hundred and thirteen (113) respondents participated in the webinar – participants were most likely to be the Responsible Official or the Alternate Responsible Official for the entity. The findings that SNL/IBCTR found relevant to improving risk management of BSAT are:

- Entities identified the most likely and credible incidents at their facility to be occupational exposure to agent, theft of agent, facility failure, release of agent, severe weather or disaster, loss, spill, or security failures.
- Entities utilized a variety of means to determine what incidents might be credible for their facility. They rely heavily on communication to/from regulated laboratories; self-reporting; and monitoring of inventory, access logs, and alarms; as well as risk assessment.
- In general, each entity has a site-specific risk assessment process[6] and/or each relies on guidance from FSAP to develop security and incident response plans. For data to inform effective risk assessments, entities often rely on debriefs from

[6] Most entities did not provide detail on what comprised their risk assessment process.

incidents, drills, and exercises. Regulated entities reported that a team convened specifically for review of a BSAT laboratory or an Institutional Biosafety Committee (IBC) reviewed, and in some cases, approved risk assessments. A majority of entities utilize the same risk assessment process for activities involving biological agents and toxins within their organization regardless of whether FSAP regulated the activities.

- Entities were less articulate when asked how they selected and aligned control measures relative to the risks identified via risk assessment. In general, they stated that they followed their security, biosafety, and incident response plans, utilized the results from drills and exercises, or discussed with the laboratory.
- Nearly half of the entities responding felt that no change was required in their risk assessment process. Others expressed a desire for a standardized approach across the Federal select agent program.
- When asked how risk assessment could be used by FSAP inspectors during inspections, over 50% of entities indicated that they would like inspectors to provide guidance on best practices for risk reduction and/or to review, collaboratively, the entity risk assessment while on-site.
- Entities overwhelmingly agree that FSAP targets risks that are credible for both their own organization and for other organizations and that FSAP helps the organization reduce the risk from BSAT. However, entities are less inclined to agree that inspection reports identify areas where risks need to be reduced.

This report highlights other findings in discussions of key questions below.

3. KEY RESEARCH AREAS & ANALYSES

General Risk Assessment & Risk Management Terminology & Method

The term "risk assessment" is widely used across a variety of industries and for a diversity of hazards but it is rare to find agreement on terms and specific methods, even among well-respected frameworks (e.g., ISO 31000, International Risk Governance Council, etc.). In order to gather and analyze options for strengthening risk assessment of entities registered for their use of BSAT, a first step is to review and synthesize the literature on risk assessment.

The U.S. Department of Homeland Security (DHS) endorsed the importance of establishing a structured approach, regardless of risks examined, by adopting a Homeland Security Risk Management Doctrine (Department of Homeland Security, 2011). DHS states that, "[a]n essential first step in the integration of risk management is the establishment of doctrine and guidance." The doctrine was developed to "promote a common understanding of and approach to risk management for homeland security; establish a common foundation that enables risk management and application and training; and support the development of a risk management culture and philosophy across DHS." (Department of Homeland Security, 2011).

This study seeks to identify a similar "doctrine" that is applicable for biological select agents and toxins and the entities where they are used.

Terminology

As mentioned in the introduction, lack of a commonly understood vocabulary inhibits effective communication about risk management. DHS recognized this constraint and developed a DHS Lexicon Program to assure that "language associated with DHS's work would be as descriptive, accurate, precise, and as widely understood as possible." Of course, DHS's work (and, thus, their lexicon) involves topics other than risk management (and associated concepts). Because of the focus at DHS on risk and threat reduction, the 2015 lexicon was recommended by the expert panel for use in standardizing terminology (U.S. Department of Homeland Security Office of Policy, 2015). For the purposes of this study, report, and recommendations, utilizing DHS definitions allows for 1) more precise use of terminology and 2) a pilot test of a known and evaluated lexicon as a tool for strengthening the dialogue of risk for FSAP. As such, terms used in this report (and some that may be related) that are found in the DHS Lexicon are listed in Appendix D (and in footnotes, upon the first use of the term).

The results of interviews of FSAP staff and the webinars for regulated entities underscored the value of standardizing terminology where common terms meaning different things were used interchangeably. Nearly every respondent utilized the term "risk assessment' confidently, but further discussion revealed different meanings for that same term. Most commonly, "risk assessment" is used to mean consideration of both the identification and characterization of risks and the control measures put in place to reduce those identified risks.

Method

Once terminology is clearly defined, a common method for risk management[7], which includes risk assessment[8], emerges, regardless of the framework examined. Table 3 synthesizes

[7] Risk management = "process of identifying, analyzing, and communicating risk and accepting, avoiding, transferring or controlling it to an acceptable level considering associated costs and benefits of any actions taken "

[8] Risk assessment = "product or process evaluating information based on a set of criteria and assigns values to risks for the

terminology, method steps, and inputs that have been gleaned from the literature and are commonly included when considering methods for risk management (APHL 2016; Buyon undated; CEN 2011; Caskey and Sevilla-Reyes 2014; Committee on Establishing and Promoting a Culture of Safety in Academic Laboratory Research 2014; Dickmann, Sheeley and Lightfoot 2015; Ezell, et al. 2010; Gaudioso, et al. 2009; Gribble, Tria and Wallis 2015; International Risk Governance Council 2012; International Risk Governance Council 2005; International Risk Governance Council 2015; International Standards Organziation 2009; S. Kaplan 1997; Kaplan and Garrick 1981; Rundmo 1997; Salerno and Gaudioso 2015; Sandia National Laboratories undated; Starr 2001; Stern 2014). This summary views "risk management" as comprised of four distinct activities: 1) risk assessment, 2) risk evaluation[9], 3) risk control[10], and 4) risk management performance[11]. In general, the steps involved in risk assessment and risk evaluation involve collection and analysis of (generally) pre-existing information which generate knowledge and understanding (knowledge-based). The steps involved in risk control and risk management performance are decisions on and implementation of actions (action-based) (International Risk Governance Council, 2005).

Figure 2 is a visual depiction of the basic method. Please note that neither Table 3 nor Figure 2, below, are intended to represent a general risk management approach, not specific to biorisk management. This report provides further elaboration of this approach and its relevance to managing the risks from biological select agents and toxins below.

purpose of informing priorities, developing or comparing courses of action, and informing decision making "

9 Decision to accept, avoid, transfer, or control risk.

10 Risk control = "deliberate action taken to reduce the potential for harm or maintain it at an acceptable level

11 Defined by DHS lexicon as "evaluation" = "process of examining, measuring and/or judging how well a entity, procedure, or action has met or is meeting stated objectives"

Table 3. Risk Management Method and Terminology

Terms commonly used[12]	Steps	Inputs	Output
Risk Assessment Risk Analysis Risk Appraisal Risk Characterization	Define situation Define risk[13] Identify hazards, threats, vulnerabilities Characterize likelihood of adverse event occurring Characterize consequences of adverse event if it occurs	What can go wrong? Under what circumstances can something go wrong? How likely is it to go wrong, based on the hazards, threats, vulnerabilities, and existing control measures? What are the consequences if something does go wrong, based on the hazards, threats, vulnerabilities, and existing control measures? Is the risk, based on the likelihood and consequence, low, medium, or high?	For X situation, Y risk is, for example, low, medium, or high.
Risk Evaluation Risk Acceptance	Determine if characterized risk is to be: Accepted Avoided Transferred Controlled to a level where the remaining risk can be accepted	Will the organization accept the risk, without further control, using the resources currently in place? Will the organization avoid the risk by completely eliminating the hazard from its activities and premises? Will the organization transfer the risk (by transferring hazard and activities) to another organization or activity? Will the organization implement control measures that will reduce the likelihood and/or consequences of the risk to a level where remaining risk can be accepted?	Accept: skip to Performance Avoid: remove all hazards from premises; cease all activities utilizing the hazard. Move to Performance. Transfer: identify another entity/activity to whom to transfer hazard and activities. Complete risk avoidance actions. Move to Performance. Control: Move to Control, below

[12] Terms provided in **bold** are those chosen for use in this report.

[13] "Risk" = "potential for an unwanted outcome as determined by its likelihood and the consequence"

Table 3. Risk Management Method and Terminology, continued

Terms commonly used	Steps	Inputs	Output
Risk Control Risk Mitigation Risk Management Risk Reduction	Determine what controls will reduce the likelihood of the adverse event occurring. Determine what controls will reduce the consequences of the adverse event occurring. Determine whether existing controls will reduce either likelihood or consequence. Determine which additional controls, if any, are required to reduce likelihood or consequence to a point where the remaining risk can be accepted.	What control measures are available in the given setting? What features of the control measures reduce likelihood of the adverse event occurring? What features of the control measures reduce the consequences of the adverse event if it occurs? Which control measures that reduce either likelihood or consequences already exist in the setting? Which control measures are needed to reduce risk to a level where the remaining risk can be accepted?	Identify control measures. Document in a risk management plan. Implement control measures. If control measures to reduce likelihood or consequences of risk cannot be implemented, return to risk evaluation to determine whether risk acceptance, avoidance, or transfer should be chosen. No other options are acceptable.
Risk Management Performance	Determine if control measures have been implemented. Determine if control measures are functioning as designed. Determine if control measures are contributing to risk control. Determine if inputs to risk assessment are accurate. Determine if risk evaluation is still valid.	What indicators and data sources exist to provide evidence that control measures: Have been implemented? Are functioning as designed? Are contributing to risk reduction? What new or updated inputs exist for risk assessment and/or risk evaluation?	Performance indicators and metrics for control measures. Evaluation of performance indicators and metrics. Corrective and preventive action plans to assure intended implementation, function, and risk reduction. Action plan to move towards improved implementation and function IF risk reduction will be improved. Revised risk assessments and/or risk evaluations utilizing new or revised inputs.

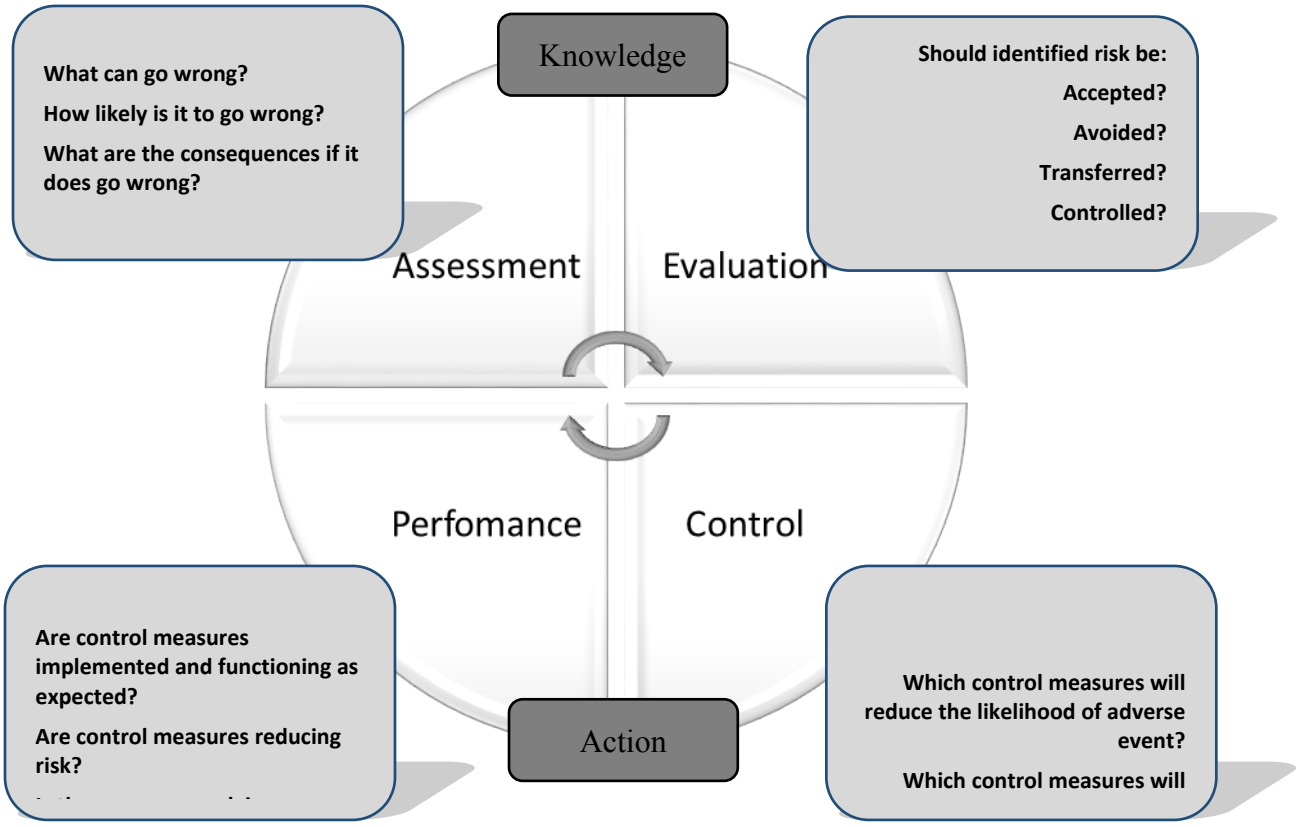


Figure 2. Visual Depiction of Risk Management Method

Implications and Applicability for FSAP

Currently, regulated entities are required to conduct a risk assessment or consider risk in the development of segregated biosafety, security, and incident response plans. The regulations reference several publications that regulated entities can utilize for plan development, along with some prescribed risk control measures, primarily for security (Box 1). FSAP publishes guidance documents to provide additional context and methodology. The inspectors utilize inspection tools when they assess entity compliance. While all of these different resources and guidance contribute important information towards BSAT risk reduction, the diversity of approaches can confuse and complicate compliance. The use of a common language, structured approach, and a single risk management plan across all FSAP activities (regulations, guidance, regulated entity plans, inspections, inspection findings, etc.) will benefit, at a minimum, the communication and dialogue around risk management of BSAT (See Finding 1 and Recommendations 1.1, 1.2, and 1.3, below).

Box 1. Publications Listed in Select Agent Regulations Recommended for Regulated Entities to Utilize in Development of Entity-Specific Risk Management Plans

Biosafety and Biocontainment Plan
Biosafety in Microbiological and Biomedical Laboratories (BMBL)
NIH Guidelines for Research Involving Recombinant DNA Molecules[14]
OSHA Hazard Communication Standard
OSHA Hazardous Chemicals in Laboratories Standard
Security Plan
FSAP Security Guidance for Select Agent or Toxin Facilities as posted at SelectAgents.gov
Incident Response Plan
None listed

Using Table 3 to evaluate the terminology used in FSAP regulations and guidance, the current FSAP use of the term "risk assessment" appears to be intended to mean the entire risk management method, not just the risk assessment step. The lack of an explicit requirement for utilizing the entire risk management method may cause differences in perception of expectations between FSAP and regulated entities

Table 4 lists some suggested actions, some more immediately applicable (near-term) and some with extended timelines that require more deliberations or actions from multiple parties (long-term), that could move FSAP towards more structured and precise terminology and method for BSAT risk reduction.

[14] These guidelines are currently published by NIH as *Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules*.

Table 4. Suggested Actions for Standardized Risk Management Terminology and Structured Method

	Near-Term Actions	Long-Term Actions
Regulated Entity	Examine currently-utilized terminology and method used for alignment with terminology and method outlined in Figure 2 and Table 3, above. Increase entity literacy with risk management terminology and method (Recommendation 1.2).	Utilize risk management terminology and method adopted by FSAP to develop BSAT risk management plan(s) (Recommendation 1.2).
Regulator (FSAP)	Examine currently-utilized terminology and method in FSAP documents for alignment with terminology and method described above. Adjust terminology as applicable and identify gaps or conflicts (Recommendation 1.1). Convene a technical working group (Recommendation 1.1) to develop a structured BSAT risk management method. A suggested scope-of-work for a technical working group is provided in Appendix Ia.	Develop or revise guidance to reflect adopted risk management terminology and method. Utilize adopted risk management terminology and method adopted by FSAP to review and inspect entity compliance with entity-developed BSAT risk management plan(s) (Recommendation 1.2).
Regulations	N/A (revisions of regulations cannot reasonably be accomplished in the near-term time-frame intended by this discussion).	Revise regulatory provisions to align with adopted BSAT risk management terminology and method (Recommendation 1.2).

Biorisk Assessment and Management Approaches &Terminology

While the risk management method summarized in Table 3 can be applied to a variety of hazards and situations, the focus of this study is, of course, on the risks presented by BSAT and the measures that should be used to reduce those risks.

Definition of Risks of BSAT (What can go wrong?)

Biorisk is defined by CWA 15793[15] 3.2 to be the, "combination of the probability of occurrence of harm and the severity of that harm where the source of harm is a biological agent or toxin (CEN, 2011)."

Asking "what can go wrong?" for BSAT then includes laboratory-acquired infection (or poisoning, if from a toxin); release of a pathogen or toxin beyond the laboratory resulting in infected or poisoned humans, plants, or animals; and theft of biological agents or toxins from the laboratory and subsequent misuse, among others.

The most commonly cited biorisks (by both regulators and regulated community) to be addressed by FSAP are theft, loss, and release. There are several different risks embedded in each of those

[15] CWA 15793 (2011) is a Laboratory Biorisk Management framework developed by a group of international experts. "CWA" means "CEN Workshop Agreement." CEN is the European Committee for Standardization (the abbreviation, CEN, derives from the French translation). "A CWA is an agreement developed and approved in a CEN Workshop; the latter is open to the direct participation of anyone with an interest in the development of the agreement." http://www.cen.eu/work/products/CWA/Pages/default.aspx , accessed 12 March 2016

terms. Table 5 presents a suggested example break-down of the risks and adverse events inferred by the terms, "theft, loss, release".

Table 5. Definition of Risks and Examples of Incidents for Biological Agents

	Risks (What can go wrong?)	Example scenarios where adverse event might occur
Theft	Intentional release to community with intent to harm. Sabotage or intellectual property given to competing facilities. Unintentional release to community with intent to remove BSAT from approved facility.	Theft of agent by insider or outsider. Theft of information about securing the agent, increasing the likelihood of an adversary gaining unauthorized access.
Loss	Loss of control of security of BSAT, with potential to lead to: Intentional release to community with intent to harm by unauthorized person(s). Unintentional release into the community resulting in infection ((or intoxication) of humans, plants, animals.	Diversion of agent by insider or outsider. Lack of inactivation or treatment leading to loss of control and accountability for agent. Lack of agent or sample identification leading to loss of control of and accountability for agent.
Release	Unintentional release beyond primary containment resulting in laboratory-acquired infection (or intoxication) of workers. Unintentional release beyond secondary containment into the community resulting in infection (or intoxication) of humans, plants, animal. Intentional release to community with intent to harm.	Exposure of laboratory workers. Contamination resulting in release to environment. Spills. Lack of inactivation or treatment. Mechanical failures of laboratory ventilation or equipment. Undetected communicable illness in laboratory worker.

Note that FSAP includes risks related to both security and safety. The newer terminology of "biorisk management" integrates the assessment, evaluation, control, and performance evaluation of risks to both security and safety into a common framework. This integration is beneficial due to the common strategies used to manage biorisk and only rarely conflicts. The inputs used to assess the risk of an agent being stolen and used for harm are necessarily different from the inputs used for determining the likelihood and consequences of an unintentional lab infection or release; however, control measures may be markedly similar.

Defining risks and determining likelihood and consequences for BSAT involves three key steps:

1. Hazard identification – which agents or toxins are being utilized and what are the characteristics that make them hazardous? At this time, FSAP lists BSAT (Appendix E) by taxonomic nomenclature. The expert panel, as described in Recommendation 3.1, suggests that listing BSAT taxonomy along with a phenotypic description of the agent will provide additional information on the characteristics of the agent that impact risk. Adding phenotypic description might also obviate lengthy modifications to the BSAT list should a non-listed agent be found or be engineered to express a "controlled" phenotype.

A suggested scope of work[16] for an effort to evaluate, develop, and integrate phenotypic descriptions in the BSAT list and in FSAP communications is provided in Appendix Ib.

2. Hazard analysis of procedures used – what manipulations of agents are occurring and what types of exposures might occur during those manipulations? What are the types of releases from a laboratory that might occur during work, storage, transfer, or disposal of an agent? Are there additional security vulnerabilities introduced during manipulations? This analysis should also include an examination of any genetic modifications or synthetic construction of agents and a determination of whether additional consequences (commonly termed "dual-use research of concern") might reasonably be anticipated. Further discussion regarding genetic modifications or synthetic biology is below.
3. "Host" factors – who are the potential hosts (persons, animals, or plants) that might be exposed – whether in the laboratory or in the community? Do these hosts (some or all) have vulnerabilities (e.g., lack of vaccination, pre-existing conditions, etc.) that might make them more susceptible to infection (or injury from exposure) by the agent(s) or toxin(s) if they are exposed? Likewise, are there host factors that would make the hosts less susceptible to infection (or injury from exposure)?

Likelihood of Risks of Adverse Events with BSAT (How likely is it to go wrong?)

The likelihood for each scenario described above will be different for each laboratory using BSAT and, indeed, for each individual manipulation of BSAT. There are literally hundreds of different scenarios to be considered when looking at the 291 entities registered with FSAP multiplied by the number of BSAT to be considered. This complexity underlines the difficulty of prescribing risk control measures of universal value and the extreme difficulty of inspecting for compliance. The concept of "likelihood" can be difficult, especially in a discipline where realization of the risks (e.g., infection, theft, etc.) is rare. Even where incidents may occur, the lack of common reporting mechanisms makes determining likelihood of occurrence difficult. Evaluating risk scenarios, discussed below in more detail, can assist entities in determining, consistently and comparably, even across diverse settings, the risks from BSAT, given a specific scenario.

Consequence of Risk of Adverse Events with BSAT (What are the consequences if it does go wrong?)

While each BSAT laboratory differs significantly in the likelihood of adverse events impacting safety or security, it is somewhat easier to define the consequences of an anticipated incident with BSAT as the consequences generally relate to the nature of the agent, for most known wild-type agents. While data about the nature of agents is generally available, the use of similar data for risk assessment between entities is not assured with the current requirements. In addition to the availability of widely disparate information, existing information generally only relays data about agents with regard to community infection. The characteristics of an agent may be different in a laboratory where the agent is amplified and manipulated in ways that are not common to more typical community-acquired disease infection and transmission. Attention to improving availability, accessibility, quality, and relevance of information on BSAT should increase the fidelity and comparability of risk assessments and risk-based decision making across an entity, between entities, and across the FSAP. Development and maintenance of BSAT-

[16] As mentioned in the introduction, scopes of work are included, at FSAP request, for some recommended actions.

specific data sheets (similar to Safety Data Sheets required by the Occupational Safety and Health Administration (OSHA) to communicate hazardous characteristics of chemicals, to the Pathogen Data Sheets pioneered by the Public Health Agency of Canada, and which provide greater detail on agent characteristics pertinent to BSAT safety and security than is currently contained in the BMBL) might serve this purpose. A novel approach might be the facilitation of BSAT pathogen data sheets via a wiki strategy[17], where members of the FSAP community could update information about pathogens as science brings forward new information. Appendix Ic provides a possible strategy for a suggested scope-of-work.

Consequences of risk from BSAT become increasingly more unpredictable when dealing with activities where the agents are genetically modified or synthetically created. In any manipulation where a genetic modification is introduced, additional considerations for consequences must be considered. Discussion of these additional considerations has been robust over the past decade or so. Entities conducting risk assessments can refer to publications such as Biotechnology Research in an Age of Terrorism (2004) or the guidance for reviewing experiments for dual-use concerns provided by the NIH (excerpts from each may be found in Appendix F).

The risk assessment must take all of these factors into account when the consequence of BSAT risk is considered.

Accessibility, Availability, and Quality of Data Used in Risk Assessment

As mentioned above, risk assessment and risk evaluation require pre-existing information for the analyses required. The current regulatory environment tends to leave decisions on which data to utilize in risk assessments up to the regulated entities. Due to the nature of the activities that use BSAT, data sets will necessarily evolve and will never be complete, but increasing standardized accessibility to and availability of data by all regulated entities will likely increase the fidelity of risk assessments. Centralized evaluation of and improvement in the quality and relevance of various data sets to settings where BSAT are used will also contribute to the confidence in risk assessments and subsequent risk-based decision-making. Examples of data sets that may be beneficial to explore and leverage, or generate, for this purpose, are:

- Characteristics of BSAT that influence the likelihood and consequences of the risk under examination,
- Laboratory activities that may be of greater risk with certain BSAT,
- Security vulnerabilities of greater risk when considering security of BSAT (and BSAT assets (e.g., information)),
- Evidence-based best practices,
- Incidents with BSAT and lessons-learned from those incidents

Minimizing Invalid Assumptions in Risk Assessment

Unfortunately, there is no shortcut for risk assessment, and, due to the many differences between entities and activities, there is no substitute for site-specific risk assessment. However, using a common, more-standardized source of information for the inputs into a site-specific risk assessment can benefit the quality of risk assessments (and thus risk evaluation and control) at

[17] A wiki is a website that provides collaborative modification of its content and structure directly from the web browser.

both an entity-specific level and on a national, FSAP-wide basis. If risk management terminology and methods are standardized, and the data used to answer the questions required to assess and evaluate risk are of higher quality and more consistent, the confidence and consistency of the entity and FSAP in risk-based decision-making should be improved.

FSAP inspectors commented, during interviews for this study, that many entities do not accept some of the risks targeted by the SAR and FSAP as credible for their laboratories. As an example, entities with significant controls in place feel that the likelihood of a release to the community, and especially to the animal or plant community, is negligible and should not be considered. This assumption is often based on the ongoing function of control measures where the entity feels that the likelihood of residual risk is extremely low – requiring no further action. Assumption-based risk assessment, as proposed by Leveson (Leveson, 2015), compels examination of this type of assumption and the ways in which the assumption may reasonably be expected to fail (and the subsequent controls to necessarily minimize those failures), regardless of the perception of likelihood. Another technique, referred to as a pre-mortem (Heath & Heath, 2013), allows prospective examination of possible failures given a specific setting, which may bring to light possible additional concerns and/or controls.

The use of standardized risk scenarios can guide the use of both of the techniques described above. The DHS program overseeing the Chemical Facility Anti-Terrorism Standard (CFATS) utilizes attack scenarios to aid the regulated community in evaluating the risks of concern to the regulator. For example, regulated entities are asked to consider, as they design their risk controls, that their facility may be subjected to attacks by aircraft, assault team, maritime, sabotage, stand-off, theft/diversion, and Vehicle Borne Improvised Explosive Device (VBIED) (Department of Homeland Security, May 2009). For FSAP, risk scenarios might include the possible situations under which BSAT would be released from a laboratory (see Box 2 below for potential critical control points for BSAT).

Informing Risk-Based Decision Making

Using risk assessments to drive decisions for risk control allows prioritization of resources towards areas of higher risk. This is true for a single lab, a larger multi-laboratory entity, or across an entire regulated program. The use of a consistent approach for risk assessment (and subsequent risk control decisions) increases the comparability at all levels. For biological agents, current decisions for control of safety risks such as laboratory-acquired infection often begin and end by assignment of a biosafety level. While biosafety levels comprise different combinations of risk controls designed to address safety risks of a group of agents with common characteristics, the entirety of the controls may not be applicable to the given situation. Additional controls may be prudent – and, given the original intent in developing biosafety levels, security risks are likely to be only partially addressed. Using only the biosafety level approach to assign risk control measures without assuring suitability for reduction of identified risks limits critical thinking about how control measures function to reduce specific risks. All personnel who hold responsibilities for activities to reduce risk from BSAT must be literate and knowledgeable about how those actions reduce risk. This knowledge and understanding may be essential to making unexpected decisions in the face of an unanticipated incident. Routinely mapping risk control measures back to the risks assessed assures the integration of this knowledge and critical thinking into everyday activities, strengthening BSAT risk management as a way of doing work.

Table 6 details simplified examples of risk-based decision-making derived from the method outlined in Table 3 for the selection of specific control measures that map to specific risks. In reality, this can be taken a step further, to include a breakdown of factors contributing to increasing likelihood and/or consequences, and measures that reduce likelihood, consequences, or both. The relevance of this mapping will depend on the agent(s) being utilized and the manipulations involved. For example, the first two examples involve a potential aerosol exposure. If the agent or toxin in question does not cause a concern from an aerosol exposure, under the conditions it is being used, the risk controls identified in those examples may not be necessary.

The development of a facility-specific BSAT risk management plan which outlines the inputs and outputs of risk assessment, risk evaluation, risk control, and risk management performance should serve as the primary document used by both the entity and the regulator to evaluate if BSAT risks are being addressed and controlled as intended by the SAR. By consolidating the knowledge and actions related to BSAT use and subsequent risk at a facility, rather than spreading the information and analysis across several documents, both entities and regulators can literally work "off the same page" to assure that BSAT risks are reduced. As it serves such an important role, the regulated entities must review and update the plan routinely. The current SAR require annual update of the various plans required; the review and revision, as necessary, of a aggregated BSAT risk management plan should follow the same provisions.

Table 6. Examples of Measures that are Directly Aligned with the Risk Assessed

What can go wrong?	**How can the adverse event happen?**		**How can adverse event be controlled or avoided?**
Unintentional infection of laboratory workers	Exposure via inhalation	Procedures creating aerosol	Perform procedures creating aerosol in a biosafety cabinet
Unintentional infection of humans, animal, plants beyond laboratory boundary	Release into air beyond lab boundary	Mechanical failure of equipment or HVAC	Design and equip facilities with redundant HVAC
Intentional infection of humans, animal, plants beyond laboratory boundary	Theft of materials or equipment from laboratory and subsequent misuse	Insider: breach or lack of physical security, personnel reliability, materials control & accountability	Implement authorized access procedures and equipment. Only personnel who successfully complete screening, have a need to access, and who are assigned responsibility for oversight of the agent(s) or toxin(s) are allowed to access the agent(s) or toxin(s).

Prioritize Highest Risks

Not only should personnel at a regulated entity be literate about how control measures reduce the risks from BSAT, but they should also assure that, for these agents and toxins of high consequence, the potential for release into the community (intentionally or unintentionally) is interrupted. Box 2 lists some of these critical control points. A BSAT risk management plan

must take each of these critical control points into consideration and clearly document why they are not applicable to the laboratory or what specific control measures are in place and why those control measures are expected to reduce risk.

The expert panel suggests that ongoing focus on laboratory-acquired infections from BSAT limits the resources and attention given towards greater societal, more catastrophic risks that might occur if a BSAT is released from a laboratory, either intentionally or unintentionally. The panel recommends tiering regulated entities (and the regulatory requirements they are subject to)

Box 2. Example Critical Control Points for BSAT Laboratories

- Authorized release from lab
  - Waste removal
  - Liquid effluent removal
  - Air effluent removal
  - Unaltered agent/sample transfer
  - Inactivated agent/sample transfer
- Unintentional release from lab
  - Communicable infection of/from lab worker
  - Spill that goes beyond laboratory boundary
  - Unfiltered aerosol release from laboratory boundary
- Unauthorized release from lab
  - Unauthorized access to and removal of:
    - Agents/Samples
    - Information relating to safety and security of BSAT
    - Equipment
    - Waste
    - Agents/Samples undergoing transfer

based on potential external societal risks, rather than on internal occupational risks.

Peer Assistance for BSAT Risk Management Plans

Interviews with regulators and with regulated entities highlighted the diversity not only of the type of entity but of the diversity of biosafety and biosecurity expertise found at those entities. Many entities participating in the webinars expressed a desire to hold an open discussion with inspectors regarding the risk control measures to be used to minimize risk, using the experience and perspective the inspectors gain from their time at many different facilities. Inspectors interviewed expressed the view that current program practice limits them from making specific recommendations. The panel advocates the development of an assistance model that would allow entities to submit site-specific risk assessments and risk control plans for review by an appropriate entity or group, for example, by FSAP, peers, or via an interactive risk management tool. This assistance would allow for non-binding suggestions and adjustments to an entity's plan that prior to submission and regulatory review of the plan, with the feedback enhancing the expertise at the entity and also populating the assistance model with examples of risk assessment and, most importantly, risk-aligned control measures. Appendix Id provides a draft suggested scope of work for developing one option of an iterative, interactive risk management tool.

Other mechanisms for peer assistance include reciprocal peer reviews (between entities or among entities of a given sector) or the use of a peer audit (an example, more fully described in Appendix J, is the laboratory accreditation process developed by the American Biological Safety

Association (ABSA International) for non-Select Agent laboratories). Non-regulatory incentives for using a peer review or audit include strengthening the evidence across the community of which control measures are beneficial for reduction of various biorisks and provides entities with more confidence in preparing for regulatory visits. Regulatory incentives for utilizing peer assistance could include a reduction in inspection frequency (or time spent on inspections) due to more confidence from regulators in the risk management strategies of an entity that has been reviewed by peers.

Harmonization of BSAT Oversight Programs

The Federal select agent program is not the only U.S. government oversight program for biological agents and toxins. Depending on a variety of factors, scientists have several requirements for risk management of the same agents. Appendix G is a table listing examples of additional U.S.-agency based oversight of biological agents and toxins. In addition, the United States is subject or signatory to several international frameworks that require risk management of biological agents and toxins. Appendix H lists these international requirements. Within these various requirements is generally some implied or explicit risk determination –indeed, these documents exist due to an anticipated risk to the United States or global health from biological agents and toxins.

Special note must be made regarding the publication, *Biosafety in Microbiological and Biomedical Laboratories*, published jointly by the CDC and NIH (U.S. Department of Health and Human Services (CDC, NIH), 2009). This document, often called the BMBL, is included specifically in the Select Agent Regulations as a primary source for risk control requirements for BSAT. CDC and NIH first published the BMBL in 1984 as a compilation of best practices in biosafety for those working with biological agents, along with a suggested stratification of risk control measures for agents with common characteristics into biosafety levels. Risk assessment, as identified in the BMBL, is targeted towards prevention of laboratory-acquired infection. Many consider the publication as guidance for self-governance, as BMBL provisions are not used as requirements for compliance (although it has been widely adopted across many organizations for internal compliance). The Select Agent Regulations recommend consideration of the BMBL when a biosafety plan is developed and regulators have used provisions of the BMBL as criteria for inspection in the past. Reliance on the BMBL by either FSAP regulators or regulated entities as a "checklist" of prescribed measures undermines the original intended purpose of the document. Although some regulated entities report that recent inspections have not utilized the BMBL as a regulatory document (with citations issued based on BMBL language), many of the entities involved in the webinars described rely rather singularly on the BMBL to assign a biosafety level, rather than evaluating control measures for risk reduction. The BMBL advocates the use of risk assessment to guide choices for risk control and acknowledges that site-specific risk management is imperative by stating that, "[r]isk assessment is an important responsibility for directors and principal investigators of microbiological and biomedical laboratories (pg. 9)." Those directors and principal investigators should then "make a determination of the appropriate biosafety level and select additional precautions indicated by the risk assessment."

While this report will not further belabor this point, the alignment, duplication, or potential conflict between the different requirements will affect the overall risk management process of the agent – especially if the oversight body uses different risk management processes and assumptions. Harmonization of risk management terminology, method, and data could be

beneficial to risk reduction and enable the effective use of resources to manage multiple risks. The panel recommends that requirements be reviewed and harmonized requirements.

Table 7 lists some suggested actions, some more immediately applicable (near-term) and some with extended timelines that require more deliberations or actions from a different party (long-term), that could improve availability, access, and quality of data informing risk assessments and improve the alignment of BSAT risk controls with identified BSAT risks

Table 7. Suggested Actions for Standardized Risk Assessment Inputs, Risk Control, and Risk Prioritization

Increase availability, access, and quality of data informing risk assessment and risk-based decisions		
	Near-Term Actions	**Long-Term Actions**
Regulated Entity	In BSAT plans (biosafety, security, incident response), document the sources of information utilized for risk assessment and decisions on risk controls. (Recommendation 1.3, 2.2, 3.2)	Utilize data sources published or facilitated by FSAP; contribute data to FSAP collections. (Recommendations 2.2, 3.2)
Regulator	Evaluate the data sources currently used to inform programmatic decisions (e.g., listing, FSAP procedures, etc.) and the data collected during FSAP activities. Facilitate a mechanism to compile and publish these data for entity and FSAP use to inform BSAT risk management. (Recommendations 2.2, 3.2)	Publish guidance that encourages and facilitates the use of compiled data by entities and FSAP to inform BSAT risk management. (Recommendation 2.2, 3.2)
Regulations	N/A	N/A
Improve alignment of risk controls with identified risks		
Regulated Entity	Explicitly document, in biosafety, security, and incident response plans, how control measures selected reduce identified risk. (Recommendation 3.3).	Utilize assistance from peers and/or FSAP to evaluate alignment of control measures with identified risk. (Recommendations 2.2, 3.3) Utilize FSAP-provided risk scenarios to conduct risk assessments and risk evaluations. (Recommendation 3.2, 3.4)
Regulator	Expect, and guide, entity documentation and literacy on why and how control measures selected will reduce identified risk. (Recommendation 1.3, 3.3) Facilitate development of mechanism (peer assist, program review, or other) to guide entity development of a BSAT risk management plan where control measures align with identified risks. (Recommendation 3.3) Develop risk scenarios for use by regulated entities to assure consideration of all risks of concern in their site-specific risk assessments and risk evaluations (Recommendations 3.3, 3.4)	Utilize BSAT risk management plan to assess entity actions of risk reduction (and, thus, compliance with SAR). (Recommendation 1.2, 3.3). Initiate discussions with other U.S. government agencies to harmonize risk management approaches, if publications by those agencies are cited by either regulation or program documents, as references to be used to determine risk control measures. (Recommendation 1.1)

Regulations	N/A	Revise SAR to reflect development of and reliance on entity-specific BSAT Risk Management Plan to reduce FSAP-targeted risks (Recommendation 1.2)
Table 7, continued. **Prioritize risks to society over occupational risks to individuals**		
Regulated Entity	Continue to report incidents as required.	Follow tiering, if implemented, per revised regulations
Regulator	Evaluate reported incidents to determine the likelihood and consequences of different biorisks from the incident. Map these results to the agents or toxins involved and the reported root cause of the incident. Analyze this information to determine if the incidents (and reporting facilities) can be tiered into those with greater risk to society versus those most impacting internal occupational safety.	Propose tiering scheme based on results of incident evaluation (left), if those results demonstrate that tiering would allow a focus of government resources to greater societal risk.
Regulations	N/A	Revise regulations to adopt tiering scheme, if such an approach appears to be appropriate.

Risk Management Systems and Culture

Nearly every high-risk industry utilizes risk assessment and risk management in some fashion. Specific inputs for risk assessment may differ as do(es) the risk(s) targeted – for example, financial decisions or environmental, ecological, or public health impacts, etc.

Despite the significant differences between industries and the risks targeted, literature review of common risk management practices in several industries reveals that the risk management method is similar and is reflected, above, in Table 3 (Committee on Establishing and Promoting a Culture of Safety in Academic Laboratory Research 2014; Rusek and Lowenthal 2015; Committee on the Effectiveness of Safety and Environmental Management 2012; Eherts 2008; Garcia 2008; International Risk Governance Council 2015; Le Coze 2008; Mack, Snair and Choffnes 2016; Salerno and Gaudioso 2014; OECD Environment Directorate 2008).

Common benefits and challenges in risk management exist across all industries examined as part of this study:

- Clear, concise, and consistent terminology
- Understanding and utilization of a common process
- Documentation
- Alignment of control measures with reduction of identified risks
- Platform for prioritization, communication, and resource allocation

Many industries developed current risk management strategies in response to significant and catastrophic incidents. Over time, those who study safety science have noted an evolution in

responses to incidents (Martinez-Corcoles, Gracia, Tomas, & Peiro, 2011). Early incident response centered on technology – the application of engineering or other technical measures to control hazards and prevent injuries. This approach presumes that a linear chain of events causes accidents. Further examination of the root causes of incidents led to a more systems-based approach – utilizing understanding of interactions between people, tasks, technology, and the environment to pursue risk reduction goals and an acknowledgment that accidents result from complex interactions. More recently, risk management strategies have focused on the underlying organizational shared values, assumptions, and beliefs towards and relative importance of workplace safety – often termed "culture." Highlighted by management commitment and involvement, this approach recognizes that it is rare that a single individual bears the entire responsibility for an undesirable outcome (Committee on Establishing and Promoting a Culture of Safety in Academic Laboratory Research, 2014).

All of these approaches are relevant and critical to reducing risk; however, this evolution acknowledges that for technical- and systems-approaches to succeed, an organizational culture that holds safety and security as integral and imperative parts of its mission is necessary.

Failures identified with incidents across researched industries (Committee on the Effectiveness of Safety and Environmental Management 2012; Rusek and Lowenthal 2015; Salerno and Gaudioso 2014), including the biosciences, tend to be similar:

- Prioritization of production over safety
- Unclear lines of responsibility and accountability
- Adherence to only minimal standards with no question as to whether additional measures might be necessary to address risk
- Lack of recognition of hazards and risks
- Safety and security not considered in decision-making
- Corrective action addresses symptoms not causes
- Failure to integrate and apply experience and lessons-learned
- Lack of effective training programs
- Lack of non-punitive incident or near-miss reporting
- Disregard for safety and security expertise

While there is still not a consistent definition for safety (or security) culture across the many industries that are currently discussing it, key features that define a safety culture are (Committee on Establishing and Promoting a Culture of Safety in Academic Laboratory Research, 2014; Rusek & Lowenthal, 2015):

- Strong leadership and management for safety – "walk the talk"
- Lines of authority and accountability are clear
- Two-way communication and free exchange
- Continuous learning about safety; information flow and self-criticism are incentivized

- Strong safety attitudes, awareness, and ethics
- Learning from incidents; assign greater importance to problem-solving than finding blame
- Collaborative efforts to build safety culture; responsibility for success is shared by all
- Promoting and communicating safety
- Institutional support for funding safety
- Prioritize expertise, not seniority, in decision-making
- Non-punitive reporting
- Internal peer group review

When these observations are aggregated, as in the lists above, a need to focus risk management activities beyond the laboratory and the scientists in the lab becomes obvious. Unfortunately, the more technical risk management approach described as "complex" in the discussion of biorisk assessment, above, becomes even more complex when adding in attributes of positive organizational culture as a key risk control measure.

As will be discussed in more detail below, industries struggling with this additional complexity have developed safety management systems (SMS) and require that regulated entities develop a more holistic, organizational approach to risk management. Regulators still monitor industry compliance via targeted inspections, but the entities must also develop and implement an audit program (internal and/or 3rd party – approved by regulators). Different configurations of groups of technical experts are also being utilized to gather industry-specific information (best practices, incidents, lessons-learned, etc.) to monitor trends and to provide information to regulators and regulated entities. In many industries, performance-based regulations have replaced prescriptive regulations where decisions on risk control reside with the entity, in order to reverse accountability for risk management back to the regulated community and to avoid the perception that compliance is equivalent to safety.

A hallmark of a management system is the measurement and analysis of performance indicators (Burnett & Olinger, 2014). Without the feedback loop, often represented by the Plan-Do-Check-Act (or PDCA) cycle, a systems-approach is not in place. This reliance on performance measurements acknowledges that any system will, left on its own, degrade over time, and that only continuous observation and maintenance will prevent this degradation. Unfortunately, performance assessment programs often degrade as well, due to complexity and an overwhelming level of detail. The complexity and detail is, however, necessary. The trick is to focus attention and resources on subsets of the system (key issues of concern) and/or on aggregated or higher-level indicators (key performance indicators). Table 8 contains a listing of possible areas of focus and accompanying performance indicators regulated entities and regulators. For the most part, these example indicators were derived from those developed by the Organisation for Economic Co-operation and Development (OECD) for the chemical industry (OECD Environment Directorate, 2008). Strategic development of performance indicators relevant to FSAP requires a longer and more focused effort and is included in the suggested scope of work for the technical working group in Appendix Ia.

Table 8. Example Performance Indicators for Entities Working with BSAT

Area of focus	Outcome Indicator(s)	Activity Indicators (to support outcomes)
"GOOD SAFETY CULTURE" FEATURES		
Biorisk management policy	A policy is written and communicated to emphasize the importance and priority of safety and security of biological materials. Extent to which employees act in accordance with the policy.	Is policy conveyed to employees? Is policy reviewed and updated? Is the policy clear that safety and security of biological materials is a priority for the entity?
Documented and assigned roles and responsibilities	Roles and responsibilities for activities impacting BSAT are documented and communicated across entity (not just lab). Extent to which roles and responsibilities are adhered to.	Is there a system for establishing roles and responsibilities? Do those working with BSAT help to develop the roles and responsibilities?
Literacy with roles, responsibilities, and risk management plan	All personnel assigned a role(s) and responsibilities for BSAT can explain their role, responsibilities, and how the BSAT risk management plan identifies and reduces risk.	Are roles and responsibilities effectively communicated? Does training and other communication address how risk controls reduced risk?
Incident reporting and investigation	A non-punitive reporting and investigation system for incidents, excursions, concerns, etc., exists and is utilized	Are reportable incidents defined? Are employees encouraged to report concerns? Is there an open atmosphere for reporting without fear of punishment?
Two-way safety and security communication	Extent the key findings of risk assessment are communicated to employees. Extent to which suggestions and complaints result in changes to the system.	Is it obvious that safety and security of biological materials takes priority in cases where there is a conflict between safety/security and operational goals? Are there systems for appraisal and feedback to employees?
Strategic and collaborative resource allocation discussion for BSAT (money, time, people)	Extent to which resource allocation to BSAT activities is discussed. Extent to which resource allocation discussions involve all representatives of those assigned BSAT roles and responsibilities.	Is there a mechanism to identify and communicate the need for resources to implement a BSAT risk management plan? Are there funds available to implement BSAT risk management plan? Is there a mechanism to determine which BSAT activities can move forward if resource allocation is not adequate to provide effective risk reduction for all activities?
Peer review of BSAT risk management plan	Peer review (and oversight) including safety and security SMEs for BSAT risk management activities routinely occurs for BSAT activities. Extent to which peers are utilized, including safety and security experts, to review BSAT activities and the risk management plan.	Is expertise and experience in BSAT risk reduction actively cultivated? If internal expertise is not adequate, is external expertise solicited?

Table 8, continued.

Area of focus	Outcome Indicator(s)	Activity Indicators (to support outcomes)
CRITICAL CONTROL POINTS (see Box 2)		
Waste treatment	Waste treatment is documented and validated prior to release from laboratory.	Is a method for treatment of the specific types of waste from the BSAT facility documented? Is the process validated for test loads? For real loads? Is there are process to hold waste prior to release if validation is not complete or cannot be confirmed?
Effluent (liquid, air) treatment	Effluent (liquid, air) treatment is documented and validated prior to release from laboratory.	Is a method for treatment of the specific types of effluents from the BSAT facility documented? Is the process validated for test effluents? For real effluents? Is there are process to hold effluents prior to release if validation is not complete or cannot be confirmed?
Transfer of unaltered samples	Unaltered samples are transferred from the laboratory in secure packaging (e.g., triple packaging) and are transferred to sites authorized to receive them. Extent to which samples reach their destination without release from packaging. Extent to which transfers are made to authorized parties. Extent to which authorization is received prior to transfer.	Is training provided on proper packaging for transfer? Is a transporter's authorization to transfer BSAT reviewed prior to transfer?
Sample inactivation prior to transfer from laboratory or to lower containment	Extent to which inactivation procedures are identified, documented, and validated for the specific BSAT and the specific procedure.	Are inactivation procedures researched for the specific BSAT and validated for the specific BSAT and procedure? Is inactivation validated for all transfers moving out of the laboratory or to lower containment?
Communicable disease surveillance	Extent of enrollment in communicable disease surveillance by those potentially exposed to communicable BSAT. Extent to which potential and known exposures and illnesses are reported and evaluated.	Does BSAT personnel work in collaboration with medical personnel to establish communicable disease surveillance appropriate for the BSAT? Are requirements and notifications established and supplies provided for monitoring and reporting potential exposures and illnesses?
Spill response	Spill response (especially for spills moving outside laboratory boundary) is timely and limits or mitigates impact of the spill beyond the laboratory. Time required for response to a BSAT spill beyond the laboratory boundary. Extent of spill beyond laboratory boundary. Extent of mitigation measures utilized to minimize impact of spill beyond laboratory boundary.	Are spill response procedures developed specifically for the BSAT and procedures utilized? Are spill response procedures drilled? Are outside experts identified and retained for response if needed?

Table 8, continued		
Area of focus	**Outcome Indicator(s)**	**Activity Indicators (to support outcomes)**
Equipment malfunction response	Equipment malfunction response (especially for malfunctions that would potentially result in aerosol or other release outside laboratory) is timely and limits or mitigates impact of the release beyond the laboratory. Time required for response to minimize impact of equipment malfunction on release of BSAT from the laboratory. Extent of release of BSAT due to equipment malfunction beyond laboratory boundary. Extent of mitigation measures utilized to minimize impact of release beyond laboratory boundary.	Are equipment malfunction response procedures developed specifically for the BSAT and procedures utilized? Are response procedures drilled? Are outside experts identified and retained for response if needed?
Access control	Extent to which access control is assigned and utilized correctly for access to BSAT repositories, laboratories, information, equipment, and waste.	Are BSAT repositories, laboratories, equipment, and waste secured by access control measures that allow access only to authorized personnel? Is access to information regarding BSAT provided only to authorized personnel? Is release of information about BSAT and BSAT procedures evaluated for sensitivity prior to release?
Authorized access assignment	Extent to which the roles and responsibilities of personnel are reviewed for appropriate levels of access. Extent to which access is assigned for different levels of access control. Extent to which training is assigned, required, and completed prior to access being authorized. Extent to which unauthorized access was provided or attempted.	Is there a documented review procedure for those requesting access? Is there a training and competency program required prior to access to different areas? Is there a mechanism to monitor and/or report unauthorized access or attempts of unauthorized access?
Emergency planning	Extent to which entity has considered and addressed potential BSAT releases outside laboratory boundary that might be caused by natural disasters or man-made events (e.g., earthquake, hurricane, tornado, fire, bomb (threat or incident), etc.).	Does the entity have an emergency planning process? Does the entity conduct drills and exercises to assure that the emergency plan is evaluated and validated to achieve the outcomes of preventing (or addressing) BSAT release outside laboratory boundary?

Another key finding in reviewing the change in mindset in response to catastrophic incidents in several industries is the distinction between "occupational safety," and, for many of the industries reviewed, "system safety." This approach acknowledges that occupational safety incidents (injuries, illnesses, etc.) are generally caused by hazards that can be contained within the boundaries of the entity. System safety, on the other hand, targets those points in the process where a mechanical or other failure would result in an incident with impact beyond the boundaries of the entity and cause significant impacts to humans, animals, plants, environment, infrastructure and/or economy. Increasingly, these failures are targeted by safety management

systems and improved safety culture (Committee on Establishing and Promoting a Culture of Safety in Academic Laboratory Research 2014; Committee on the Effectiveness of Safety and Environmental Management 2012; Eherts 2008; Martinez-Corcoles, et al. 2011; OECD Environment Directorate 2008; Rusek and Lowenthal 2015).

Table 9 lists some suggested actions, some more immediately applicable (near-term) and some with extended timelines that require more deliberations or actions from a different party (long-term), that could assure that BSAT risk reduction is supported by the entire organization and is considered a high priority.

Table 9. Suggested Actions for Risk Management Culture and Organization Support

	Near-Term Actions	**Long-Term Actions**
Regulated Entity	Document top management commitment and active engagement to BSAT risk reduction. Document roles and responsibilities for supporting and contributing to BSAT risk reduction across the entity. Require literacy with plans developed for BSAT laboratories across the entity (Recommendation 4.1). Examine training programs to assure that both concepts and procedures are included, to increase knowledge transfer from setting to setting as well as critical thinking (Recommendation 4.3).	Include risk reduction measures that target the organization top-to-bottom in BSAT risk management plan (Recommendation 4.1).
Regulator	Document organization-wide engagement (or lack) during inspections. Expect literacy across the entity with BSAT plans (Recommendation 4.1).	Expect top management involvement and literacy during inspections (Recommendation 4.1).
Regulations	N/A	[evaluate if system-approach would require revision of regulations]
Key Performance Indicators		
Regulated Entity	Identify any performance indicators already in place for verifying that BSAT risk management is functioning as designed (Recommendation 4.2).	Collect performance measures as specified by FSAP and as identified in the site-specific BSAT risk management plan (Recommendation 4.2).
Regulator	Develop performance indicators that focus on key concerns for FSAP (Recommendation 4. 2). Collect best practices for measuring performance from entities.	Provide guidance to entities for collecting measurements for the performance indicators identified for FSAP. Utilize these indicators during inspections and request that these be reviewed and reported as part of the entities self-inspections (Recommendation 4.2).
Regulations	N/A	N/A, unless it is appropriate to specify collection of performance measurements as part of the regulations.

4. ALTERNATE OVERSIGHT APPROACHES AND APPLICABILITY TO FSAP

Regulatory Oversight Approaches in Other High-Risk Industries

Review of reports and regulations from other industries reveals a natural division of oversight into four primary categories:

- Self-governance – stakeholders within an industry mutually choose to operate under a given code of conduct including moratoria on conducting certain types of activities.
- Voluntary Compliance with Industry Standards – stakeholders within an industry develop standards comprised of consensus best practices and mechanisms for accreditation or certification of facilities or individuals who meet those standards.
- Performance-Based Regulation – regulations are drafted that specify the outcome required but not the action required to generate the outcome; the regulated community generally relies on best practices to meet the requirements.
- Prescriptive Regulation – exact or nearly exact actions are specified and required of the regulated community.

Table 10 compares the advantages and disadvantages of these four categories of oversight.

Oversight of biological agents have implemented all four categories, to some degree. As mentioned earlier, the BMBL is a good example of a guidance produced to prompt effective self-governance (and the wide adoption of it by many organizations is a good indicator of its success). The NIH Guidelines emerged at scientist request to address concerns regarding early recombinant DNA technology and as an outcome of a concurrent self-imposed moratorium and scientist dialogue around the issues. The BMBL might also qualify (loosely) as an industry standard, despite its government authorship, as the process to develop the BMBL relies on subject matter experts across the biosafety and infectious disease spectrum. The development of the CWA 15793 consensus document and the current work to transition this document to an ISO publication, has utilized the input of biosafety and biosecurity professionals across the globe and is intended as a standard to which an organization can be certified. The OSHA Bloodborne Pathogen Regulation (29 CFR 1901.1030) is intended to be a performance-based regulation, where the regulated employer is required to develop a site-specific exposure control plan that determines which employees are at risk and details site-specific actions designed to meet the goals set out in the regulation. A wholly prescriptive regulation is not widely-use in the United States for oversight of biological agents; however, the additional requirements contained in the SAR for entities possessing Tier 1 agents are prescriptive.

A hypothesis could be put forward that self-regulation would be the most desirable oversight model – where an industry voluntarily sets and meets goals for risk reduction and the government is not needed to provide resource-intense oversight with taxpayer dollars. The analysis below examines this hypothesis and ultimately concludes that while self-regulation is often at the origin of moving an industry from no oversight to some form of standardized governance, in general, self-governance is not sustainable and, ultimately, more prescriptive regulations appear. While this initial evolution towards prescription is seen across many industries, a somewhat counter-evolution appears once prescriptive regulations are established

(and failed in certain cases). Ultimately, regulatory oversight becomes reliant on standards developed by industry, initiated during the self-governance phase, to provide guidance for the regulated community to make (at least some) site-specific decisions on risk control, using risk-based performance standards. Whether this balance between self-governance and strict regulatory oversight remains stable or if it naturally swings between the two remains to be seen. Most of the industries reviewed represent ongoing technological innovation that is, by default, unpredictable. Any oversight model will necessarily be reactive to and cognizant of this innovation, uncertainty, and unpredictability.

Table 10. Comparison of Different Models for Oversight

	Advantages	**Disadvantages**
Self-Governance	Initiated and developed by industry experts Motivated by peer pressure and acceptance Low (or no) cost to government; cost borne by individual businesses Flexible – can be adapted more quickly to emerging issues	No mechanism to compel compliance Perspective may be limited by individual experience and can create (or lead to perception of) conflict of interest Inconsistent application
Industry Standards	Relevant to industry Seen as stamp of approval by peers and community Can be linked to licensing or funding Low (or no) cost to government; cost borne by industry groups and individual businesses	Voluntary may not be truly voluntary (may be linked to critical operational requirements such as licensing or funding) Development and implementation may take a long period of time
Performance-Based Regulation	Allows site-specific decision making Clear entity accountability Flexible – enables regulators and entity to adapt to emerging issues	Requires significant training and technical depth for inspectors and regulated entities More resource-intensive for both regulators and the regulated entities. Due to lack of specificity, letters of interpretation are often needed to supplement the regulation
Prescriptive Regulation	Clear requirements and expectations Inspectors and regulated entities require less technical depth	Little flexibility for unique or diverse situations Requires time to update Difficult to develop provisions that are equally applicable across many entities and risks Can lead to a mindset that safety/security is equivalent to compliance

Self-Regulation

In considering the development of regulations related to safety culture in other industries, it is useful first to consider the development of self-regulation more broadly to understand what conditions must be met for self-regulation and why industries choose to self-regulate. Regardless

of why self-regulation develops, the industry must meet four criteria for self-regulation to occur: 1) data collection, 2) data analysis, 3) monitoring, and 4) compliance (Gupta & Lad, 1983). First, information about any given industry and its operating environment must be collected to understand what should be regulated and why. Second, any information collected must be processed in a systematic way. Third, firms must be monitored to determine the degree of compliance, i.e., to determine if they are self-regulating. Lastly, for regulation to be effective, standards must be enforced.

Why Self-Regulation Develops

Self-regulation of industries (including regulations rooted in safety) can arise for many reasons (von Englehardt & Maurer, 2013). Industries may choose to self-regulate due to actual or *perceived* risks. In this context, risk refers to a variety of detrimental consequences to the success of the industry including bad publicity, loss of funding, litigation, and loss of life. For example, following the 1979 incident at Three Mile Island, the nuclear power industry developed the Institute of Nuclear Power Operations (INPO) to set forth industry standards for safe nuclear power operations (http://www.inpo.info). Some industries choose to pursue self-regulation for the fear of government action. One prime example of this is the creation of youth antismoking programs by the tobacco industry (Sharma, Teret, & Brownell, 2010). From this analysis of why self-regulation develops, it becomes apparent that the development of regulations is not strictly limited to the nature of the risks, but includes the mission, organization (publically-traded, state institution, etc.), and nature (research, public health monitoring, consumer products, etc.) of the industry regulated.

Evolution of Self-Regulation to Prescriptive Governance

A review of several industries indicates that when actual, perceived, or potential risks are severe (such as loss of life), the evolution of regulatory frameworks is strikingly similar. Initially, individual institutions begin to self-regulate for any of the reasons aforementioned. Individual self-regulation tends to lead to some sort of industry-wide standards, though the reasoning for institutional level self-regulation may differ from industry-wide standards. For example, a company may self-regulate to please customers while industry-wide regulations may arise as an alternative to government regulation. Ultimately, as more research/evidence emerges about the consequences of an industry (ex: effect of smoking on lung cancer) or some sort of stimulus or incident occurs (ex: a nuclear meltdown) more prescriptive regulations appear from one or more government agencies. For example, the risks of antimicrobial resistance to medically relevant antibiotics is a great threat to the efficacy of treating certain infections in humans. In 2013, in an effort to reduce antimicrobial resistance, the US Federal Drug Administration (FDA) requested that suppliers of antibiotics voluntarily phase-out medically important antibiotics (FDA Guidance #213) from livestock use. After voluntary participation, the FDA proceeded to more prescriptive regulations that ban the use of antibiotics for purposes of increased meat production and require veterinarian oversight in the use of medically important antibiotics (21 CFR Part 558).

Application of Other High-Risk Industry Oversight Models to FSAP

A review of several industries subject to infrastructure protection security regulations[18] demonstrates that the nature of government oversight of high-risk activities may be driven by a

[18] nuclear, chemical, marine, rail, and explosives

variety of factors: 1) size, complexity, and diversity of regulated community; 2) primary source of industry funding; 3) ubiquity; and the age of regulatory initiative. Below is a discussion on each of these factors as it relates to the FSAP.

Size, Complexity, & Diversity

The 291 entities registered with FSAP in 2015 represent a small, but widely diverse regulated community. Table 2 compared the distinct differences between the two largest sectors registered – academic laboratories and state public health laboratories. The remaining roughly 40% of registered entities are divided across three additional sectors: federal government, commercial (labs for hire), and privately owned (e.g., pharmaceutical companies and vaccine manufacturers) laboratories (Federal Select Agent Program, 2016). While these three smaller sectors have similarities to either the academic or public health laboratories (or both), they also possess unique sector-specific features as well. The largest sector represents 93 entities; the smallest is comprised of 17 entities. These numbers are very small compared to the overall size of the U.S. life sciences, public health, and animal health complex.

A initiative of FSAP, recently released to regulated entities for feedback, is to score entities based on their complexity. Proposed FSAP derived complexity scores "(range -1.0 to 11.4) is based on the total number of biosafety levels operated, Tier 1 status, possession of BSAT status, additional BSAT specific required enhancements, approval to conduct restricted experiments, and work objectives (i.e., work with animals, arthropods, plants, quantity of BSAT propagated or purified). These scores are used to group entities into super, high, moderate, and low complexity categories (FSAP, personal correspondence)." This initiative is currently in the proposed stage, but the draft results demonstrate that this small, regulated community is extremely diverse with labs distributed across each category of complexity.

In addition to this "procedural" complexity, each entity is registered to work with a different portfolio of BSAT. Appendix E lists the 66 BSAT agents. These differences highlight the point that no entity is likely to be similar to another entity and that providing oversight over this small, but stunningly diverse community, requires an oversight mechanism that takes into account the diversity of regulated entities but also allows consistency in review of these entities across the entire spectrum.

Industry Funding

Most of the industries reviewed for this study are commercial industries and private enterprises – they produce a product for sale in the domestic and/or international marketplace. The profits from those sales support their infrastructure and their compliance with oversight regulations. In stark contrast, fewer than 25% of FSAP regulated entities are commercial or private. The majority of entities receive funding for activities involving BSAT from government grants or federal, state, or local public funding. Funding dictates what activities are designated for the use of these public grants or funds (e.g., specifically designed research objectives, public health activities, animal health activities, etc.). Institutions receiving public funding are expected to provide infrastructure and administrative support via their own means or with the indirect funding that is "taxed" to the funder by the institution for housing the funded activity. The dispersal of indirect costs across the institution is largely discretionary – this mechanism may or may not adequately fund safety and security efforts.

Other industries (e.g., nuclear power, aviation, off-shore drilling, etc.) have contributed some of their profit to the support of industry associations that can be utilized to develop industry standards, independent from government oversight.

Ubiquity

Legitimate users of biological materials are in every municipality in every state of the United States via medical and public and animal health offices. The community or environment can contain many of the agents on the BSAT list, outside of laboratories. Discoveries that might have a dual-use implication (ability to use the discovery to harm, rather than help, society) arise from explorations designed to benefit society. This vast complex of medical and life sciences complicates the identification and restriction of uses and users, as has been done with nuclear materials and explosives, where the targeting and containment of uses and users is more straightforward without damage to societal necessities like medical care.

Age of Regulatory Initiative

FSAP is a relative newcomer to providing oversight for a high-risk industry – Congress mandated the expansion of the Select agent program to include possession of BSAT in 2002 and the resulting regulations went into effect in early 2003. Contrast those few years with the Nuclear Regulatory Commission which was established by the Energy Reorganization Act of 1974. Age matters because as was pointed out above, regulatory approaches evolve over time as oversight modulates with the need for the industry to do its work and/or in response to additional incidents (or the lack thereof).

Application of Other US-Based Regulatory Oversight Models to FSAP

As discussed above, the evolution of regulatory oversight for several industries has moved from self-governance towards prescriptive oversight and then, when more prescription failed to stop incidents, "backwards" towards less-prescription with a broader and deeper systems-approach to assure application and oversight beyond just technical risk controls – targeting precursors such as management engagement and buy-in, etc. As a relatively young regulatory initiative, FSAP may have yet to find the balance between prescription- and performance-based oversight which is complicated by the extremely small, but highly diverse regulated community. What is clear is that a single set of prescriptive measures cannot address all the risks in all of the entities in the FSAP community while also preserving each entity's ability to conduct legitimate research, production, clinical, and/or diagnostic services. These results reinforce the focus and findings of this study on improving and "front-loading" the risk assessment process and the quality and consistency of the information used to conduct risk assessments to enable informed and effective choices for risk control measures.

Some of the dichotomies ripe for analysis in seeking lessons-learned from other industries include:

- Carrot versus stick: Is risk reduced more effectively by providing incentives or punishments?
- Compliance versus risk-based inspections: Should inspections target compliance with specific regulatory provisions or should inspectors determine if effective risk-reducing measures are in place?

- Regulator versus entity accountability: Do the regulations put the burden of proof of compliance on the regulator or the regulated entity? How does this burden of proof affect ownership (on either parties' part)?
- Delegated versus direct oversight: Can third-parties participate in oversight activities (e.g., third-party audits) without diluting either the credibility or the interest of the regulator?
- Disclosure versus non-disclosure of information about safety[19] events: Should the nature and occurrence of incidents be disclosed to facilitate sharing and lessons-learned (presumably to prevent another similar incident elsewhere in the community)?
- Simulated versus real-life events: Can drills and simulations effectively mimic real-life events and identify areas for improvement in incident response and risk management before a real-life incident discloses those gaps?

Frustratingly, review of these issues across many industries reveal that no single method is clearly more effective and that oversight usually comprises a mixture of all of these strategies – some more successfully than others at different points in the timeline of regulatory evolution or in response to incidents. The nuances between these different strategies are also often anecdotal; examination of the regulations or the carefully scripted program documents does not tease out some of these aspects.

Application of Other Countries' Oversight of Biological Agents and Toxins to FSAP

Due to the extensive dissimilarities between other high-risk industries and enterprises possessing BSAT, as discussed above, directly comparing oversight mechanisms to find potentially applicable alternates is difficult (although, as will be discussed below, some of the tools utilized in oversight and risk management for these industries could serve FSAP well, with appropriate modification to the FSAP setting). This report attempts to make a more direct comparison between countries regulating biological agents and toxins – in particular those agents and toxins with properties that, in the US, would qualify them as BSAT. Several countries[20] regulate all hazardous biological agents, regardless of security concern. Oversight mechanisms, in various applications, include publication of codes of practice (guidance (non-binding) or standard (binding)), laboratory registration, laboratory certification, agent/process permitting, and/or personnel certification. In some cases, regulatory authorities conduct routine inspections, some inspect only with cause, and in others, the regulatory authority exists to maintain the guidance or standard and to serve as a resource.

After review of applicable regulations from the countries listed, two countries in particular stand out for comparison to the U.S. FSAP – Australia and Canada. Both regulate a list of agents deemed by the country as Security Sensitive Biological Agents (SSBAs). Australia regulates SSBAs strictly from a security perspective, while Canada's newly enacted Canadian Biosafety Standard (CBS) harmonized several previously separate regulations and include additional

[19] Non-disclosure of security events is generally less controversial due to sensitivity; however, non-disclosure of security events can limit the sharing of lessons-learned.

[20] Australia, Canada, European Community, Israel, Japan, Singapore, South Africa, United Kingdom

security requirements for SSBAs. Highlights from the two regulations that are of particular relevance to BSAT and FSAP follow.

Australia

Three features of the Australia SSBA standard (2013) reflect observations and recommendations elsewhere in this report – namely, development a risk management plan, using a systems-based approach, and developing performance indicators. Excerpts of SSBA standard follow:

> *2.3 Risk management plan*
>
> *(1) The entity must ensure a risk management plan is developed, documented and implemented, following the risk assessment. At a minimum the risk management plan must include: (a) treatment of the risks identified in Subclause 2.2.2 [Risk Assessment] and plans for monitoring and review of the risk management process. (2) The risk management plan must be effectively communicated to all personnel handling SSBAs or sensitive information relating to SSBAs and to others as relevant. (3) As part of the risk management plan, standard operating procedures (SOPs) for secure handling of SSBAs must be developed, documented and implemented.*
>
> * * *
>
> *Part 8 SSBA management system*
>
> *8.1 Objective*
>
> *(1) To establish a systematic approach to the management of the biosecurity of SSBAs that takes into account risk and incident management, personnel management, physical security, information management, transport, and inactivation and decontamination in accordance with the requirements of the NHS Act, the NHS Regulations and these Standards.*
>
> > *The management system approach implies that identifying, understanding and managing a system of interrelated processes for a given objective improves the entity's effectiveness and efficiency for managing SSBAs.*
> >
> > * * *
>
> *8.4.1 Performance management and analysis of data*
>
> *(1) The entity must ensure that data is identified, collected, stored and analysed to assess the suitability and effectiveness of the SSBA management system and to evaluate where continual improvement of the system can be made. Outcomes of this process must be documented.*

Another unique oversight tool found in the Australia SSBA is the use of four different inspection types: comprehensive, mid-cycle, spot-check, and desktop. The comprehensive inspection is a two-day inspection reviewing all aspects of compliance while the mid-cycle inspection is a single day and focuses on issues of concern during the comprehensive inspection or any changes to the facility or to the regulations. Inspections alternate between a comprehensive and mid-cycle approach. Spot-checks are used for focused follow-up on specific issues of concern. Regulators conduct desktop inspections remotely, working with the Responsible Officers to review reports and other paperwork required[21].

The SSBA standard requires that regulated entities identify hazards and assess risks. The standard states:

> *"[h]azards/risks to be identified should include what can happen, when and where it can happen, and how and why it can happen. Some examples of potential hazards are: theft of SSBAs; failure to properly screen staff; loss of records required to remain secure (for example, inventories); infection of personnel or visitors with an SSBA; disgruntled personnel causing a non-compliance or theft of an SSBA; inadequate access control and/or physical security allowing unauthorised access to SSBAs or secure records; inability of the entity to properly account for the storage or handling of an SSBA; and/or loss of an SSBA during transport. *** The identified risks should be analysed by determining the likelihood and consequences of the risk occurring and identifying existing controls and their effectiveness (Australia SSBA Standard, 2013).*

Canada

Canada's new CBS (2015) is markedly different than the approach from Australia in that the standard harmonizes regulations (the Australia SSBA standard targets only security-sensitive biological agents (SSBA) – the CBS targets all human and terrestrial animal pathogens and toxins, including listed SSBA[22]). To develop the CBS, the Public Health Agency of Canada (PHAC) utilized "an extensive multi-year consultation strategy to inform the development of Canada's regulations and other key national program elements. PHAC believes that stakeholder involvement throughout the process will lead to increased buy-in, ownership, and the potential to champion institutional change (Mantha, 2016)"

To develop the standard, the PHAC convened an Expert Working Group with the following stated mandate:

> *"The EWG shall provide technical advice and recommendations relating to biosafety and biocontainment pertaining to human and animal pathogen containment during the Expert Review and Consultation Phases of the CBSG development. Although the Agencies will be seeking comments on the entire document, the EWG will be asked to focus on sections requiring their specific expertise and input, as some sections are regulatory in nature and not eligible for debate or comment. All final decisions regarding any proposed content or changes to the CBSG are the responsibility of PHAC/CFIA in their role as the regulatory authority[23]."*

The CBS utilizes licensing as the primary tracking tool for compliance and requirements are highly prescriptive. A license is required to conduct the following activities with human pathogens and toxins in Canada: 1) possessing, handling, using 2) producing 3) storing 4) permitting any persons access to 5) transferring 6) importing or exporting 7) releasing or otherwise abandoning. A separate license is required for each risk group utilized and for SSBAs. The CBS requires the development of several different risk assessments (overarching, biosecurity, and local) and plans (biosafety manual, biosecurity, risk management, etc.).

---

[21] http://www.health.gov.au/ssba#inspection

[22] The CBS consolidates and harmonizes the following regulations: Human pathogens and toxins: Laboratory Biosafety Guidelines, 3rd Edition, 2004 (PHAC) 2. Terrestrial animal pathogens: Containment Standards for Veterinary Facilities, 1st Edition, 1996 (CFIA) 3. Prions: Containment Standards for Laboratories, Animal Facilities and Post Mortem Rooms Handling Prion Disease Agents, 1st Edition, 2005 (CFIA)

[23] http://canadianbiosafetystandards.collaboration.gc.ca/tor-mandat-eng.php

The Canadian government conducts agent risk assessments and assigns risk groups and containment levels. The regulation specifies the requirements for containment levels. Individuals are encouraged to perform risk assessments especially on uncharacterized or modified pathogens and toxins.

Relevance to FSAP

Because of the recent enactment of current versions of the Australia SSBA Standard and the CBS, extrapolation of the value of various features as alternate oversight mechanisms for the US is challenging. The primary highlights of this analysis are the provisions noted above that reflect observations from research and subsequent recommendations contained in this report, namely, the use of a single risk management plan, requiring a management system approach, the development and evaluation of performance indicators, the use of an expert working group, and broad consultation with the regulated community.

A Potential Model and Tools for Oversight and Relevance to FSAP

As noted above, only limited comparisons can be made between FSAP and other industries and other countries. Potential models and tools derived from elsewhere, then, must be carefully examined for applicability to the oversight of BSAT. Just because there is not a perfect alignment, however, does not mean there is no applicability. The case below – derived from a detailed analysis by the Transportation Research Board (TRB) for offshore drilling activities – recommends approaches that are similar to many of the above described. As part of their research, the Transportation Research Board invited representatives from the U.S. OSHA, Mine Safety and Health Agency, US Coast Guard, California State Lands Commission, United Kingdom Health and Safety Executive, and the UK Petroleum Safety Authority to discuss experiences utilizing safety management systems in regulatory oversight. Many of the recommendations derived for the off-shore drilling community in this report are broadly applicable, as seen in the range of industries and agencies interviewed and researched in this case.

Increasingly, regulators of industries with the demonstrated potential for catastrophic incidents are utilizing performance-based regulations and supplementing those with other tools designed to better support a culture of safety and reduction of risk to society. A good representation of these efforts (by regulators and industry) is the study completed by the TRB of the National Academies on Evaluating the Effectiveness of Offshore Safety and Environmental Management Systems published in 2012 (Committee on the Effectiveness of Safety and Environmental Management, 2012). This report recommends that the Bureau of Safety and Environmental Enforcement (BSEE – the regulator of U.S. offshore drilling operations – under the Minerals Management Service of the U.S Department of the Interior) adopt a "holistic approach to evaluating the effectiveness of SEMS [Safety and Environmental Management System – required by regulation] programs. ("Safety" in this case refers to system safety, rather than occupational safety - see the prior discussion on prioritization on catastrophic risks.) This approach should, at a minimum, include inspections, audits (operator and BSEE), key performance indicators, and a whistleblower program (pg. 5)." The following discussion highlights features of the following mechanisms and tools (drawn from the TRB report and other industry examples) and their potential utility to FSAP:

Oversight approach:

- Performance-based regulations
- Management System
- Priority on catastrophic risks

Tools to determine and support effectiveness:

- Input from technical working groups or organizations
- Peer Assist
- Targeted Inspections
- Audit
- Performance Indicators
- Emphasize Critical Thinking

Oversight Approaches

Performance-Based Regulations

As discussed above, performance-based regulations establish goals for the regulated community to meet, along with some benchmarks and guideposts, but require that the regulated entity develop its own organization-specific mechanisms to meet those goals. In the example of offshore drilling, the shift to performance-based oversight requires, by regulation, adoption of a safety management system utilizing industry standards developed by the American Petroleum Institute. This shifted the burden for demonstrating compliance from the regulator to the regulated entity. The regulator was then able to apply limited resources to addressing areas of concern.

The current SAR utilize this performance-based approach to a certain extent – requiring regulated entities to develop biosafety, security, and incident management plans based on the agents and activities they utilize. The regulations are very specific on requiring each plan to cover general topics and often inspections have focused on those specifics rather on whether the plan meets the goal of reducing risks from BSAT. Because the regulation separates the plans rather than integrating them into a holistic risk management strategy, it suggests different methods, via FSAP guidance, for the development of each plan. Integration of the plans into a comprehensive BSAT risk management plan, guided by a systems-approach (see below) and utilized as the primary guide to compliance, should focus both regulated entity and regulator on the goal of reducing risk, rather than enhancing a paperwork and compliance mindset (meeting and documenting only minimum standards).

Management System

As previously stated, several industries demonstrate an evolution beyond the sole reliance on technical measures that directly contain or control hazards. This evolution acknowledges that the hazards and thus, risks, are housed within an organizational system and culture that must be engaged and properly equipped to support and prioritize the containment and control required. Management systems (across many disciplines) are cyclical – with feedback based on performance, an emphasis on continuous improvement, and reliance on these critical actions:

1. Set a policy

2. Plan actions to support the policy
3. Implement the plan
4. Monitor and measure the performance of the implementation
5. Establish corrective and preventive action to address areas where performance requires improvement
6. Conduct regular program and management review of the entire system

Many management systems refer to this as Plan-Do-Check-Act or PDCA. In addition to this cyclical approach, management systems require participation by nearly every member of an organization, not just those who may encounter the hazard at the working level. The success of any risk reduction strategy relies on engagement and literacy of top management on risk and risk reduction– a management system explicitly requires this. The development and adoption of management systems is one of the most common responses to catastrophic or frequent incidents across many industries including aviation, healthcare, chemical production, minerals extraction, and more (Committee on the Effectiveness of Safety and Environmental Management, 2012; Salerno & Gaudioso, 2014).

In 2008, a CEN Workshop Agreement developed a biorisk management system for laboratories documented in CWA 15793 (later supplemented by an implementation guide CWA 16393). This international effort is underway to transition this agreement into an ISO publication. The biorisk management approach, or at least the elements to be included in a management system designed for reducing biorisks, may be of benefit to FSAP.

Priority on Catastrophic Risks

The TRB report distinguished between a focus on occupational safety and on "system" safety. For off-shore drilling, reducing the risks of a catastrophic incident require a different approach than keeping workers safe. While occupational safety is essential, it cannot prevent a blowout on an off-shore rig. Industries design system safety to manage the, "very rare but very high-consequence incidents that can lead to multiple losses of life, substantial property damage, and extensive environmental damage (pg. 30)."

For BSAT, prevention of laboratory-acquired illness is extremely important, but the genesis of the SAR (events involving the acquisition and malicious use of biological agents) prompted a focus towards managing those rare events that might lead to societal impacts such as community infection, epidemic spread, or malicious release of BSAT. These potential incidents necessarily involve the intentional or unintentional release of BSAT beyond secondary containment. This might occur during intentional removal of materials or waste without sufficient treatment, compromised or inadequate packaging measures for shipping, theft of agent or information, unintentional spills that extend beyond the laboratory barrier, mechanical failure that releases aerosols or effluent into the environment, contamination of personnel or materials leaving lab, and undetected and/or untreated highly communicable illness of laboratory workers. A focus on incidents within functional primary and secondary containment can be considered near-misses under this strategy, but should not be considered equivalent to events with significantly more consequence to the community. As discussed earlier in this report, a focus on critical control points and potential tiering entities based on this distinction between occupational and "system" risk could assist FSAP and entities in allocating resources and activities more efficiently.

Tools to Determine and Support Effectiveness

Input from Technical Working Groups or Organizations

The TRB report spotlights the Center for Offshore Safety (COS) – a "self-policing organization" that was set up by and for the companies working offshore in the aftermath of the Deepwater Horizon incident. COS was modeled after INPO that was established after the Three-Mile Island event.

The COS website provides the following description (www.centerforoffshoresafety.org):

> "*"The Center for Offshore Safety (COS) is an industry sponsored group focused exclusively on offshore safety on the U.S. Outer Continental Shelf (OCS). The Center serves the US offshore oil & gas industry with the purpose of adopting standards of excellence to ensure continuous improvement in safety and offshore operational integrity.*
>
> *The Center is responsible for:*
>
> - *Development of good practice documents for the offshore industry in the areas of Safety and Environmental Management Systems (SEMS)*
> - *Assuring that third party certification program auditors meet the program's goals and objectives*
> - *Compiling and analyzing key industry safety performance metrics*
> - *Coordinating Center sponsored functions designed to facilitate the sharing and learning process*
> - *Identifying and promoting opportunities for the industry to continuously improve*
> - *Development of outreach programs to facilitate communicating with government and external stakeholders"*

The creation of COS (and presumably other similar organizations) acknowledges that regulators do not possess the technical depth of the industry – these organizations were established to provide more independent technical assistance than either a self-governance (industries relying on internal technical expertise) or regulatory (relying on inspector and regulator technical expertise) model will.

While the budget required might alone disqualify a similar "industry-funded" independent organization for providing technical assistance to FSAP and regulated entities, the development of a working/advisory group – independent of regulatory oversight – could provide needed analysis and support.

Discussions with FSAP staff and regulated entities spotlighted that FSAP inspectors could provide a wealth of information on selection of risk control measures for use in securing and containing BSAT. The ability to provide a working group with this information to feed back into the regulated community and FSAP would allow contribution of this knowledge to the program without compromising the objectivity of the inspectors.

Peer Assist

"Peer assist" is a less formal and more targeted means of lending assistance—an approach used heavily in the (very competitive) airline industry (Greens undated, as cited by NRB). In this case,

respected peers from outside the organization (including, but not exclusive to, those who are similarly regulated) review an organization's compliance performance and management system implementation and offer helpful suggestions for improvement. The goal is strictly to help an organization improve and to be prepared for successful inspections and audits – results are not to be shared for any other purpose.

Peer assist could be of great benefit to BSAT regulated entities and to FSAP by facilitating the sharing of best practices and improving the quality of risk management plans prior to inspections, presumably resulting in a reduction of inspection and post-inspection time due to fewer compliance concerns.

Audits

Distinguishing between the terms "inspection" and "audit" can be difficult. For purposes of this discussion, an examination that determines if requirements are met is called an inspection, while an audit is an evaluation that an entity is actually doing what they say they are doing. The TRB report recommends that audits of SEMS programs consist of "a comprehensive, systematic collection and review of information to ensure the program is being maintained and operated as intended. Where possible, the audit should verify objective evidence that shows conformance with the SEMS program (pg. 38)." Audits can be first-, second-, or third- party. First-party audits are conducted by internal staff. External persons in an associated organization conduct second-party audits, while persons completely independent from the audited entity conduct third-party audits. The TRB report advocates that entities conduct or facilitate audits, via a BSEE-approved audit plan, to measure and document management system effectiveness. However, the TRB cautions, "[a]udits, in and of themselves, are not sufficient to improve safety. For audit results to be effective, the operator needs to detect trends, identify deficiencies, take appropriate corrective action, and document the actions taken."

The TRB continues, "[a] properly conducted, truly independent internal audit is potentially more effective than an independent, third-audit, as it reinforces ownership of the safety culture. * * * A properly motivated, active in-house safety program can be the best vehicle for discovering and correcting unsafe practices." The TRB further concludes that by assuring that the entity is accountable for conducting a meaningful audit, regulators transition ownership for safety and compliance back to the entity.

Requiring an audit plan and expecting that entities will conduct or facilitate audits themselves could beneficially supplement FSAP inspections of entities. Moving an entity towards a holistic self-evaluation of their risk management system, rather than just preparing to "pass" an inspection should encourage a deeper and more committed evaluation at regulated laboratories and may also promote integration of safety and security considerations beyond the BSAT lab into the broader organization.

Targeted Inspections

If a regulation requires certain actions (whether prescriptive or performance-based), inspection by regulators is a strong method of determining compliance. Inspections generally only affirm that the minimum standard has been met— required elements have been addressed (via paperwork checks) and risk controls have been put into place in accordance with the entity's plan (via visual checks). When a systems-approach is in place, rather than needing to validate overall compliance, inspections can be utilized to target areas where problems have been seen–either

with that entity or in other similar situations—or can be prioritized to high-risk activities. The TRB report stressed that the "routine presence of competent inspectors is essential" for compliance and that the inspectors also benefitted from their time and evolving understanding of the regulated facility.

Focusing FSAP inspections on areas of highest priority (supplemented by audit results supplied by the entity for the larger BSAT risk management plan) with spot-checks for compliance in other areas could reduce time on inspections and post-inspection paperwork. A review of nuclear security culture also stressed the importance of the presence of inspectors to support safety and security culture (Rusek & Lowenthal, 2015).

Performance Indicators

One of the hallmarks of a systems-approach is the measurement of performance of the various components of the system. An honest systems-approach acknowledges that the entire system will naturally degrade subtly or drift toward failure if not maintained. Too often, failure data, such as incidents or actions of non-conformance, serves as the basis of the assessment of performance (Burnett & Olinger, 2014). In these cases, the system has already failed. Establishing performance indicators and metrics that can provide an early-warning against failures is imperative in the systems-approach. A review and evaluation of developed indicators and metrics over time is important for assuring that progress is made towards achieving the goals of a management system. A quick check on progress can use indicators as a "dashboard," rather than requiring an in-depth audit (OECD Environment Directorate, 2008).

Indicators can be either "leading" or "lagging." Alternately, they can be called "activity" or "outcome" indicators (Burnett & Olinger, 2014) (OECD Environment Directorate, 2008). Outcome indicators are those that are the outcome of the system component being measured – an everyday example of an outcome indicator would be weight loss (the metric would be the number of pounds lost measured on a specified frequency). Activity indicators measure the elements that need to be in place to create the outcome. For example, for weight loss, a restricted calorie diet (where the metric would be calorie intake per day) and exercise program (where the metric could be steps taken per day) might be activity indicators. This pairing of indicators addresses one of the difficulties of measuring system performance. In the simplest, technology-driven approach, failures are assumed to be related to a linear causality ("x" action causes "y" outcome). However, this is too simplistic for a systems-approach. As a start to recognizing that performance is impacted by a variety of factors and not linearly, activity indicators measure the system components that must be in place to assure a positive outcome.

The requirement for developing and evaluating thoughtful and meaningful performance indicators and metrics at all levels of a regulated entity as an essential part of a BSAT risk management plan would encourage a systems-based mindset, moving away from compliance with a minimum standard. The ability to assess progress quickly would create efficiencies for both the regulated entity and the regulators.

Emphasize Critical Thinking

One of the more counter-intuitive findings when examining tools that industries have used to improve risk management is that introducing more prescriptive and procedural measures into a workplace as a response to an incident (e.g., more SOPs) does not ultimately equate to increased compliance because workers were not equipped with the capacity, authority, or flexibility to

address an unexpected issue (Committee on the Effectiveness of Safety and Environmental Management, 2012; Rusek & Lowenthal, 2015). Factors defining a high-reliability organization[24] include assuring the workers are not just mindlessly following SOPs, but also have sufficient knowledge of the abstract principles guiding the procedures to transfer that learning effectively to a novel situation, should it arise. Simply learning to perform procedures and only in a single context (e.g., a specific laboratory setting) does not promote this flexibility. Effective transfer, and thus critical thinking, comes from a balance of specific examples and general principles, not from either one alone. The ability to transfer learning increases or creates the capability to make complex decisions under stress (Committee on Developments in the Science of Learning, 2000).

When workers are aware of what they are supposed to know and do and they know the principles supporting that knowledge and behavior, they tend to participate in self-assessment over time. This, in turn, prompts a desire for and action towards additional improvement, learning, or practice. Organizations that support this type of learning and the resulting desire for improvements find that their workers are not only better prepared for novel situations, but also tend to be more satisfied and more easily retained. Studies have also shown that, in environments with more uncertainty and specialization, workers given higher autonomy for their own behavior demonstrate more positive safety behavior (Martinez-Corcoles, Gracia, Tomas, & Peiro, 2011).

As easily as a culture of paperwork (focusing only on paperwork rather than on the activities that paperwork represents) can be established, so, too, can a culture of training – where training is undertaken only to meet minimum compliance requirements. In risk management, training can be a powerful and influential risk control measure if structured correctly. Effective training targets desired actions and behaviors and gives workers the information and practice they need to make critical decisions in unexpected and uncertain situations. A major flaw in biosafety training practices is to offer training to increase awareness but to expect that awareness to translate, without assistance or guidance, into behaviors and competency. In addition, capacity and competency building activities such as mentoring, peer observation, teach-back, etc. supplements the most effective training.

[24] High reliability organizations (HRO) are commonly considered to be organizations that have succeeded in avoiding catastrophes in an environment where normal accidents can be expected due to risk factors and complexity. Healthcare settings predominantly use this term.

5. FINDINGS

Based on the research, discussions, and deliberations detailed above, the following findings highlight key areas for strengthening risk assessment for BSAT:

Finding 1. The Select Agent regulations, FSAP regulators, and regulated entities are imprecise and inconsistent in the use of terminology and processes to manage risks deriving from BSAT. In addition, well-accepted publications on risk assessment and risk management of biological agents and toxins (regardless of Select Agent status) differ in their use of terminology and processes. Dialogue on risks from and risk management of BSAT would benefit from common terminology and understanding.

Finding 2. Entities possessing BSAT may be similar only in the fact that they each have a regulated agent. Given this diversity, the use of risk assessment can, in a site-specific manner, tease out and focus control measures on the agents and situations that present the highest risk in that setting. The focus of risk management should lead to the control of the identified risk(s) in addition to compliance with regulations. However, the diversity of settings and the broad universe of valid and effective risk control measures could make oversight more difficult and resource-intensive.

Finding 3. Even with a standardized, harmonized, ideal risk assessment process, risk assessment is only as good as the input. Likewise, decisions on risk control measures are only as good as the understanding of the risk derived from a fully-informed risk assessment. Using data that is relevant, reliable, and current, regulated entities could prepare more consistent and effective risk assessments and risk management plans. FSAP could then more consistently evaluate those documents.

Finding 4. Lessons-learned from a wide variety of industries addressing catastrophic or critical incidents increasingly identify failures at the top management and organizational level as key precursors to the incidents. The focus on applying additional technology to avoid incidents has evolved, across many industries, to a focus on the organizational system and culture. As an example, many industries noted that additional prescriptive measures were less beneficial to risk management than increased training and mentoring designed to improve critical thinking.

Finding 5. An examination of the risk management methods and strategies developed for other industries reveals that oversight of regulated industries involves utilizing a management system approach in essentially three ways: 1) supplemental validation using industry standards (e.g., accreditation, certification, etc.), 2) performance-based regulation, or 3) a blend of both. Supplementing these mechanisms with tools that increase technical depth, peer assistance, entity accountability, and critical thinking provide options for consideration in strengthening risk reduction without undue burden to the regulated community.

Table 11 repeats these findings along with recommendations, sub-recommendations, and proposed actions for FSAP consideration.

Table 11. Findings, Recommendations and Proposed Actions

Findings, Recommendations and Proposed Actions

Finding 1

The Select Agent regulations, FSAP regulators, and regulated entities are imprecise and inconsistent in the use of terminology and processes to manage risks deriving from BSAT. In addition, well-accepted publications on risk assessment and risk management of biological agents and toxins (regardless of Select Agent status) differ in their use of terminology and processes. Dialogue on risks from and risk management of BSAT would benefit from common terminology and understanding.

Recommendation 1.1 Establish a standardized, harmonized BSAT risk management method with precise terminology and steps. Update regulation, program guidance, and inputs from the regulated community to utilize this method as a basis for evaluation of a regulated entity's compliance with FSAP provisions.

Sub-Recommendation	Proposed Actions	Comments
Adopt relevant terminology in DHS lexicon (Appendix D) for use in all FSAP communication	Evaluate FSAP documents for the use of terms defined in the lexicon and compare the lexicon definition with the FSAP intended use of the term. Assure that definitions/intent is aligned or identify revisions to increase precision and clarify intent	
Develop a biorisk management method that maps to a known standard and which integrates safety and security risks into a BSAT risk management plan.	Convene a technical working group to define and develop inputs relevant to biorisk management of BSAT using Table 2, above, and these publications (at a minimum): Biosafety in Microbiological and Biomedical Laboratories, 5th edition Quick Guide to Risk Assessment for Biological Hazards in the Laboratory, from Prudent Practices in the Laboratory Laboratory Biosafety and Biosecurity Risk Assessment Technical Guidance Document (SNL/IBCTR and IFBA) Chapter 5: Risk Assessment of Biological Hazards, from Biological Safety: Principles and Practices MMWR: Guidelines for Safe Work Practices in Human and Animal Medical Diagnostic Laboratories A Strategy for Assessing and Managing Occupational Exposures, 3rd edition. References highlighting additional consideration for certain types of genetic modification (as excerpted in Appendix F) Laboratory Biosecurity Handbook Laboratory Biorisk Management: Biosafety and Biosecurity Any method developed must require written documentation via a BSAT biorisk	See Appendix Ia for a suggested scope of work for a Technical Working Group.

	management plan	
	The technical working group will validate the method by assuring alignment (terminology, process, inputs, outputs, etc.) with at least one of the following known standards: ANSI/AHIA Z10, IRGC Risk Governance Framework, ISO 31000, DHS, and others, as identified. Include a statement the indicates that the method is aligned with the chosen framework	
	The technical working group will outline guidance that will lead regulated entities to development of a BSAT risk management plan that will serve as the primary discussion guide and basis for evaluation during inspections	
	The BSAT risk management method will be field-tested with select stakeholders from each sector working with BSAT. The method will be updated based on field results and re-validated with the chosen framework.	
	FSAP will work with the CDC/NIH BMBL editorial board to assure harmonization between the BSAT risk management method, where applicable.	
Recommendation 1.2: Increase literacy and communication regarding risks and risk management of BSAT by requiring documented risk management plans that articulate and document organizational choices based on risk reduction. Utilize this documentation as the primary discussion guide and basis for evaluation during inspections.		
Revise regulation and establish guidance to require documented BSAT risk management plan to serve as the primary discussion guide and basis for evaluation during inspections	FSAP will finalize guidance to regulated entities for development of a BSAT risk management plan that will serve as the primary discussion guide and basis for evaluation during inspections	
	FSAP will make recommendations to update regulations with revised language as necessary to reflect precise terminology and revised processes	
Utilize the BSAT risk management plan as the primary discussion guide and basis for evaluation during inspections	Implement	
Recommendation 1.3: Use familiarity and literacy (of all involved personnel) with the risk management process and plan as a key performance indicator for the regulated entity and for FSAP staff.		
	Develop criteria for determining familiarity and literacy	Validate during field test of BSAT risk management method (above)
	Implement during inspections	
	Utilize familiarity and literacy with BSAT risk management process in routine personnel evaluation of FSAP staff	

Finding 2

Entities possessing BSAT may be similar only in the fact that they each have a regulated agent. Given this diversity, the use of risk assessment can, in a site-specific manner, tease out and focus control measures on the agents and situations that present the highest risk in that setting. The focus of risk management should lead to the control of the identified risk(s) in addition to compliance with regulations (See 1.1, above). However, the diversity of settings and the broad universe of valid and effective risk control measures could make oversight more difficult and resource- intensive.

Recommendation 2.1: Prioritize highest risks at each entity and within the entirety of FSAP. For example, a situation where the agent and activities present a greater societal risk via community and epidemic spread might warrant higher priority for FSAP oversight. Within an entity, focus oversight on "critical control points" which historically have been associated with incidents or where scenarios evaluated during risk assessment identify a critical concern(s).

Sub-Recommendation	Proposed Actions	Comments
Determine if regulated entities can be tiered by the relative risk to society based on BSAT holdings, volume, and activities	Based on what is known about current regulated entities, identify which, if any, criteria exist for determining the risks a regulated entity poses to society versus risks to individual lab workers.	The DHS CFATS program utilizes tiering to differentiate a gradient of higher and lower risks
	If no criteria exist or if criteria are incomplete, develop criteria to distinguish between regulated entities based on potential safety or security consequence to society and the nation	
	Apply criteria to current regulated entities	
	Determine if tiered oversight system (differences in inspection schedule, frequency, etc.) would more effectively target FSAP resources without impacting effective biorisk reduction.	
	If tiered oversight would be beneficial to both biorisk reduction and to FSAP resources, develop a strategy to implement this approach.	
Determine which laboratory activities could be considered critical control points	Determine which laboratory activities and agents have historically been associated with incidents that increased biorisk	See Box 2 as a starting point for critical control points
	Conduct risk assessment to identify unanticipated activities and agents that may result in incidents that increase biorisk.	
	Gather best practices and evidence-based standards that provide options for addressing the given risks	
	Make this list to regulated entities and inspectors through mechanisms identified elsewhere in these recommendations	
	Prioritize attention during inspections on identified critical control points; if not identified, or not adequately controlled, prioritize corrective actions towards these points.	

	Conduct biennial review of data on and risk management of critical control points	
Recommendation 2.2: Increase transparency, collaboration, and data-sharing between and among regulators and regulated entities. While entities utilizing BSAT may diverge significantly across the regulated community, sharing lessons-learned, evidence-based standards, and innovative best practices increases the pool of information to inform risk-based decision-making and critical thinking and improves the likelihood of effective action in the face of unanticipated or uncertain situations		
Improve communication from FSAP regarding information on deficiencies and incidents collected by the program	Consider develop of formal communication mechanism akin to technical bulletins used by equipment manufacturers to advise on safety issues. For example, for a specific agent/activity/equipment, how did an incident occur, lessons-learned, new control measures, etc.	
	Consider the benefit of developing a record of key performance indicators regarding the performance of individual entities. This score could be used as benchmarking across entities and be utilized by entities in community outreach at their discretion.	See Table 8
Facilitate communication between regulated entities	Consider inviting peer auditors on inspections or supporting development of a peer audit process separate from inspections. This relationship would allow peer auditors to contribute their personal experiences and practices to the target entity's risk management process, while allowing the peer auditor to also gain practical experience and perspective from the target entity and inspectors.	See further discussion of peer assist under Finding 5; see Appendix J for a description of the American Biological Safety Association (ABSA International) laboratory accreditation process
Share best practices among regulators and regulated entities	Develop a mechanism to evaluate and share evidence-based best practices throughout the program (and beyond). Options include, among others, a Federal Advisory Committee as recommended by FTAC and to issue recommendations similar to OSHA letters of interpretation. Another mechanism would be to create the means to feed best practice information into the process utilized to provide feedback on risk control strategies within a BSAT risk management plan.	

Finding 3

Even with a standardized, harmonized, ideal risk assessment process, risk assessment is only as good as the input. Likewise, decisions on risk control measures are only as good as the understanding of the risk derived from a fully-informed risk assessment. Using data that is relevant, reliable, and current, regulated entities could prepare more consistent and effective risk assessments and risk management plans. FSAP could then more consistently evaluate those documents

Recommendation 3.1: Utilize phenotypic descriptions of listed agents, rather than just taxonomic, so that the characteristics of the agent, regardless of name, are utilized as inputs into the risk assessment and assure thoughtful hazard identification, rather than merely compliance with a list of biological agent and toxins.

Sub-Recommendation	Proposed Actions	Comments
	Consider developing a phenotypic description of BSAT, as possible, to provide additional clarity to regulated entities for conducting risk assessment and determining risk controls.	For example, see the phenotypic definition of Exotic Newcastle Disease See Appendix Ib for a suggested scope of work to more thoroughly explore this recommendation.
	Evaluate the phenotype via the standardized risk assessment process to assure that it continues to meet the risk criteria as determined by FSAP for listing.	
	Allow the scientific community to review the definitions and to provide feedback.	
	Consider the benefit of including the phenotypic descriptions to the list of BSAT in the regulations and/or develop a guidance document with this information. Consider the development of pathogen data sheets that include this information highlighted as key input for risk assessments.	
Recommendation 3.2: Assure collection and communication of historic data on incidents, lessons-learned, best practices, etc., while also documenting assessments of the likelihood and consequences of incidents not yet seen or anticipated. Use this information to inform risk assessment inputs and decisions about risk control.		
Assure that incidents not yet seen or anticipated have been evaluated for their likelihood and consequence.	Develop scenarios for incidents that have not yet been seen or anticipated that reflect concerns voiced by the scientific community or the public	
	Conduct risk assessments, based on the standardized risk management method, to characterize the likelihood and consequences of the scenario. Provide this information to regulated entities.	

Assure collection and communication of historic data	See actions for 2.2 above	
Recommendation 3.3: Minimize the prescription of risk control measures. Pre-determined risk control measures may not be sufficient to address some risks and may lead to over-control of others. Instead, develop guidance and support of risk management plans that are specific and align controls with the risk to be reduced. Require documented justification for the choice of a risk control measure that demonstrates an understanding of both the risk and the means to control the risk.		
Sub-Recommendation	**Proposed Actions**	**Comments**
Utilize BSAT risk management plan as the primary discussion guide and basis for evaluation during inspections**.**	See 1.2 above for steps to utilize the entity BSAT risk management plan as the primary discussion guide and basis for evaluation during inspections**.**	
Provide data to increase consistency for inputs into risk assessments and decisions on risk control measures	Develop pathogen data sheets (containing phenotypic description)	See Appendix Ic for a suggested scope of work to develop wiki sites for BSAT-specific pathogen data sheets.
	Determine if there are common security vulnerability inputs for regulated entities by type (e.g., public health laboratories) that can be documented for use to guide entity BSAT risk management plans. If so, develop document(s). Leverage DHS expertise with CFATS and other programs.	
Develop a system to guide iterative, interactive development of BSAT risk management plans	Develop mechanism for entity to submit their BSAT risk management plan for review.	See Appendix Id for a suggested scope-of-work to develop a iterative, interactive risk management tool
	Determine who will review. Options include FSAP staff, a peer review group, and/or a computer-based tool (or a hybrid approach).	
	Determine mechanism of review. A focus on critical control points is suggested.	
	Determine a mechanism to capture evidence-based best practices that will inform future reviews and can be utilized in communication with FSAP and regulated entities (see 2.2 and 3.2, above)	
	Determine if use of this system will be required or optional. If optional, consider incentives to encourage optional use (e.g., reduced inspection frequency, etc.).	

Recommendation 3.4: Develop risk scenarios to be used as guidance to assure consideration of potential incidents that are often disregarded or are unanticipated.		
Sub-Recommendation	**Proposed Actions**	**Comments**
	Using identified critical control points (2.1, above) and information from prospective risk assessments (3.2, above), develop guidance documents containing risk scenarios to be considered by the regulated entity as they develop their BSAT Risk Management Plan.	
Finding 4 Lessons-learned from a wide variety of industries addressing catastrophic or critical incidents increasingly identify failures at the top management and organizational level as key precursors to the incidents. The focus on applying additional technology to avoid incidents has evolved, across many industries, to a focus on the organizational system and culture. As an example, many industries noted that additional prescriptive measures were less beneficial to risk management than increasing training and mentoring designed to improve critical thinking.		
Recommendation 4.1: Reframe the focus on reducing risk from just the laboratory level to also include the organization and management. Assure and adhere to clear roles and responsibilities regarding BSAT throughout the organization.		
Sub-Recommendation	**Proposed Actions**	**Comments**
Include organizational activities and top management engagement as risk control measures in the entity BSAT risk management plan.	Provide guidance on expectations for BSAT risk management actions and engagement with for top management and other key non-laboratory personnel	
	Require roles and responsibilities for BSAT risk management to be included in the BSAT risk management plan. Evaluate literacy and familiarity with roles and responsibilities, as well as implementation, during the inspection (see 1.3 above)	
Recommendation 4.2: Develop performance indicators for critical control points identified as failures in incidents with BSAT (and other industries, where appropriate) including organizational and management commitment, engagement, and resource allocation.		
	Develop suggested performance indicators for critical control points (which will depend on risk control measures utilized).	See Table 8
	Require inclusion of performance indicators for critical control points identified at the regulated entity as part of the BSAT risk management plan	

Recommendation 4.3: Design training and mentoring for activities to encourage and support critical thinking skills and competency relevant to risk management of BSAT in the workforce (top to bottom), rather than merely procedural compliance. Include discussions of lessons-learned, best practices, and evidence-based standards from regulators and other entities and, where appropriate, other industries.		
Training and mentoring should be included as critical risk control activities in the BSAT risk management plan	Develop guidance on strategies for the entities to develop training and mentoring that has been demonstrated to encourage and support critical thinking skills and competency building.	
	Evaluate personnel familiarity and literacy with the BSAT risk management plan and risk management in general during the inspection as an indicator of plan implementation.	
Finding 5 An examination of the risk management methods and strategies developed for other industries reveals that oversight of regulated industries involves utilizing a management system approach in essentially three ways: 1) supplemental validation using industry standards (e.g., accreditation, certification, etc.), 2) performance-based regulation, or 3) a blend of both. Supplementing these mechanisms with tools that increase technical depth, peer assistance, entity accountability, and critical thinking provide options for consideration in strengthening risk reduction without undue burden to the regulated community.		
Recommendation 5: Consider amending the regulation and FSAP documents to utilize a management system approach. Develop tools that allow site-specific risk management to drive the oversight process, without removing the imperative for compliance.		
Sub-Recommendation	**Proposed Actions**	**Comments**
Evaluate options for a systems-approach to support BSAT risk management	Expand on this study's review of published management systems that are applicable to high-hazard risk management and/or laboratory settings and evaluate applicability to BSAT risk management.	
	Develop a strategy to encourage (or require) management system audits from entities.	
Consider supplemental tools for supporting BSAT risk-management	Consider options for convening an expert body to consider and provide technical advice on BSAT risk management to regulated entities and to FSAP	
	Consider options for creating a BSAT Peer Assist model	See Appendix J for a description of the American Biological Safety Association (ABSA International) laboratory accreditation process

	Develop key performance indicators that can be used to assess BSAT risk management effectiveness on a systems-basis and could be used across entities for benchmarking (for FSAP and the entities).	See Table 8

6. REFERENCES

APHL. "Risk Assessment Best Practices." 2016.

Burnett, LouAnn, and Patricia Olinger. "Evaluating Biorisk Management Performance." In *Laboratory Biorisk Management: Biosafety and Biosecurity*, by Reynolds M. Salerno and Jennifer Gaudioso, 145-168. Boca Raton, FL: CRC Press, 2014.

Buyon, Lucas. *Biological Laboratories: Risks and Regulations.* Council for Responsible Genetics, undated.

Caskey, Susan, and Edgar E. Sevilla-Reyes. "Risk Assessment." In *Laboratory Biorisk Management: Biosafety and Biosecurity*, by Reynolds M. Salerno and Jennifer Gaudioso, 45-64. Boca Raton, FL: CRC Press, 2014.

CEN. CWA 15793:2011: Laboratory biorisk management. CEN, 2011.

Committee on Developments in the Science of Learning. *How People Learn: Brain, Mind, Experience, and School: Expanded Edition.* Washington, D.C.: National Academies Press, 2000.

Committee on Establishing and Promoting a Culture of Safety in Academic Laboratory Research. *Safe Science: Promoting a Culture of Safety in Academic Chemical Research.* Washington, D.C.: National Academies Press, 2014.

Committee on the Effectiveness of Safety and Environmental Management. *Evaluating the Effectiveness of Offshore Safety and Environmental Management Systems.* Transportation Research Board Special Report 309, Washington, DC: National Academies Press, 2012.

Dickmann, Petra, Heather Sheeley, and Nigel Lightfoot. "Biosafety and biosecurity: a relative risk-based framework for safer, more secure, and sustainable laboratory capacity building." *Frontiers in Public Health* 3, no. Article 241 (October 2015): 1 - 6.

Eherts, David M. "Lessons Learned from Aviation Safety." *Journal of Safety Research* 39 (2008): 141-142.

Ezell, Barry Charles, Steven P. Bennett, Detlof von Winterfeldt, John Sokolowski, and Andrew J. Collins. "Probabilistic Risk Analysis and Terrorism Risk." *Risk Analysis* 30, no. 4 (2010): 575-589.

Federal Select Agent Program. "2015 Annual Report of the Federal Select Agent Program." Annual Report, 2016.

Garcia, Mary Lynn. "The Design and Evaluation of Physical Protection Systems, 2nd edition." 2008.

Gaudioso, Jennifer, Susan A., Burnett, LouAnn, Heegaard, Erik Caskey, Jeffrey Owens, and Philippe Stroot. *Strengthening Risk Governance in Bioscience Laboratories.* Sandia Report: SAND2009-8070, Albuquerque, NM: Sandia National Laboratories, 2009.

Greens, Kent A. Peer Assist: Learning Before Doing. x, x x, undated.

Gribble, Lisa Astuto, Edith Sangalang Tria, and Laurie Wallis. "The AMP Model." In *Laboratory Biorisk Management: Biosafety and Biosecurity*, by Reynolds M. Salerno and Jennifer Gaudioso, 31-44. Boca Raton, FL: CRC Press, 2014.

International Risk Governance Council. *An introduction to the IRGC Risk Governance Framework.* Laussane: IRGC, 2012.

International Risk Governance Council. Comparing Methods for Terrorism Risk Assessment with Methods in Cyber Security. IRGC, 2015.

International Risk Governance Council. *Guidelines for Emerging Risk Governance.* IRGC, 2015.

International Risk Governance Council. *Improving Risk Regulation.* Lausanne: IRGC, 2015.

International Risk Governance Council. IRGC White Paper No 1 "Risk Governance - Towards an Integrative Approach". Geneva: IRGC, 2005.

International Standards Organziation. ISO 31000: Risk Management - Principles and Guidelines. 2009.

Kaplan, Stan. "The Words of Risk Analysis." *Risk Analysis* 17, no. 4 (1997).

Kaplan, Stanley, and B. John Garrick. "On the Quantitative Definition of Risk." *Risk Analysis* 1, no. 1 (1981).

Le Coze, Jean-christophe. "Disasters and organisations: From lessons learnt to theorising." 46 (2008): 132-149.

Mack, Alison, Megan R Snair, and Eileen R Choffnes. *Global Health Risk Framework: Governance for Global Health: Workshop Summary.* National Academies Press, 2016.

Martinez-Corcoles, Mario, Francisco Gracia, Ines Tomas, and Jose M Peiro. "Leadership and employees' perceived safety behaviours in a nuclear power plant: A structural equation model." *Safety Science* 49 (2011): 1118-1129.

Morse, Stephen A. "Pathogen security - help or hindrance?" *Frontiers in Bioengineering and Biotechnology* 2, no. Article 83 (January 2015): 1-12.

National Science Advisory Board for Biosecurity. (2009). *Enhancing Personnel Reliability among Individuals with Access to Select Agents.*

National Research Council. *Science and decision: advancing risk assessment.* National Research Council, 2009.

OECD Environment Directorate. Guidance on Developing Safety Performance Standards related to Chemical Accident Prevention, Preparedness and Response. Vol. No. 19. Paris: OECD Environment, Health, and Safety Publications, 2008.

Rundmo, Torbjorn. "Associations between risk perception and safety." *Safety Science* 24, no. 3 (1997): 197-209.

Rusek, Benjamin, and Micah Lowenthal. Brazil-U.S. Workshop on Strengthening the Culture of Nuclear Safety and Security: Summary of a Workshop. Washington, D.C.: National Academies Press, 2015.

Salerno, Reynolds M., and Jennifer Gaudioso. "Introduction: The Case for Biorisk Management." In *Laboratory Biorisk Management: Biosafety and Biosecurity*, by Reynolds M. Salerno and Jennifer Gaudioso, 1-29. Boca Raton, FL: CRC Press, 2014.

Sandia National Laboratories . *Laboratory Biosafety and Biosecurity Risk Assessment Technical Guidance Document.* International Federation of Biosafety Associations, undated.

Starr, Chauncey. "Hypothetical Fears and Quantitative Risk Analysis." *Risk Analysis* 21, no. 5 (2001): 803-806.

Stern, Paul C. Risks and Risk Governance in Shale Gas Development: Summary of Two Workshops. National Academies Press, 2014.

Trevan, Tim. "Rethink Biosafety." *Nature* 527 (November 2015): 155-158.

U.S. Department of Health and Human Services (CDC, NIH). *Biosafety in Microbiological and Biomedical Laboratories, 5th edition.* HHS Publication No (CDC) 21-1112, Washington, D.C.: U.S. Department of Health and Human Services, 2009.

U.S. Department of Homeland Security Office of Policy. *DHS Lexicon: Terms and Definitions.* Washington, D.C.: U.S. Department of Homeland Security, 2015.

U.S. Department of Homeland Security. "Risk-Based Performance Standards Guidance." 2009.

Vrijling, J.K., W. van Hengel, and R.J. Houben. "A framework for risk evaluation." *Journal of Hazardous Materials* 43 (1995): 245-261.

APPENDICES

APPENDIX A – RESEARCH QUESTIONS

- What risks are targeted by the FSAP program?
- Who are the current regulators and how do they do their work? How is risk assessment currently used?
- Who comprises the current regulated community and how do they do their work? How is risk assessment currently used?
- What would desired utilization of risk assessment look like for regulators?
- What would desired utilization of risk assessment look like for regulated community?
- Where has the current program been successful? Are these successes translatable to other areas?
- Where has the current program been less-than-successful? What is the perception of the reason for the lack of success?
- What comprises risk assessment? What are relevant examples/models of risk assessment?
- How has consistent, standardized risk assessment been used elsewhere to reduce risks, particularly within a regulatory framework?
- What are examples of mechanisms to support and encourage use of risk assessment by 1) regulators and 2) regulated community, especially within a regulatory framework?
- What are examples of mechanisms to support and encourage timely and effective corrective and preventive action by regulated community?
- What are examples of regulatory models and methods from other industries used to reduce safety and security risks?
- What are examples of regulatory frameworks and oversight mechanisms to address unknown and emerging risks?

APPENDIX B – REGULATED ENTITY WEBINAR RESULTS

Questions for FSAP Risk Assessment Forum

Sandia National Laboratories (SNL) is conducting, on behalf of the Federal Select Agent Program, a study on evaluating and improving risk assessment in the management and oversight of biological select agents and toxins (BSAT). SNL seeks the input of the regulated community on how risk assessment is currently utilized in your organizations and on improvements in risk assessment that would be beneficial to safety and security of BSAT.

The following are the questions for the forum. They are being provided to give attendees time to consider and prepare answers. You are not obliged to answer any of the questions.

Part 1 – Demographic Poll

1. My organization is:
    a. Academic
    b. Commercial
    c. Government – Federal
    d. Government – State
    e. None of the above
2. My role with Select Agents Labs in my organization is: _____
3. We utilize the following Select Agents at my organization (check all that apply):
    a. HHS Select Agents and Toxins
    b. Overlap Select Agents and Toxins
    c. USDA Select Agents and Toxins
    d. USDA Plant Protection and Quarantine Select Agents and Toxins
    e. Tier 1 Select Agents and Toxins
4. Select Agents and Toxins are utilized at my organization in a (check all that apply):
    a. Biosafety Level 2 laboratory
    b. Biosafety Level 3 laboratory
    c. Biosafety Level 4 laboratory
    d. Animal Biosafety Level (any level)
    e. Greenhouse (any)
    f. Insectary (any level)
    g. BSLx-Ag (any level)
5. My file is held by the following lead agency:
    a. HHS – CDC Division of Select Agents and Toxins (DSAT)
    b. USDA – Agriculture Select Agent Services (AgSAS)

Part 2 – Chat Room Questions

(you may wish to have these answers ready to cut and paste into the chat)

1. The risks targeted by the Federal Select Agent Program are:_____
2. The incidents that could credibly occur involving biological select agents and toxins AT MY ORGANIZATION are:_____
    a. What process did you use to determine that these potential incidents are credible?

    b. How would you detect that the incident occurred?
3. The incidents that could credibly occur involving biological select agents and toxins ANYWHERE are:_____
4. Describe the process your organization uses to conduct risk assessments for Biological Select Agents and Toxins:_____
5. How do you assure that the control measures in place align with the risk to be reduced?
6. When is risk assessment conducted?
7. I feel that risk assessment would benefit the safety and security of biological select agents and toxins at my organization if conducted in this manner:
8. I would like FSAP inspectors to utilize risk assessment in this manner:

Part 3 – Procedures and Perceptions

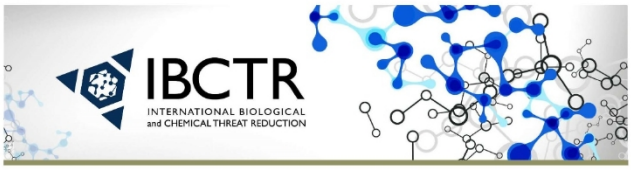
1. The risks that the Federal Select Agent Program targets are credible risks for my organization.
    a. Strongly agree
    b. Agree
    c. Neither Agree nor Disagree
    d. Disagree
    e. Strongly Disagree
2. The risks that the Federal Select Agent Program targets are credible risks for OTHER organizations.
    a. Strongly agree
    b. Agree
    c. Neither Agree nor Disagree
    d. Disagree
    e. Strongly Disagree
3. My organization uses the same process for risk assessment regardless of whether the activities are regulated by the Federal Select Agent Program.
    a. Yes
    b. No
4. Who in your organization conducts risk assessments for activities utilizing biological select agents and toxins?
    a. Short answer:_____
5. Who in your organization conducts risk assessments for activities with biological agents and toxins that are NOT regulated by FSAP?
    a. Short answer:_____
6. I believe that the oversight provided by the Federal Select Agent Program helps my organization reduce the risks from Select Agents and Toxins.
    a. Strongly agree
    b. Agree
    c. Neither Agree nor Disagree
    d. Disagree
    e. Strongly Disagree

7. I feel comfortable sharing my practices, experiences, and opinions about reducing risk from biological select agents and toxins with my colleagues at other institutions.
    a. Strongly agree
    b. Agree
    c. Neither Agree nor Disagree
    d. Disagree
    e. Strongly Disagree
8. Inspection reports from DSAT or AgSAS identify areas where risks need to be reduced.
    a. Strongly agree
    b. Agree
    c. Neither Agree nor Disagree
    d. Disagree
    e. Strongly Disagree
9. I am AWARE OF the criteria and processes used to list or delist agents
    a. Yes
    b. No
10. I UNDERSTAND the criteria and processes used to list or delist agents.
    a. Yes
    b. No
11. In general, I agree that the agents and toxins listed require special safety consideration.
    a. Strongly agree
    b. Agree
    c. Neither Agree nor Disagree
    d. Disagree
    e. Strongly Disagree
12. In general, I agree that the agents and toxins listed require special security consideration.
    a. Strongly agree
    b. Agree
    c. Neither Agree nor Disagree
    d. Disagree
    e. Strongly Disagree

Part 4 – Open Chat

Open chat room for any additional comments pertaining to the use of risk assessment in the Federal Select Agent Program. Please feel free to add anything you feel would be beneficial to our study.

Webinar Forum Results



Biological Select Agents and Toxins: Risk Assessment and the Regulated Community

Webinar forum
International Biological and Chemical Threat Reduction
Sandia National Laboratories

SAND2016-6098 O

Introduction

CDC 90-day Internal Review finding:

- Observation C: Select agent laboratories do not currently implement a standardized risk assessment process to identify the highest risks.
  - *Recommendation 3: Review and implement options for standardized risk assessment. CDC, in collaboration, with APHIS, shall convene an independent scientific body to review the science and practice of risk assessment in the modern select agent laboratory and provide recommendations that improve the timeliness and effectiveness of the inspection process*

IBCTR

Introduction

CDC, on behalf of FSAP, contracted Sandia/IBCTR to evaluate and make recommendations to strengthen the biorisk assessment process utilized in facilities that possess biological select agents and toxins (BSAT).

Study comprises:

- Interviews and research
- Expert discussions
- Recommendations
- Implementation strategies

IBCTR

Expert Panel Composition

As a whole, the panel will have expertise and experience in:

- the principles of risk assessment,
- the application of risk assessment in the biosciences and other industries,
- the use of risk-based decision-making in a regulatory context,
- the use of site visits to determine compliance with regulations and/or industry best practices, and
- settings where work with select agents and toxins is performed.

IBCTR

Interviews

- Meetings with FSAP staff
- Webinar Forum for regulated entities
  - Purpose of webinars:
    - *Gather regulated community input on use of risk assessment with work involving BSAT*
    - *Provide context for expert discussions, report, and recommendations.*
  - Four sessions – approximately 113 persons participated
- Other interviews as needed to complete research

IBCTR

Structure of Forum

- Four sections
  - Demographic information (poll)
  - Discussion questions (chat)
  - Procedures and Perceptions (poll)
  - Open chat

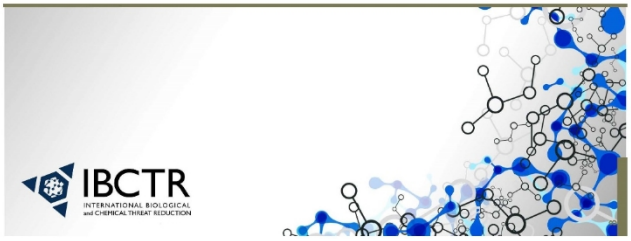
IBCTR

Ground Rules for Forum

- All responses will be summarized for presentation to the panel and in the report. No direct quotes, attributions, or links to demographic information will be made.
- If you are not a representative of a regulated entity, please do not participate in the forum.
- This forum is designed to gather information on risk assessment. Please refrain from commenting on other aspects of the program.
- If you are uncomfortable participating on-line, please email your responses to: lcburne@sandia.gov.

IBCTR

Aggregate Webinar Forum Results



Caveats

- This forum was not designed as a statistically-valid survey and should not be interpreted as such.
- Respondents were not required to answer any question. Thus, there is a large proportion of "no response" on each poll question. The poll feature counts all registrants logged into the session, whether they were active or not.
  - This might be due to one of several factors:
    - *a choice not to respond,*
    - *the poll not being submitted before it was closed,*
    - *respondents arriving late or leaving the forum early,*
    - *some registrants might also have chosen to observe the forum, rather than providing responses, or*
    - *several persons were logged in multiple times due to technological difficulties*
- Some poll questions allowed respondent to "check all that apply." The intent was to derive a snapshot of the general distribution and diversity of types of agents utilized and laboratories/space in which they are housed, rather than an entity-by-entity statistical accounting.

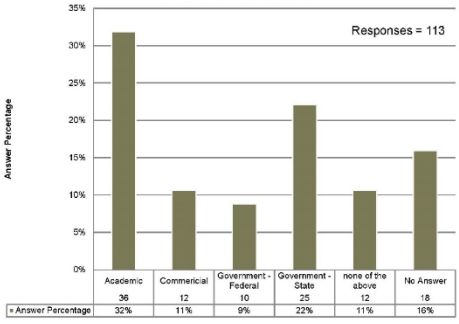
IBCTR

9

Poll 1: Demographic Data

IBCTR
INTERNATIONAL BIOLOGICAL and CHEMICAL THREAT REDUCTION

#1 My organization is:

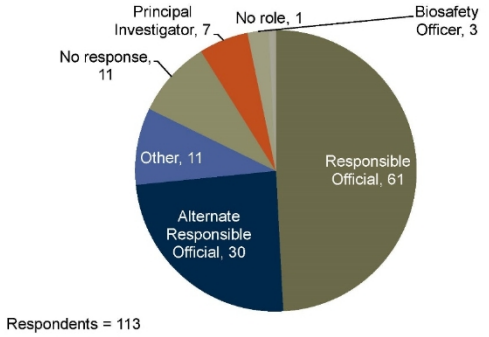


	Academic	Commericial	Government - Federal	Government - State	none of the above	No Answer
Answer Percentage	36	12	10	25	12	18
	32%	11%	9%	22%	11%	16%

IBCTR

11

My role with Select Agents Labs in my organization is: _____



Respondents = 113

IBCTR

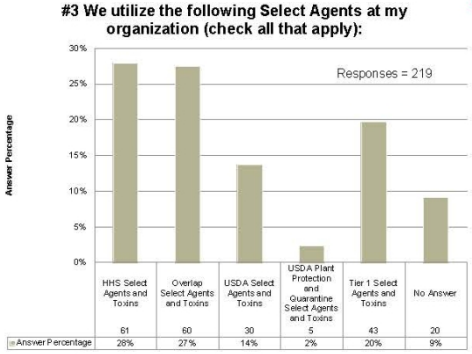
12

Notes: Select Agent Lab Role

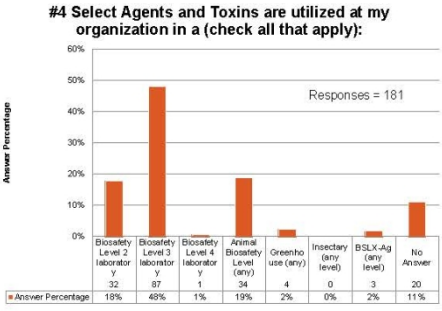
If more than one role was listed for a respondent, the role most relevant to the Select Agent Program was noted. For example, many respondents listed that they were biosafety officers but also held either a Responsible Official or Alternative Responsible Official role. The RO or ARO roles was the role tallied.

Some "individual" respondents were actually multiple persons associated with the BSAT program.

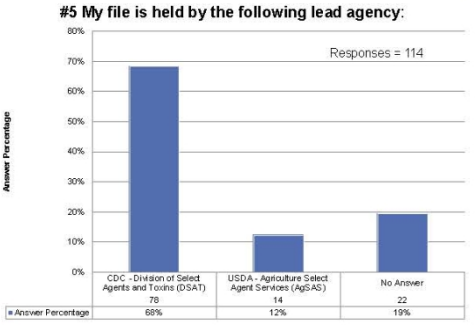
IBCTR 13



IBCTR 14



IBCTR 15



IBCTR 16

Chat Results

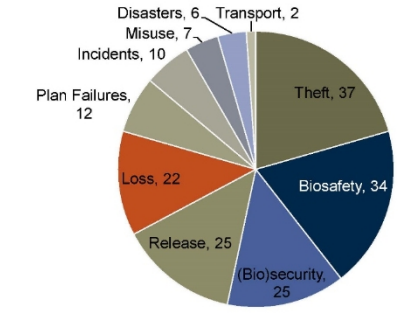
Chat Caveats and Context, 1

- Chat questions were intentionally posed as open-ended with no defined "right way" to respond. Some answers were a few words; others were entire paragraphs.
- Answers were generally categorized by SNL using professional judgement. Where more granularity beyond those categories will assist in interpretation of what that category comprises, a notes page has been inserted following the chart that provides that additional information.
- If the chart or specific answers on the chart were self-explanatory, or there was no deeper information to provide, no notes are given

Chat Caveats and Context, 2

- Any answer provided by a respondent was counted; thus, if the respondent included multiple answers fitting into multiple categories, those answers were tallied in the separate categories. The total number of responses tallied is indicated on each page, but has no relationship to the number of respondents.
- Response to any question during the forum was optional and not traced. Many respondents may not have answered.
- PLEASE NOTE: this summary can tally only what respondents chose to provide in a limited time. This aggregation represents only generalities and a general distribution of responses and should not be interpreted beyond that purpose.

The risks targeted by the Federal Select Agent Program are:



Tallied responses = 160

Notes – Risks targeted by FSAP program

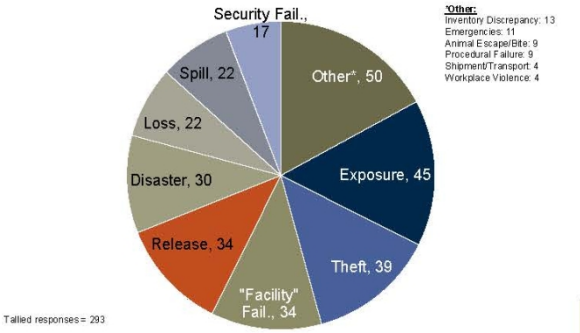
The following categories include answers mentioning:

- **Biosafety:** biosafety, accidental exposure, lab-acquired infection, and accidentally infected animals
- **Release:** release, accidental release to public and environment
- **Theft:** theft, insider theft, outsider theft
- **Misuse:** misuse, dual-use misuse
- **Biosecurity:** biosecurity, security, unauthorized access
- **Incidents:** safety incidents, bomb threats
- **Plan failures:** failures in plans for facilities, procedures, and personnel suitability

IBCTR

21

The incidents that could credibly occur involving biological select agents and toxins AT MY ORGANIZATION are:



IBCTR

22

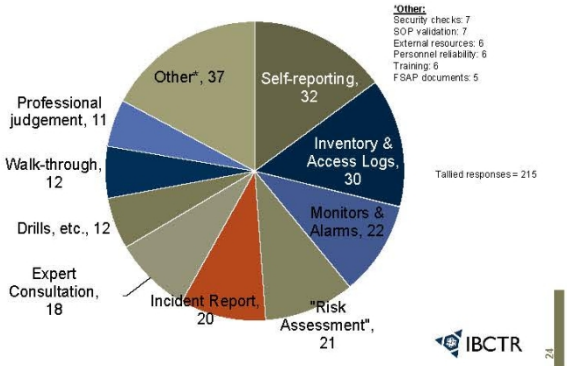
Notes – Credible incidents at organization

- **Theft:** Insider theft was listed 5 times more than outsider theft
- **Disasters** included earthquake, tornado, ice storm, high wind, hurricane, blizzard, inclement weather, wildfire
- **Security failures** included security breech, compromised IT security, unauthorized access, break-in, vandalism, loss of ID card
- **Facility failure** includes utility outages, equipment failure, HVAC failure, flooding, damage to infrastructure
- Specific categories of **release** (beyond primary containment) included were improper waste treatment and aerosolization
- **Exposures** included lab-acquired infection and needlesticks
- **Emergencies** included fire, medical, bomb threat, suspicious package, gas leak, chemical spill, physical injury
- **Workplace violence** included disgruntled employee, active shooter

IBCTR

23

What process did you use to determine that these potential incidents are credible? How would you detect that the incident occurred?



IBCTR

24

Notes – Process to determine or detect credible incident

- While two separate questions were asked, the nature of reviewing chat responses made it nearly impossible to discern which question was being answered. Thus, we have grouped the response to both questions in the same summary.
- **Expert consultation** included select agent team, IBC, first responder groups, security, internal and external subject matters experts.
- **Risk assessment** (when specified) included using FSAP guidance, biosafety manual, BioRAM, risk matrices, established processes

IBCTR 25

The incidents that could credibly occur involving biological select agents and toxins ANYWHERE are:

The incidents credible to occur anywhere listed were primarily the same as those listed for the specific organization. The only additional incident that was more frequently cited as being credible for organizations anywhere was the threat of outside theft and bioterrorism.

IBCTR 26

Describe the process your organization uses to conduct risk assessments for Biological Select Agents and Toxins:

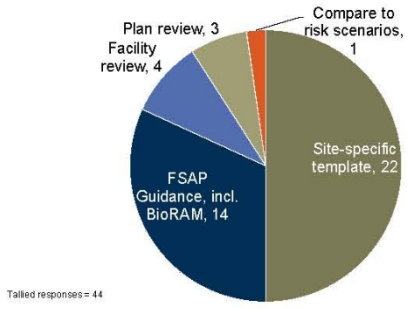
Three distinct categories emerged in the responses. These have been separated to provide clarity on processes used:

- Process Used
- Inputs
- Review/Approval

Note: the total tallied responses for this question equals 104. Some respondents provided responses that met all three categories above, some only one or two.

IBCTR 27

Risk Assessment Process



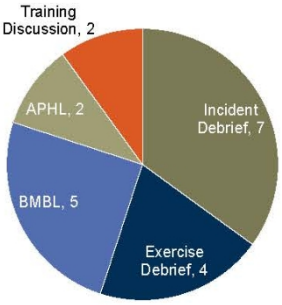
IBCTR 28

Notes – Risk Assessment Process

The majority of respondents utilize a risk assessment developed or adapted for their site-specific use, but provided no specific steps or details about those processes; two respondents listed steps comprising risk assessment.

IBCTR

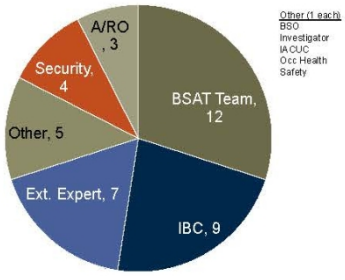
Risk Assessment Inputs



Tallied responses = 20

IBCTR

Risk Assessment Review/Approval



Other (1 each)
BSO
Investigator
IACUC
Occ Health
Safety

Tallied responses = 40

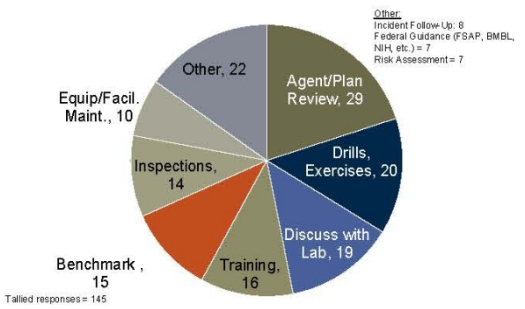
IBCTR

Notes – Risk Assessment Review/Approval

- What SNL termed **"BSAT team"** is variable by entity but generally includes the responsible official (and alternates), lab director/principal investigator, safety and security professionals, and/or occupational health SMEs
- **External expertise** was via laboratory certification; 3rd party risk assessment development and/or review; external subject matter expertise

IBCTR

How do you assure that the control measures in place align with the risk to be reduced?



Other:
Incident Follow-Up: 8
Federal Guidance (FSAP, BMBL, NIH, etc.) = 7
Risk Assessment = 7

Tallied responses = 145

IBCTR

33

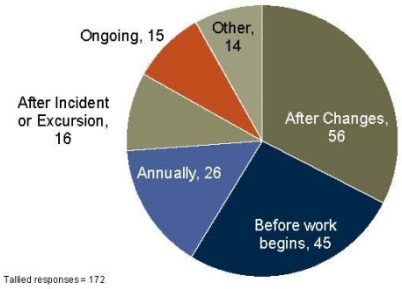
Notes – Risk-based mitigation strategies

Benchmarking comprises literature review, best practice sharing, benchmarking with other comparable entities, etc.

IBCTR

34

When is risk assessment conducted?



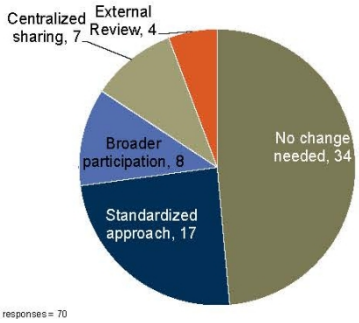
Other:
<Annual: 5
After drill: 4
Protocol review: 3
>Annual: 1

Tallied responses = 172

IBCTR

35

I feel that risk assessment would benefit the safety and security of biological select agents and toxins at my organization if conducted in this manner:



Tallied responses = 70

IBCTR

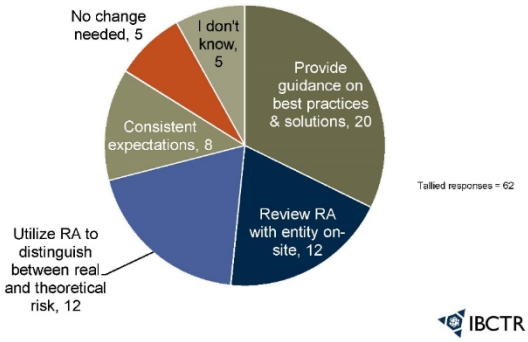
36

Notes – Ideas for improved risk assessment

- Responses for **"standardized approach"** included:
  - Definitions of standard risks to be assessed
  - Fixed template
  - Standardized process
  - Examples of successful risk assessment approaches for comparison
  - Quantitative risk assessment
  - Examples of sufficient documentation
  - Rated scoring tool (e.g., BioRAM or similar)
- **Centralized sharing** includes cross-entity sharing of best practices and lessons-learned
- Options for **external review** included peer review of risk assessment, 3rd party review, review and approval by FSAP

IBCTR 37

I would like FSAP inspectors to utilize risk assessment (RA) in this manner:



Tallied responses = 62

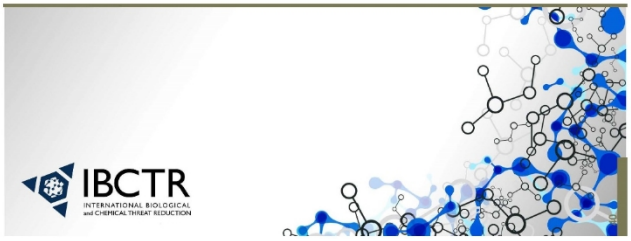
IBCTR 38

Notes – Use of risk assessment during inspections

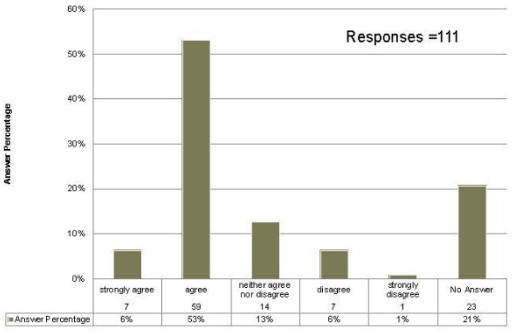
- The majority of respondents sought greater collaboration with and feedback from inspectors to:
  - Benefit from inspector experience in multiple entities
  - Spend time walking inspectors through risk assessment and plans to provide greater context for decisions made

IBCTR 39

Poll 2: Procedures & Perceptions



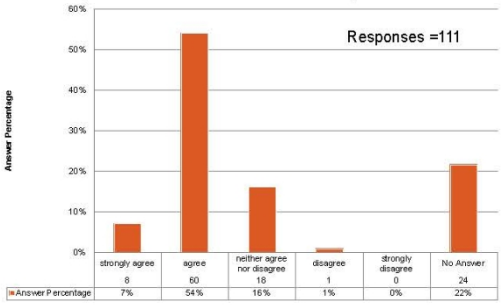
#1The risks that the Federal Select Agent Program targets are credible risks for my organization.



IBCTR

41

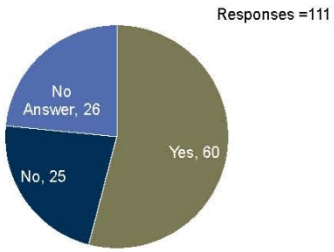
#2 The risks that the Federal Select Agent Program targets are credible risks for OTHER organizations.



IBCTR

42

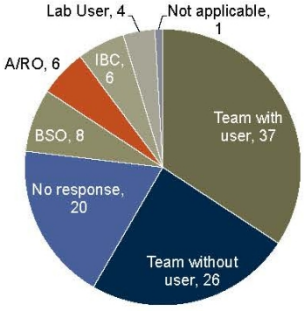
#3 My organization uses the same process for risk assessment regardless of whether the activities are regulated by the Federal Select Agent Program.



IBCTR

43

Who in your organization conducts risk assessments for activities utilizing biological select agents and toxins?



n = 111

IBCTR

44

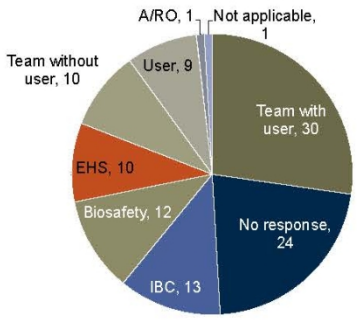
Notes: Who conducts BSAT Risk Assessment?

- **User** = investigator or lab director/staff
- **Team with user** = variable membership across entities, but explicit mention of investigator or end user
- **Team without user** = variable membership across entities, but NO explicit mention of investigator or end user
- **IBC** = Included responses where biosafety officer (BSO) contributed to Institutional Biosafety Committee (IBC) review
- **BSO** = Biological Safety Officer
- **A/RO** = Alternate Responsible Official and/or Responsible Official

IBCTR

45

Who in your organization conducts risk assessments for activities with biological agents and toxins that are NOT regulated by FSAP?



n = 111

IBCTR

46

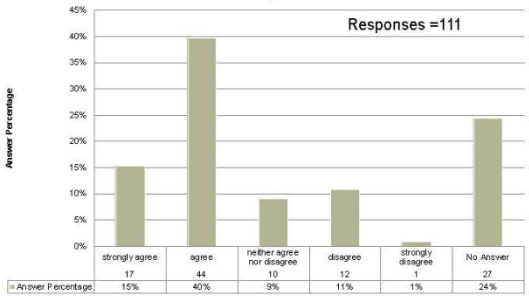
Notes: Who conducts non-BSAT Risk Assessments?

- **User** = investigator or lab director/staff
- **Team with user** = variable membership across entities, but explicit mention of investigator or end user
- **Team without user** = variable membership across entities, but NO explicit mention of investigator or end user
- **IBC** = Included responses where biosafety officer (BSO) contributed to Institutional Biosafety Committee (IBC) review
- **BSO** = Biological Safety Officer
- **A/RO** = Alternate Responsible Official and/or Responsible Official
- **EHS** = Environmental, Health, and Safety Office

IBCTR

47

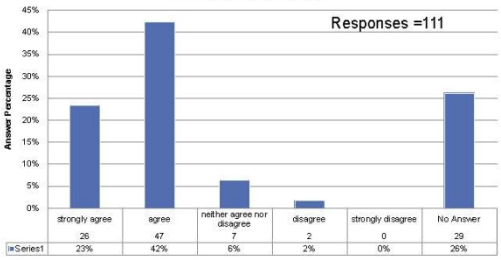
#6 I believe that the oversight provided by the Federal Select Agent Program helps my organization reduce the risks from Select Agents and Toxins.



IBCTR

48

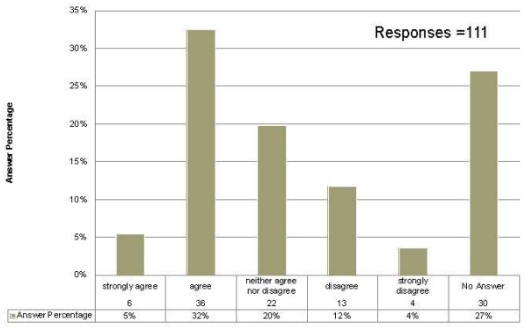
#7 I feel comfortable sharing my practices, experiences, and opinions about reducing risk from biological select agents and toxins with my colleagues at other institutions.



IBCTR

49

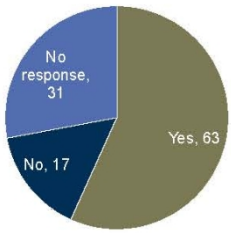
#8 Inspection reports from DSAT or AgSAS identify areas where risks need to be reduced.



IBCTR

50

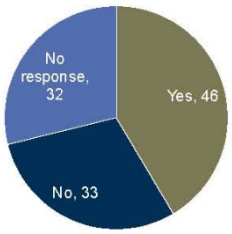
#9 I am AWARE OF the criteria and processes used to list or delist agents



IBCTR

51

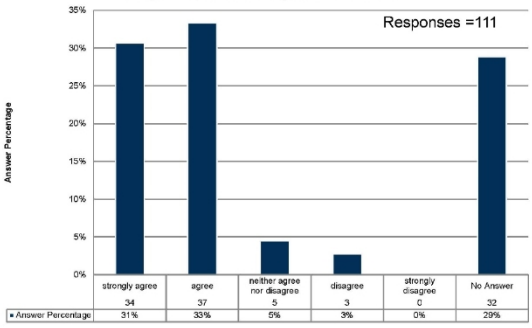
#10 I UNDERSTAND the criteria and processes used to list or delist agents.



IBCTR

52

#11 In general, I agree that the agents and toxins listed require special safety consideration.

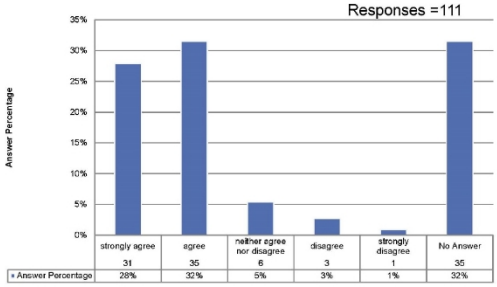


	strongly agree	agree	neither agree nor disagree	disagree	strongly disagree	No Answer
Answer Percentage	34 31%	37 33%	5 5%	3 3%	0 0%	32 29%

IBCTR

53

#12 In general, I agree that the agents and toxins listed require special security consideration.



	strongly agree	agree	neither agree nor disagree	disagree	strongly disagree	No Answer
Answer Percentage	31 28%	35 32%	6 5%	3 3%	1 1%	35 32%

IBCTR

54

Open Chat

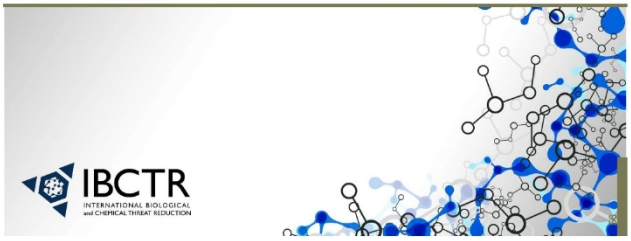
Responses received in open chat were generally suggestions about the conduct of the webinar or notes of thanks for conducting the forum.

Specific comments about risk assessment were generally answers that had not been provided during the chat session. Those comments were included for summary in the aggregate information for the intended chat question.

IBCTR

55

End of Report



APPENDIX C – PANEL COMPOSITION & BIOGRAPHIES

Panel Members

Rocco Casagrande, Ph.D.
Managing Director
Gryphon Scientific

Patrick Condreay, PhD RBP
pc Biosafety Consulting Services, LLC

Barry C. Ezell, Ph.D.
Senior Principal Analyst | Innovative Decisions, Inc.

Julie Fruetel, Ph.D.
Systems Research and Analysis
Homeland Security and Defense
Sandia National Laboratories

Diane O. Fleming, PhD, RBP, CBSP
Retired Biological Safety Professional

David Hill, CIH, CBSP
Director of Safety
Wadsworth – New York Department of Public Health

Thomas Inglesby, MD
CEO and Director
UPMC Center for Health Security

Todd Klessman, JD
Senior Policy Advisor
Infrastructure Security Compliance Division
Department of Homeland Security

SNL/IBCTR Study Leaders

Benjamin Brodsky, PhD
Manager, Risk Management Department

LouAnn C. Burnett, MS, CBSP
Study Lead
Principal R&D Scientist

Jennifer Gaudioso, Ph.D.
Senior Manager

Observers

Daniel M. Sosin, MD, MPH, FACP
Acting Director, Division of Select Agents and Toxins
Office of Public Health Preparedness and Response

James D. Holt, BA, JD, LLM
Senior Attorney, CDC Branch, Public Health Division
HHS Office of General Counsel

Freeda E. Isaac, DVM
Director, Agriculture Select Agent Services
National Import Export Services
USDA, APHIS, Veterinary Services

Caroline E. Laverriere
Veterinary Medical Officer
Agriculture Select Agent Services (AgSAS)
National Import Export Services
USDA, APHIS, Veterinary Services

Panel Biographies

Rocco Casagrande, Ph.D. is the Managing Director of Gryphon Scientific, LLC. His projects at Gryphon Scientific focus on bringing rigorous scientific analysis to problems of science policy, risk analysis and homeland security. For the past dozen years, Dr. Casagrande has lead more than 50 projects to evaluate and improve US preparedness efforts for a CBRN attack or emerging infectious disease event, supporting a better understanding of the threat. Dr. Casagrande also served as the principal investigator of several projects supporting the US government's stance on emerging biotechnologies including the guidance to the synthetic DNA industry and its moratorium on funding research involving engineered influenza viruses. From December 2002 to March 2003, Dr. Casagrande served as an UNMOVIC biological weapons inspector in Iraq where he acted as the chief of the UN biological analysis laboratory. Prior to working for UNMOVIC, Dr. Casagrande worked in private industry as an inventor in a nano/bio-technology company. Dr. Casagrande holds a B.A. in chemistry and biology from Cornell University, where he graduated magna cum laude, and a Ph.D. in biology from MIT.

Patrick Condreay, PhD, RBP received his undergraduate degree in biochemistry from Rice University and his graduate degree in microbiology from the University of Texas at Austin. For over thirty years he pursued a career in research, studying the molecular biology of different systems. His interests varied from the study of bacteriophages and human pathogenic viruses, to the development of recombinant viral-mediated gene delivery technology and its application to cell-based assay development. He is the author of over 40 scientific publications. Pat is an accomplished trainer who has developed and taught a number of classes on the use and biosafety implications of recombinant viral vectors in biomedical research for both ABSA and the Eagleson Institute. He developed curriculum for, and is regularly on the faculty for, ABSA International's Principles and Practices of Biosafety and Risk Assessment courses. Pat serves on the governing Council of ABSA International and was recently elected President of the Carolinas Biological Safety Association. In 2005 he received the John H. Richardson Special Recognition Award from ABSA. After a 28-year career with GlaxoSmithKline Pat retired as a Group Leader in the Biological Sciences division of GSK Molecular Discovery Research. Pat served on GSK's EHS Executive Committee and chaired the Institutional Biosafety Committee and Biological Safety Committee at GSK's Research Triangle Park site for 15 years. He also serves as a community member of the Duke University IBC. Upon leaving GSK Pat started a consulting business and currently works with a variety of clients to manage their biological safety programs and fulfill training needs.

Barry C. Ezell, Ph.D. has 27 years of risk and decision analysis experience in the U.S. Department of Defense, U.S. Department of Homeland Security, and the Commonwealth of Virginia. Dr. Ezell retired from the U.S. Army with 24 years of service as a Soldier, Commanding Officer, Staff Officer, and Operations Research Systems Analyst, including tours in South Korea, Desert Shield and Desert Storm, and the Republic of Georgia. Dr. Ezell has been chief scientist at the Virginia Modeling, Analysis and Simulation Center at Old Dominion University leading research since 2008. In addition, Dr. Ezell has been consulting on projects with Innovative Decisions, Inc. part-time since 2007. Dr. Ezell is best known for developing multi-objective decision models, terrorism and cyber risk assessments, key performance indicator models, and resource allocation models to support senior leader decisions, often in environments with multiple stakeholders and competing objectives. Dr. Ezell has led projects for a variety of State and government agencies including the DHS National BioSurveillance Integration Center, DHS National Program and Protection Directorate, National Institute of Standards and Technology, Sandia National Labs, National Nuclear Security Administration, and seven years of portfolio resource allocation for the Virginia Homeland Security Grant Program. Dr. Ezell's decision and risk analysis expertise has been recognized by the DHS Science and Technology Directorate and National Academies through his invited participation National Academies' committees and national lab blue ribbon panels. Dr. Ezell was the last President of the Security Analysis Risk Management Association, 2013-2015, successfully merging with the Military Operations Research Society in March 25, 2016 to form the Risk Community of Practice. Dr. Ezell has been a member of the Hampton Roads All-Hazards Advisory Committee representing higher education since 2009. Dr. Ezell is a founding board member of Toby's Dream Foundation, a non-profit that brings dreams to children with serious illness and former president of the Salem Woods Association in Virginia Beach, 2005-2009. Dr. Ezell earned his Ph.D. from Old Dominion University in 2005, Master of Science from the University of Virginia in 1998, and Bachelor of Science (Honors) from the University of Southern Mississippi in 1988.

Diane Oakerson Fleming, PhD attained emeritus status in the American Biological Safety Association (ABSA), and their Mid-Atlantic (MABSA) and Chesapeake Area (ChABSA) chapters, and in the American Society for Microbiology (ASM) after her retirement in 2008. She received her BS in Biology from the College of William and Mary in Williamsburg, VA in 1957, an MS in Biology (Medical Parasitology) from Emory University in Atlanta, GA in 1958 and a PhD in Medical Microbiology and Immunology in 1969 from Duke University in NC where she was supported by a Public Health Service training grant. Over the years, she held faculty appointments at The Johns Hopkins School of Medicine and School of Hygiene and Public Health from 1959-62 and again from 1981-88 when she served on the Senior Staff. She was also on the faculty of Memphis State University in TN, the Open University, University of Maryland and Central Texas College while in the UK and Wright State University School of Medicine in Dayton OH from 1978-1980.

In the late 70's, Dr. Fleming became involved in biosafety as an IBC Chairman at Wright State University. She participated in the first NIH sponsored course for Biosafety officers at The Johns Hopkins Medical Institutions (JHMI) in 1980 and became their biosafety officer. After 7 years, she left to begin developing and revising biosafety programs for pharmaceutical firms (Sterling Drug, Merck) and for government agencies (NIH/NCI Frederick). From 1992-2007, she consulted for clients from industry, academic and government agencies including Aventis, Aventis Pasteur, The Dana Farber Cancer Research Inst., Connaught Laboratories, Inc., Exponential Biotherapies,Inc., Genentech, Inc., Fort Dodge Labs, George Washington University, Hoechst-Marion-Roussel PI, Immune Response,Inc., Lenox Hill Hospital, Maxygen, Merck & Co. Inc., Midwest Research Institute, NIH, NYU Medical Center, North American Vaccine, Rhone Poulenc Rorer, Inc., Southern Research Institute, University of Maryland, College Park, USDA, ARS Beltsville, and Wyeth-Ayerst.

Diane published research papers, book chapters and co-edited three editions of the ASM book, Biological Safety: Principles and Practices. Diane is a past president of ABSA, MABSA, and ChABSA (Chesapeake Area Biosafety Association). As chairman of the ASM laboratory safety subcommittee of the Public and Scientific Affairs committee, she petitioned the NIH to revise Appendix B to harmonize with the BMBL and served on the NIH subcommittee appointed for that purpose.

Diane served on the Committee on Biohazards, Board of Chemical Sciences and Technology, National Research Council (Authors of Prudent Practices for the Handling and Disposal of Infectious Materials) 1986-89, the Committee on Occupational Safety and Health in Research Animal Facilities, Institute of Laboratory Animal Resources, Commission on Life Sciences, National Research Council. January, 1993- Sept.'94; National Committee on Clinical Laboratory Standards, as an ASM representative for Laboratory Safety; NIAID Initial Review Groups (5) for National and Regional Bio-containment Laboratories

Dr. Fleming received the ABSA Everett Hanel Presidential Award (1994) and the Arnold G. Wedum Distinguished Achievement Award, American Biological Safety Association, 2001.

Julie (Julia A.) Fruetel, Ph.D. is a Principal Member of the Technical Staff in the Systems Research and Analysis Department at Sandia National Laboratories. She has over 19 years of experience in homeland security modeling and analysis, technology development and risk-based analyses, with an interest in chemical and biological counter-terrorism. She holds a B.S. degree in Chemistry from Harvey Mudd College and a Ph.D. in Pharmaceutical Chemistry from UC San Francisco. Prior to coming to Sandia, Dr. Fruetel worked in the pharmaceutical industry as lead principal investigator for in vivo toxicology and metabolism studies of pesticides, and led method development and validation for novel pharmaceuticals in support of FDA and EPA submissions. At Sandia, she developed novel microfluidic techniques for ultra-sensitive detection of biotoxins, viruses and bacteria, and led the integration of lab-on-a-chip technology into the hand-portable μChemlab analytical instrument and the autonomous BioBriefcase detection system for the Department of Homeland Security. Interested in the broader context of detection technologies in homeland security, Dr. Fruetel joined the systems analysis group in 2004, where she has led numerous studies developing and applying systems models, decision support tools, and risk-based approaches for the Department of Homeland Security, Department of Defense and other customers. Examples of her expertise include analysis of performance requirements and trade-offs for environmental monitoring and biosurveillance architectures; gap analysis and technical roadmap development for wide-area bio-restoration; and evaluation of use cases and requirements for next-generation medical diagnostics. Currently she is developing risk-based decision support tools. Her work has been recognized at Sandia with several Employee Recognition Awards. She has two patents and over 25 publications.

Tom Inglesby, MD is Director of the UPMC Center for Health Security, a nongovernmental organization dedicated to protecting people's health from the consequences of epidemics and disasters and to ensuring that communities are resilient to those challenges. He is a Professor of Medicine at the University of Pittsburgh School of Medicine.

Dr. Inglesby's work is internationally recognized in the fields of public health preparedness, pandemic flu and epidemic planning, and biosecurity. He is Chair of the Board of Scientific Counselors, Office of Public Health Preparedness and Response, US Centers for Disease Control and Prevention (CDC). He is Chair of the National Advisory Council of the Robert Wood Johnson Foundation National Health Security Preparedness Index. He was a member of the External Laboratory Safety Workgroup appointed by the CDC Director which examined biosafety practices of the CDC, the National Institutes of Health (NIH), and the Food and Drug Administration (FDA). He is a member of the Working Group assessing US Biosecurity on behalf of the President's Council of Advisors on Science and Technology (PCAST). He has also served on committees of the Defense Science Board and the National Academies of Sciences and in an advisory capacity to DHS and DARPA.

During the past 17 years, Dr. Inglesby has authored or co-authored more than 95 peer-reviewed articles, reports, and editorials on a range of issues related to health and security. He is Editor-in-Chief of the journal Health Security, which he helped to establish 13 years ago as the first peer-reviewed journal in its field, under its original title, Biosecurity and Bioterrorism.

Dr. Inglesby completed his internal medicine and infectious diseases training at Johns Hopkins University School of Medicine, where he also served as Assistant Chief of Service in 1996-97. Dr. Inglesby received his MD from Columbia University College of Physicians and Surgeons and his BA from Georgetown University. He continues to see patients in a weekly infectious disease clinic.

Todd Klessman, J.D. is the Senior Policy Advisor for the Infrastructure Security Compliance Division (ISCD). ISCD, which is part of the U.S. Department of Homeland Security's (DHS) National Protection and Programs Directorate, is the entity within DHS responsible for regulating chemical facility security. As Senior Policy Advisor, Mr. Klessman serves as an authority on the Chemical Facility Anti-Terrorism Standards (CFATS) regulation and the Secure Handling of Ammonium Nitrate Provisions of the Homeland Security Act, and is responsible for providing advice and counsel to the ISCD Director and Deputy Director. Mr. Klessman has been working for, or in support of, the Department of Homeland Security on critical infrastructure protection, chemical facility security, and risk management issues since 2004.

Prior to entering the Homeland Security field, Mr. Klessman was an attorney assisting clients in various types of litigation, including complex commercial disputes, copyright infringement cases, and international trade matters.

Mr. Klessman has a B.B.A. from the University of Michigan Business School and a J.D. from the University of Michigan Law School.

APPENDIX D. TERMS FROM DHS LEXICON

Absolute Risk	level of risk expressed with real-world units of measurement that allows for independent interpretation without comparison to estimates of other risks
Acceptable Risk	level of risk at which, given costs and benefits associated with reduction measures, no action is deemed to be warranted at a given point in time
Adaptive Risk	category of risk that includes threats intentionally caused by humans
Baseline Risk	current level of risk that takes into account existing risk mitigation measures
Data/Informative Risk	risk associated with the loss or misuse of data or information – includes: risk of compromise of privacy information; risk of increased burdens on citizens and businesses because of data collection requirements if the associated business processes or the project requires access to data from other sources (federal, state, and/or local agencies).
Evaluation	process of examining, measuring and/or judging how well a entity, procedure, or action has met or is meeting stated objectives
Feasibility Risk	risk that a proposed alternative fails to result in the desired technological outcome
Hazard	source or cause of harm or difficulty
Implementation	act of putting a procedure or course of action into effect to support goals or achieve objectives
Integrated Risk Management	structured approach that enables the distribution and employment of shared risk information and analysis and the synchronization of independent yet complementary risk management strategies to unify efforts across the enterprise
Level Of Risk	combined measure of the threat, vulnerability, and consequences posed to a facility from a specified undesirable incident
Mitigation	ongoing and sustained action that eliminates or reduces the potential effects of hazards
Non-adaptive Risk	ongoing and sustained action that eliminates or reduces the potential effects of hazards
Normalized Risk	measure of risk created by mathematically adjusting a value in order to permit comparisons
Operational Risk	risk that has the potential to impede the successful execution of operations
Organization and Change Management Risk	risk associated with organizational-wide cultural resistance to change and standardization
Prevention	actions taken and measures put in place for the continual assessment and readiness of necessary actions to reduce risk of threats and vulnerabilities, to intervene and stop an occurrence, or to mitigate effects

Probabilistic Risk Assessment	type of quantitative risk assessment that considers possible combinations of occurrences with associated consequences, each with an associated probability or probability distribution
Qualitative Risk Assessment Methodology	set of methods, principles, or rules for assessing risk based on non-numerical categories or levels
Quantitative Risk Assessment Methodology	set of methods, principles, or rules for assessing risks based on the use of numbers where the meanings and proportionality of values are maintained inside and outside the context of the assessment
Relative Risk	measure of risk that represents the ratio of risks when compared to each other or a control
Residual Risk	risk that remains after risk management measures have been implemented
Risk	potential for an unwanted outcome as determined by its likelihood and the consequences
Risk Acceptance	explicit or implicit decision not to take an action that would affect all or part of a particular risk
Risk Analysis	systematic examination of the components and characteristics of risk
Risk Assessment	product or process evaluating information based on a set of criteria and assigns values to risks for the purpose of informing priorities, developing or comparing courses of action, and informing decision making
Risk Assessment Methodology	set of methods, principles, or rules used to identify and assess risks and to form priorities, develop courses of action, and inform decision-making
Risk Avoidance	strategies or measures taken that effectively remove exposure to a risk
Risk Communication	exchange of information with the goal of improving risk understanding, affecting risk perception and/or equipping people or groups to act appropriately in response to an identified risk
Risk Control	deliberate action taken to reduce the potential for harm or maintain it at an acceptable level
Risk Exposure	contact of an asset, system, or geographic area with a potential hazard
Risk Governance	actors, rules, practices, processes, and mechanisms concerned with how risk is analyzed, managed, and communicated
Risk Identification	process of finding, recognizing, and describing potential risks
Risk Indicator	measure that signals the potential for an unwanted outcome as determined by qualitative or quantitative analysis
Risk Management	process of identifying, analyzing, and communicating risk and accepting, avoiding, transferring or controlling it to an acceptable level considering associated costs and benefits of any actions taken

Risk Management Methodology	set of methods, principles, or rules used to identify, analyze, assess, and communicate risk, and mitigate, accept, or control it to an acceptable level at an acceptable cost
Risk Matrix	tool for ranking and displaying components of risk in an array
Risk Mitigation	application of measure or measures to reduce the likelihood of an unwanted occurrence and/or its consequences
Risk Perception	subjective judgment about the characteristics and/or severity of risk
Risk Profile	description and/or depiction of risks to an asset, system, network, geographic area or other entity
Risk Reduction	decrease in risk through risk avoidance, risk control or risk transfer
Risk Score	numerical result of a semi-quantitative risk assessment methodology
Risk Tolerance	degree to which an entity is willing to accept risk
Risk Transfer	action taken to manage risk that shifts some or all of the risk to another entity, asset, system, network, or geographic area
Risk-based Decision Making	determination of a course of action predicated primarily on the assessment of risk and the expected impact of that course of action on that risk
Risk informed decision making	determination of a course of action predicated on the assessment of risk, the expected impact of that course of action on that risk, as well as other relevant factors
Scenario (risk)	hypothetical situation comprised of a hazard, an entity impacted by that hazard, and associated conditions including consequences when appropriate
Social Application of Risk	distortion of the seriousness of a risk caused by public concern about the risk and/or about an activity contributing to the risk
Threat	indication of potential harm to life, information, operations, the environment and/or property
Threat Assessment	product or process of evaluating information based on a set of criteria for entities, actions, or occurrences, whether natural or man-made, that have or indicate the potential to harm life, information, operations and/or property
Tiering	system of organization utilizing ranked levels to sort information or things
Unacceptable Risk	level of risk at which, given costs and benefits associated with further reduction measures, action is deemed to be warranted at a given point in time
Vulnerability	physical feature or operational attribute that renders an entity open to exploitation or susceptible to a given hazard

APPENDIX E – BIOLOGICAL SELECT AGENTS AND TOXINS

The following biological agents and toxins have been determined to have the potential to pose a severe threat to both human and animal health, to plant health, or to animal and plant products. An attenuated strain of a select agent or an inactive form of a select toxin may be excluded from the requirements of the Select Agent Regulations. A list of excluded agents and toxins may be found on www.selectagents.gov.

HHS and USDA Select Agents and Toxins
7CFR Part 331, 9 CFR Part 121, and 42 CFR Part 73

HHS SELECT AGENTS AND TOXINS

Abrin
Bacillus cereus Biovar *anthracis**
Botulinum neurotoxins*
Botulinum neurotoxin producing species of *Clostridium**
Conotoxins (Short, paralytic alpha conotoxins containing the following amino acid sequence $X_1CCX_2PACGX_3X_4X_5X_6CX_7$)[1]
Coxiella burnetii
Crimean-Congo haemorrhagic fever virus
Diacetoxyscirpenol
Eastern Equine Encephalitis virus[3]
Ebola virus*
*Francisella tularensis**
Lassa fever virus
Lujo virus
Marburg virus*
Monkeypox virus[3]
Reconstructed replication competent forms of the 1918 pandemic influenza virus containing any portion of the coding regions of all eight gene segments (Reconstructed 1918 Influenza virus)
Ricin
Rickettsia prowazekii
SARS-associated coronavirus (SARS-CoV)
Saxitoxin
South American Haemorrhagic Fever viruses:
Chapare
Guanarito
Junin
Machupo
Sabia
Staphylococcal enterotoxins A,B,C,D,E subtypes
T-2 toxin
Tetrodotoxin
Tick-borne encephalitis complex (flavi) viruses:
Far Eastern subtype
Siberian subtype
Kyasanur Forest disease virus
Omsk hemorrhagic fever virus
Variola major virus (Smallpox virus)*
Variola minor virus (Alastrim)*
*Yersinia pestis**

OVERLAP SELECT AGENTS AND TOXINS

*Bacillus anthracis**
Bacillus anthracis Pasteur strain
Brucella abortus
Brucella melitensis
Brucella suis
*Burkholderia mallei**
*Burkholderia pseudomallei**
Hendra virus
Nipah virus
Rift Valley fever virus
Venezuelan equine encephalitis virus[3]

USDA SELECT AGENTS AND TOXINS

African horse sickness virus
African swine fever virus
Avian influenza virus[3]
Classical swine fever virus
Foot-and-mouth disease virus*
Goat pox virus
Lumpy skin disease virus
Mycoplasma capricolum[3]
Mycoplasma mycoides[3]
Newcastle disease virus[2,3]
Peste des petits ruminants virus
Rinderpest virus*
Sheep pox virus
Swine vesicular disease virus

USDA PLANT PROTECTION AND QUARANTINE (PPQ) SELECT AGENTS AND TOXINS

Peronosclerospora philippinensis (Peronosclerospora sacchari)
Phoma glycinicola (formerly Pyrenochaeta glycines)
Ralstonia solanacearum
Rathayibacter toxicus
Sclerophthora rayssiae
Synchytrium endobioticum
Xanthomonas oryzae

*Denotes Tier 1 Agent

[1] C = Cysteine residues are all present as disulfides, with the 1st and 3rd Cysteine, and the 2nd and 4th Cysteine forming specific disulfide bridges; The consensus sequence includes known toxins α-MI and α-GI (shown above) as well as α-GIA, Ac1.1a, α-CnIA, α-CnIB; X1 = any amino acid(s) or Des-X; X2 = Asparagine or Histidine; P = Proline; A = Alanine; G = Glycine; X3 = Arginine or Lysine; X4 = Asparagine, Histidine, Lysine, Arginine, Tyrosine, Phenylalanine or Tryptophan; X5 = Tyrosine, Phenylalanine, or Tryptophan; X6 = Serine, Threonine, Glutamate, Aspartate, Glutamine, or Asparagine; X7 = Any amino acid(s) or Des X and; "Des X" = "an amino acid does not have to be present at this position." For example if a peptide sequence were XCCHPA then the related peptide CCHPA would be designated as Des-X.

[2] A virulent Newcastle disease virus (avian paramyxovirus serotype 1) has an intracerebral pathogenicity index in day-old chicks (Gallus gallus) of 0.7 or greater or has an amino acid sequence at the fusion (F) protein cleavage site that is consistent with virulent strains of Newcastle disease virus. A failure to detect a cleavage site that is consistent with virulent strains does not confirm the absence of a virulent virus.

[3] Select agents that meet any of the following criteria are excluded from the requirements of this part: Any low pathogenic strains of avian influenza virus, South American genotype of eastern equine encephalitis virus , west African clade of Monkeypox viruses, any strain of Newcastle disease virus which does not meet the criteria for virulent Newcastle disease virus, all subspecies Mycoplasma capricolum except subspecies capripneumoniae (contagious caprine pleuropneumonia), all subspecies Mycoplasma mycoides except subspecies mycoides small colony (Mmm SC) (contagious bovine pleuropneumonia), and any subtypes of Venezuelan equine encephalitis virus except for Subtypes IAB or IC, provided that the individual or entity can verify that the agent is within the exclusion category. 9/10/13

APPENDIX F: EXCERPTS RELATED TO ADDITIONAL CONSIDERATIONS FOR EXPERIMENTS OF CONCERN

From Biotechnology Research in an Age of Terrorism, 2004, page 5 Executive Summary:

Recommendation 2: Review of Plans for Experiments We recommend that the Department of Health and Human Services (DHHS) augment the already established system for review of experiments involving recombinant DNA conducted by the National Institutes of Health to create a review system for seven classes of experiments (the Experiments of Concern) involving microbial agents that raise concerns about their potential for misuse.

This part of the system includes both the criteria for deciding which experiments will be subject to review and the process by which the review will take place.

The Criteria for Review. The Committee identified seven classes of experiments that it believes illustrate the types of endeavors or discoveries that will require review and discussion by informed members of the scientific and medical community before they are undertaken or, if carried out, before they are published in full detail. They include experiments that:

1. Would demonstrate how to render a vaccine ineffective. This would apply to both human and animal vaccines. Creation of a vaccine resistant smallpox virus would fall into this class of experiments.

2. Would confer resistance to therapeutically useful antibiotics or antiviral agents. This would apply to therapeutic agents that are used to control disease agents in humans, animals, or crops. Introduction of ciprofloxacin resistance in *Bacillus anthracis* would fall in this class.

3. Would enhance the virulence of a pathogen or render a nonpathogen virulent. This would apply to plant, animal, and human pathogens. Introduction of cereolysin toxin gene into *Bacillus anthracis* would fall into this class.

4. Would increase transmissibility of a pathogen. This would include enhancing transmission within or between species. Altering vector competence to enhance disease transmission would also fall into this class.

5. Would alter the host range of a pathogen. This would include making non-zoonotics into zoonotic agents. Altering the tropism of viruses would fit into this class.

6. Would enable the evasion of diagnostic/detection modalities. This could include microencapsulation to avoid antibody-based detection and/or the alteration of gene sequences to avoid detection by established molecular methods.

7. Would enable the weaponization of a biological agent or toxin.

This would include the environmental stabilization of pathogens. Synthesis of smallpox virus would fall into this class of experiments.

Section 6.2.2 from United States Government Policy for Institutional Oversight of Life Sciences Dual Use Research of Concern

(accessed from http://osp.od.nih.gov/office-biotechnology-activities/biosecurity/dual-use-research-concern)

6.2.2. Categories of experiments

a) Enhances the harmful consequences of the agent or toxin

b) Disrupts immunity or the effectiveness of an immunization against the agent or toxin without clinical and/or agricultural justification

c) 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

d) Increases the stability, transmissibility, or the ability to disseminate the agent or toxin

e) Alters the host range or tropism of the agent or toxin

f) Enhances the susceptibility of a host population to the agent or toxin

g) Generates or reconstitutes an eradicated or extinct agent or toxin listed in 6.2.1, above

APPENDIX G. ADDITIONAL U.S. OVERSIGHT OR GUIDANCE ON BIOSAFETY OR BIOSECURITY OF BIOLOGICAL AGENTS

Agency	Regulation/Policy/Guidance	Relevant Dates	Activities Covered	Risk Addressed (stated)	Risk Addressed (inferred)	Risk Assessment Strategy	Risk Mitigation Strategy	Enforce-ment and Penalty
Centers for Disease Control (CDC)/ National Institutes of Health (NIH)	Biosafety in Microbiological and Biomedical Laboratories (BMBL) Guidance	First published in 1984; 5th Edition in 2009	Work with potentially infectious agents in biomedical laboratories.	"Risk assessment is a process used to identify the hazardous characteristics of a known infectious or potentially infectious agent or material, the activities that can result in a *person's exposure to an agent*, the likelihood that such an exposure *will cause an LAI*, and the probable consequences of such an infection." P. 9; LAI = Laboratory acquired infection "Risk assessment…to protect the health of laboratory workers and the public from the risks associated with the use of hazardous biological agents in laboratories."	Injuries and occupational infections in laboratory workers. "Laboratory" refers to research and production, not necessarily clinical diagnostic laboratories, for which separate, and mostly parallel, guidelines have been published by a CDC Blue Ribbon Panel (2012)	Risk assessment principles are used to "enable the appropriate selection of microbiological practices, safety equipment and facility safeguards that can prevent laboratory acquired infections." "…primary risk criteria used to define…(4) ascending levels of containment…are infectivity, severity of disease, transmissibility and the nature of the work being conducted." Risk group classifications based on human health hazards are presented for most infectious agents, as well as the recommended biosafety levels at which to work, with practices defined for each biosafety level. Laboratory directors are responsible for performing risk assessments with guidance from institutional biosafety/biosecurity officers.	Use of appropriate biosafety levels and microbiological practices, safety equipment (biological safety cabinets; annually inspected), frequent hand washing, use of appropriate disinfectants, negative airflow, written safety protocols and facility safeguards	

Agency	Regulation/Policy/Guidance	Relevant Dates	Activities Covered	Risk Addressed (stated)	Risk Addressed (inferred)	Risk Assessment Strategy	Risk Mitigation Strategy	Enforce-ment and Penalty
CDC/NIH	Guidelines for Safe Work Practices in Human and Animal Medical Diagnostic Laboratories Guidelines	2012	Work performed in diagnostic laboratories	"Persons working in clinical diagnostic laboratories are exposed to many risks." "Laboratory exposures occur more often than is generally suspected." "In this report, "laboratory exposures" refer to events that put employees at risk for an LAI and events that result in actual acquisition of LAIs."	LAIs in diagnostic laboratory employees.	Identify hazards and specific practices and procedures to eliminate them; ensure that all personnel are instructed in performing risk assessments; provide a mechanism for employees to communicate hazard identifications and risk mitigation strategies to management; educate clinicians and nurses about safe specimen procurement and transport	Dictate that a laboratory director assume responsibility for establishing and enforcing a policy instituting a culture of safety.	
Centers for Medicare and Medicaid Services/CLIA	Clinical Laboratory Improvement Amendments (CLIA); "Standards and Certification: Laboratory Requirements" Regulation	1988	Establishes quality standards for laboratory testing performed on human specimens for the purpose of diagnosis, prevention or treatment of disease	"… failure of a laboratory to comply with the standards...presents an imminent and serious risk to human health,…" 263a. Certification of laboratories (i) Suspension, revocation and limitation (2) Action before a hearing	Lack of quality standards for diagnostic testing can lead to inaccurate results and mis-diagnoses and endangerment of human health.	Inspections and proficiency testing using standardized samples	Certification of laboratories after application, inspections and proficiency testing are successfully completed; methodologies and personnel qualifications are considered in addition	Revocation of certification, fines and imprisonment
Food and Drug Administration (FDA)	Food, Drug and Cosmetic Act Law	1938	Work on human and animal drugs, food additives and pesticides (pre-market release); food and cosmetics (post-market monitoring)	None stated	Drugs can cause risk to human and animal safety; ingestion of food from genetically engineered food animals poses a risk to human and animal health; the environment can also be harmed by drug or agent disposal.	Drugs must be tested under strict conditions for efficacy and safety; data is provided by the developers. Manufacturers of food additives must show data that release into the market will present "reasonable	Pre-market review and approval of new drugs and food additives. Labeling is regulated. Monitoring of adverse event	Products may be pulled from the market based on adverse event reporting. Fines may

Agency	Regulation/Policy/Guidance	Relevant Dates	Activities Covered	Risk Addressed (stated)	Risk Addressed (inferred)	Risk Assessment Strategy	Risk Mitigation Strategy	Enforce-ment and Penalty
						certainty of no harm".	reporting.	be levied and imprisonment may ensue.
NIH	NIH Guidelines for Research Using Recombinant or Synthetic Nucleic Acid Molecules; http://oba.od.nih.gov/rdna/nih_guidelines_oba.html Guidance (required for institutions accepting NIH funding)	Initiated in 1976; most recently amended in 2013	rDNA and synthetic nucleic acid work conducted at institutions receiving NIH funding	None stated	Work with rDNA or synthetic nucleic acids may increase the pathogenicity of organisms potentially leading to increased disease occurrence or severity in laboratory workers or the general public; release into the environment may also lead to niche and biodiversity disruption	Institutional Biosafety Committees review work using recombinant or synthetic DNA on a case by case basis; investigators identify risks based on Risk Group Classification (NIH) according to "relative pathogenicity for healthy adult humans" and "the available treatments for such diseases"; Recombinant DNA Advisory Committee (NIH) also conducts reviews and advises the NIH Director	Laboratory practices, techniques, and safety equipment providing physical barriers to release; biological barriers (vector selection) to release and infectivity	Non-compliance results in "(i) suspension, limitation, or termination of NIH funds for recombinant or synthetic nucleic acid molecule research at the institution, or (ii) a requirement for prior NIH approval of any or all recombinant or synthetic nucleic acid molecule projects at the

Agency	Regulation/Policy/Guidance	Relevant Dates	Activities Covered	Risk Addressed (stated)	Risk Addressed (inferred)	Risk Assessment Strategy	Risk Mitigation Strategy	Enforce-ment and Penalty
								institution."
Environmental Protection Agency (EPA)	Toxic Substances Control Act (TSCA) Federal Insecticide, Fungicide and Rodenticide Act Laws	1976 1910	Work with genetically engineered microbes and pesticides as "new chemical substances" under the TSCA	"An Act To regulate commerce and protect human health and the environment by requiring testing and necessary use restrictions on certain chemical substances, and for other purposes".	There are potential risks to both human and animal health, as well as the environment, should genetically engineered microbes or plant pesticides inadvertently become more pathogenic to laboratory workers or the public, or animals in the environment. There are risks to environmental niche disruption should genetically engineered agents harm other naturally occurring microbes, insects or plants leading to loss of genetic diversity.	Conducts risk assessments for environmental release (TSCA Experimental Release Application) or manufacture (Microbial Commercial Activity Notice) based on information that the manufacturer provides.	EPA must approve any environmental release of genetically-modified organisms; monitors and tracks adverse event reporting; imposes conditions of safe use through labeling.	Fines and imprisonment.
U.S. Department of Agriculture (USDA)/Animal and Plant Health Inspection Service (APHIS)	Plant Protection Act (other requirements related to field trials may be found in the National Environmental Policy Act,	2000	Field trials of genetically engineered crops under its authority to regulate plant pests		There are potential risks to both animal health, as well as the environment, should genetically engineered microbes or plant pesticides inadvertently become more pathogenic to animals or other plants in the environment. There are risks to environmental niche disruption should	Review permits for growth in field trials. Review field trial results and requests to deregulate crops to be grown without a permit on a commercial scale.	Review of data and approval or denial of requests to grow genetically engineered crops in field trials or on a commercial scale.	Fines and imprisonment.

Agency	Regulation/Policy/Guidance	Relevant Dates	Activities Covered	Risk Addressed (stated)	Risk Addressed (inferred)	Risk Assessment Strategy	Risk Mitigation Strategy	Enforce-ment and Penalty
	1969) Laws				genetically engineered agents harm other naturally occurring microbes, insects or plants leading to loss of genetic diversity.			
Occupational Safety and Health Administration (OSHA)	Occupational Safety and Health Act (and various associated standards) Law OSHA Laboratory Safety Guidance Guidance	1970 2011	General duties of all employees in the workforce Duties of the non-production laboratory workforce	Employers "shall furnish to each of his employees employment and a place of employment which are free from recognized hazards that are causing or likely to cause death or serious physical harm to his employees."			Provision of Chemical Hygiene Officer, and Chemical Hygiene Plan, both of which dictate worker training, exposure monitoring, medical consultation and use of PPE and engineering controls; communication of hazards to employees; labeling of chemicals; MSDS information is retained; vaccinations offered; exposure control plans	Fines and imprisonment

Agency	Regulation/Policy/Guidance	Relevant Dates	Activities Covered	Risk Addressed (stated)	Risk Addressed (inferred)	Risk Assessment Strategy	Risk Mitigation Strategy	Enforce-ment and Penalty
							developed	
NIH/Office of Laboratory Animal Welfare (OLAW)	Public Health Service (PHS) Policy on Humane Care and Use of Laboratory Animals Policy	1986	Work with research animals that is funded by the PHS	N/A – the Policy is written to ensure the humane care of research animals	N/A	N/A	N/A	Non-compliance can result in revocation of PHS funds

APPENDIX H. SUMMARY OF SELECT INTERNATIONAL AGREEMENTS, REGULATIONS, OR GUIDANCE RELEVANT TO BIOLOGICAL AGENTS

Convention on the Prohibition of the Development, Production and Stockpiling of Bacteriological (Biological) and Toxin Weapons and on their Destruction

Commonly referred to as the Biological Weapons Convention (BWC), this was the first multilateral disarmament treaty banning the development, production and stockpiling of an entire category of weapons of mass destruction, initially open for signature in 1972, and entered into force in 1975. It draws inspiration from the Geneva Protocol of 1925 (Protocol for the Prohibition of the Use in War of Asphyxiating, Poisonous or Other Gases, and of Bacteriological Methods of Warfare). Under the BWC treaty, the signatories provide annual reports on their countries' research centers and laboratories, vaccine production facilities, information on outbreaks of infectious diseases (caused by microbiological agents or toxins) and national biological defense and development research. Although the risk being mitigated by the treaty is not explicitly stated, it can be easily inferred that use of biological weapons are dangerous to humankind and society due to their propensity for mass destruction. Although neither biosafety nor biosecurity is the focus of the BWC, voluntary implementation of national biosafety and biosecurity management standards is encouraged.

UN Security Council Resolution 1540

UNSCR 1540 focused on non-proliferation of all types of weapons of mass destruction (chemical, biological, radiological and nuclear). The resolution (2004) encourages all UN member states to adopt legislation to prevent the proliferation of such weapons of mass destruction, including their delivery systems, and establish appropriate controls over materials to prevent their illicit trafficking statin that they constitute "a threat to international peace and security".

Although the word "biosecurity" is not specifically mentioned in the text of the resolution, its principles can be inferred when the State members state that they are "*Gravely concerned* by the threat of terrorism, and the risk that non-State actors…may acquire, develop, traffic in or use nuclear, chemical and biological weapons and their means of delivery." The resolution goes on to state that "…all States, in accordance with their national procedures, shall adopt and enforce appropriate effective laws which prohibit any non-State actor to manufacture, acquire, possess, develop, transport, transfer or use nuclear, chemical or biological weapons and their means of delivery, in particular for terrorist purposes…"; "…all States shall… Develop and maintain appropriate effective measures to account for and secure such items in production, use, storage and transport;" "…Develop and maintain appropriate effective physical protection measures;" and "Develop and maintain appropriate effective border controls and law enforcement to detect, deter, prevent and combat…the illicit trafficking and brokering in such items…".

World Health Assembly Resolution 58.29 Enhancement of Laboratory Biosafety

Published by the World Health Assembly in 2005, Resolution 58.29 acknowledges that "release of microbiological agents and toxins may have global ramifications;" and "the containment of microbiological agents and toxins in laboratories is critical to preventing outbreaks of emerging and re-emerging diseases…." As such, it "URGES Member States…to review the safety of their laboratories and their existing protocols for safe handling of microbiological agents and toxins"

and "implement specific programmes…to promote biosafety laboratory practices for the safe handling and transport…of microbiological agents and toxins…in order to minimize the possibility of laboratory-acquired infections and resultant spread to the community;".

WHO International Health Regulations

The World Health Organization (WHO) published the third edition of the IHR in 2005, having originally been adopted by the Health Assembly in 1969, and preceded by the International Sanitary Regulations in 1951. Their purpose and scope are "to prevent, protect against, control and provide a public health response to the international spread of disease in ways that are commensurate with and restricted to public health risks, and which avoid unnecessary interference with international traffic and trade". Thus, they are primarily concerned with "public health emergencies of international concern" (PHEIC), and the provisions of the IHR establish standards for how nations should regulate travel and transport of persons and goods for the purpose of prohibiting PHEIC. By regulation of such transport, they are in fact addressing biosecurity principles.

IATA Dangerous Goods Regulations, 57th Edition (2016) and UN Recommendation on the Transport of Dangerous Goods (UN Model Regulations; Rev. 19, 2015)

Both of these documents address the safe packaging and transport of dangerous goods, including infectious substances known, or reasonably expected, to contain pathogens harmful to human or animal health and toxins liable to cause death, serious injury or harm to human health. In addition to microbial agents, these document address the transport of medical and clinical waste, as well as toxins and chemicals.

Others

A number of other agreements and guidelines exist relevant to biological agents. Many of these are from the World Health Organization (WHO), and provide framework and guidance on the IHR. WHO's Laboratory Biosafety Manual (2004) is widely used throughout the world, as the international equivalent to the CDC's BMBL, and covers both the risks involved with working with microbial agents, but chemical and physical laboratory hazards as well. Suggested guidance for working in medical/clinical/diagnostic laboratories is published by the International Standards Organization (ISO15189 and 15190).

The CEN Workshop Agreements on Biorisk (15793 and 16393) were published by the European Committee for Standardization (CEN) to specifically define the components of a Biorisk Management System. CWA15793 (2011) describes a performance-based biorisk management system approach based on risk assessment and mitigation principles. CWA16393 (2012) serves as the implementation guide for CWA15793.

Global Health Security Agenda Action Packages are designed such that participating nations can stand up national biosafety and biosecurity systems within a five year period. They advocate that especially dangerous pathogens are identified, secured and monitored in a minimal number of facilities under best practices. Elements of biological risk management training and educational outreach are encouraged to promote a shared culture of responsibility, reduce dual-use risks, mitigate biological agent proliferation and deliberate-use threats and ensure safe transfer of

biological agents. They champion the development of national biosafety and biosecurity legislation, which would also satisfy adherence to the BWC and UNSCR 1540.
Work with animals at the international level is governed by the World Organization for Animal Health (OIE). The OIE agreements advocate for standards that improve animal health and welfare, in both research, veterinary and food-production realms. They provide regulations for safe international trade in terrestrial and aquatic animals and their products. The Food and Agriculture Organization of the UN and the WHO published the Codex Alimentarius, also known as the "Food Code", which is the key reference national food control agencies on the safety of the international food trade.

APPENDIX I. SUGGESTED SCOPES-OF-WORK FOR ADDITIONAL ACTIVITIES

Appendix Ia. Suggested Scope of Work - Biological Select Agent & Toxin (BSAT) Risk Management Technical Working Group

Background

A recent study led by Sandia National Laboratories' International Biological and Chemical Threat Reduction program (SNL) evaluated the existing use of risk assessment in the Federal select agent program. The study utilized interviews with regulators and regulated entities, discussions and deliberations with experts, and review of scientific literature regarding risk assessment and risk management and applicability to high-risk industries.

One of the findings of this study was:

> **Finding 1.** The Select Agent regulations, FSAP regulators, and regulated entities are imprecise and inconsistent in the use of terminology and processes to manage risks deriving from BSAT. In addition, well-accepted publications on risk assessment and risk management of biological agents and toxins (regardless of Select Agent status) differ in their use of terminology and processes. Dialogue on risks from and risk management of BSAT would benefit from common terminology and understanding.

Recommendations deriving from this finding suggested the formation of a technical working group to develop a method for risk management of BSAT that maps to a known standard and which integrates safety and security risks into a BSAT risk management plan.

FSAP seeks a secretariat to convene and manage a BSAT Risk Management Working Group with the following suggested membership to accomplish the tasks listed below.

Suggested Membership:

Consider inclusion of at least one representative from each of the groups below:

- *Disciplines*
  - ABSA International (biosafety, biosecurity)
  - American Society for Microbiology (ASM, microbiology)
  - Risk Management
- *Sectors* (assure at least one representative each from human, animal, and plant focus)
  - American Public Health Laboratories (APHL) - non-federal government
  - Association of American Universities (AAU) - academic research
    - Alternately or in addition, Campus Safety Health & Environmental Management Association (CSHEMA)
  - Federal government lab(s)
  - Private labs (biotech, pharmaceutical, etc.)
  - Commercial labs
- *Federal Department- and Agency-Based Participants*
  - ISATTAC

DSAT
AgSAS
FBI (WMD Coordinator)
DHS

Suggested Tasks:

1. Using, at a minimum, the publications listed in Table 1 and the report from the SNL-led study, define risks to be targeted and develop a risk management method for those risks to be utilized by BSAT regulated entities.
2. Validate the method by assuring alignment with at least one recognized risk management standard (e.g., ANSI/AIHA Z10, IRGC Risk Governance Framework, ISO 31000, Department of Homeland Security (DHS) and/or others identified) or a hybrid approach.
3. Outline guidance that will lead a regulated entity in development of a BSAT risk management plan. This plan is intended to be used as the primary discussion guide and basis for evaluation by regulators during compliance inspections and by regulated entities during self-audits.
4. Develop core performance indicators that can be measured at all regulated entities, regardless of sector and complexity to indicate trends in reduction of risk from BSAT. The core indicators should be able to be utilized at individual BSAT labs, the larger entity, the sector, and/or the entire FSAP.
5. Develop a strategy for field-testing (by entity and inspectors) of the BSAT risk management method and plan. Field-testing should occur in all sectors at select entities (and include differing levels of entity complexity).
6. Based on the results from the field-tests, refine the method and suggested guidance. Re-validate with the risk management standard(s) utilized in #2, above.
7. Provide suggestions for updating the regulations to require use of the BSAT risk management method and plan.
8. Assess the availability, accessibility, and quality of data sources necessary to conduct risk assessments and risk evaluations, make risk control decisions, and evaluate risk management performance (See Table 2 for some possible data). Identify areas for improvement and explore mechanisms to develop and assure availability, access, and quality for use in BSAT risk management decisions. Suggest existing data sources or criteria for creating (or modifying) data sources to use to inform BSAT risk management. Where available, use existing sources in field-testing (#5, above).
9. Suggest harmonization with non-FSAP publications by identifying alignments with and/or conflicts between the identified BSAT risk management method and existing publications or approaches to biological risk management. Assure that alignments are identified and leveraged. Analyze the impact of conflicts and suggest mechanisms to harmonize.
10. Develop learning objectives and key messages for training the FSAP community about the new method.

Deliverables:

1. Working Group Membership and Charter.
2. White paper (initial draft and revised draft (after field testing)) including the following:
    a. Definitions
    b. Background
    c. Process to develop chosen method
    d. Detailed description of chosen method
    e. Validation of method with known standard(s)
    f. Data sources needed (and evaluation of availability, access, and quality of required data) for input into method
    g. Suggested updates to regulations

3. Outline for guidance for developing BSAT risk management plan (initial draft and revised draft (after field-testing)), including description and method for collection and reporting of core performance indicators.
4. Suggested strategy and detailed work plan for field-testing in select entities across all FSAP sectors (and including differing levels of entity complexity).
5. Report analyzing results of field-tests, including evaluation of core performance indicators for accuracy and relevance to BSAT risk reduction and FSAP compliance.
6. Suggested further actions to support and maintain BSAT risk management method.

Table 1:Suggested Sources for Use in Developing BSAT Risk Management Method
Biosafety in Microbiological and Biomedical Laboratories, 5th edition
Quick Guide to Risk Assessment for Biological Hazards in the Laboratory, from Prudent Practices in the Laboratory.
Laboratory Biosafety and Biosecurity Risk Assessment Technical Guidance Document (IBTR, Sandia and IFBA)
Chapter 5: Risk Assessment of Biological Hazards, from Biological Safety: Principles and Practices.
MMWR: Guidelines for Safe Work Practices in Human and Animal Medical Diagnostic Laboratories.
A Strategy for Assessing and Managing Occupational Exposures, 3rd edition.
References highlighting additional consideration for certain types of genetic modification (as excerpted in Appendix F in the SNL report)
Laboratory Biosecurity Handbook
Laboratory Biorisk Management: Biosafety and Biosecurity
NIH Guidelines
OSHA Hazard Communication
OSHA Lab Standard
ANSI/AHIA Z10
International Risk Governance Council – Risk Governance Framework
ISO 31000
DHS Risk Management Doctrine (April 2011)

Table 2:Possible types of data for use in informing BSAT Risk Management Method and Planning
Reported incidents involving BSAT or situations where BSAT may be used
Evidence-based best practices for managing risks from biological agent and toxins
Historical or anticipated risk scenarios to be used to guide development of site-specific risk management options and to test site-specific assumptions
Pathogen data sheets that lists information critical for input into risk assessment (and/or criteria for judging the quality of data on BSAT agents and toxins).
Critical control points derived from an understanding of BSAT risks, risk-based control methods, historical and potential failures of control methods, etc.
Common security vulnerabilities, especially where those vulnerabilities are common to a particular sector, procedure, and/or agent

Appendix Ib. Suggested Scope of Work - Biological Select Agent & Toxin (BSAT) Risk Management- Phenotypic Definitions

Background

A recent study led by Sandia National Laboratories' International Biological and Chemical Threat Reduction program (SNL) evaluated the existing use of risk assessment in the Federal select agent program. The study utilized interviews with regulators and regulated entities, discussions and deliberations with experts, and review of scientific literature regarding risk assessment and risk management and applicability to high-risk industries.

One of the findings of this study was:

> **Finding 3.** Even with a standardized, harmonized, ideal risk assessment process, risk assessment is only as good as the input. Likewise, decisions on risk control measures are only as good as the derived understanding of the risk from a fully-informed risk assessment. Using data that is relevant, reliable, and current, FSAP and regulated entities could prepare more consistent and effective risk assessments and risk management plans.

Recommendations deriving from this finding suggested the utilization of phenotypic descriptions of listed agents, rather than just taxonomic descriptions, so that the characteristics of the agent, regardless of name, are utilized as inputs into the risk assessment and assure thoughtful hazard identification, rather than merely compliance with a list of biological agent and toxins.

This recommendation is unscored by the recent proposal to include *B. cereus* biovar *anthracis* as a select agent. This recommendation would obviate such modifications by enabling the developing of a FSAP that automatically adapts as new data on novel pathogens emerges.

The implementation of this recommendation requires two parallel but integrated work streams. Firstly, the definitions themselves must be designed with a firm scientific basis, mindful of the need to capture risk posed by pathogens today and those that may be discovered or created in the future. Secondly, the definitions must be thoughtfully integrated into the Concept of Operations of the FSAP to avoid disruptions and confusion.

Suggested Tasks:

1. Develop draft definitions for each of the currently listed Select Agents. This task could be accomplished in phases, with Tier 1 select agents being the priority. The definitions should describe the supporting evidence basis and be accompanied by examples of specific strains that currently exist that would be captured and would be excluded by this definition. Modified or novel strains should also be included in these examples. The definitions could use phenotypic signatures (or possibly molecular).
2. In a series of meetings with FSAP stakeholders (including regulators and regulated entities), review and revise the definitions and examples of captured and excluded strains. To ensure that relevant expertise is represented, several meetings should be held to review the relevant evidence basis (one meeting of bacteriologists, animal virologist, plant pathologists, human virologists, etc.).
3. Develop a draft Concept of Operations for the integration of definitions into the FSAP. This Concept of Operations should include:
    a. Guidance on when/how/if new strains should be assayed to determine if they are captured by the phenotypic definitions.
    b. Guidance on when new strains should presumptively captured by the definitions pending assay results.

c. Guidance on communication of findings that exclude/capture new strains (and potentially new laboratories/facilities) into the FSAP.

d. Guidance on publication of results that may lead to the exclusion/capture of new strains

e. An analysis of how the number and type of regulated entities would change and associated cost implications (of the regulated and regulators).

4. In a meeting with FSAP stakeholders (including regulators and the regulated), review and revise draft Concept of Operations.
5. Finalize definitions and their associated Concept of Operations.

Deliverables:

1. Draft definitions, supporting evidence basis and examples of included and excluded strains
2. Draft Concept of Operations for inclusion of definitions into the FSAP
3. Finalized definitions and associated Concept of Operations

Appendix Ic. Suggested Scope of Work - Development and Maintenance of Community- and Web-Based Biological Select Agent & Toxin (BSAT) Pathogen Data Sites

Background

A recent study led by Sandia National Laboratories' International Biological and Chemical Threat Reduction program (SNL) evaluated the existing use of risk assessment in the Federal select agent program. The study utilized interviews with regulators and regulated entities, discussions and deliberations with experts, and review of scientific literature regarding risk assessment and risk management and applicability to high-risk industries.

One of the findings of this study was:

> **Finding 3.** Even with a standardized, harmonized, ideal risk assessment process, risk assessment is only as good as the input. Likewise, decisions on risk control measures are only as good as the derived understanding of the risk from a fully-informed risk assessment. Using data that is relevant, reliable, and current, FSAP and regulated entities could prepare more consistent and effective risk assessments and risk management plans.

Recommendations deriving from this finding suggest increasing the consistency, availability, quality, and accessibility of data on each BSAT for use by regulators and the regulated community for risk assessment and risk management decisions. The creation of community- and web-based mechanisms (e.g., wiki, etc.) to develop and populate data for each BSAT may be a beneficial solution to this problem. A wiki, for example, is a common web-based tool for sharing and collaborating on topics of interest. Proper moderation of the inputs and outputs for wikis (or similar solution) can address concerns regarding the quality of information existing on public wiki sites and information security issues. The advantages of peer review by use of a web-based collaboration have been demonstrated numerous times[25]. The development of community- and web-based mechanism to collect data for each BSAT agent will allow the BSAT community, at a minimum, or the larger biosciences community, to submit data that is current and relevant to the risk management of BSAT.

Suggested Tasks:

1. Explore options for housing and moderating via community- and web-based mechanisms that address security and data quality concerns. Document concerns and recommended solutions.
2. Determine the desired content based on relevance to FSAP and BSAT risk management processes.
3. Define roles for contributors (those with access to contribute (if not public)) and for moderators.

---

[25] Erik W. Black, "Wikipedia and academic peer review: Wikipedia as a recognised medium for scholarly publication?", Online Information Review, Vol. 32 Iss: 1, pp.73 – 88

Kwangsu Cho , Christian D. Schunn, "Scaffolded writing and rewriting in the discipline: A web-based reciprocal peer review system" Computers & Education Volume 48, Issue 3, April 2007, Pages 409–42.

4. Design a pilot test of chosen option(s) to create and populate pages and invite contributions over a defined period of time.
5. Evaluate the results via traditional (versus web-based) peer review.

Deliverables:

1. Proposed platform(s) and processes for community-based collaboration, with SWOT analysis.
2. Design for pilot test.
3. Report of pilot test results and traditional peer review.
4. Recommendations for further use of wiki methodology for BSAT data.
5. Recommendations for further use of wiki methodology, if indicated, for communication of other information relevant to BSAT risk management.

Appendix Id. Suggested Scope of Work - Biological Select Agent & Toxin (BSAT) Iterative, Interactive Risk Management Tool

Background

A recent study led by Sandia National Laboratories' International Biological and Chemical Threat Reduction program (SNL) evaluated the existing use of risk assessment in the Federal select agent program. The study utilized interviews with regulators and regulated entities, discussions and deliberations with experts, and review of scientific literature regarding risk assessment and risk management and applicability to high-risk industries.

One of the findings of this study was:

> **Finding 3.** Even with a standardized, harmonized, ideal risk assessment process, risk assessment is only as good as the input. Likewise, decisions on risk control measures are only as good as the derived understanding of the risk from a fully-informed risk assessment. Using data that is relevant, reliable, and current, FSAP and regulated entities could prepare more consistent and effective risk assessments and risk management plans.

Recommendations deriving from this finding included the minimization of the prescription of risk control measures because pre-determined risk control measures may not be sufficient to address some risks and may lead to over-control of others. Instead, it was recommended to develop guidance and support of risk management plans that are specific and aligned with the risk to be reduced.

To implement this recommendation, the development of an interactive, iterative BSAT risk management tool was recommended. This tool is envisioned as a computer-based mechanism for regulated entities to conduct a risk assessment and develop a BSAT risk management plan, which is then submitted for analysis and alignment with evidence-based best practices in BSAT risk management. This SOW details the steps to develop such a system.

Suggested Tasks:

1. Establish requirements for the system via interviews with federal FSAP stakeholders and regulated entities.
    a. Determine what granularity data transfer is desirable or feasible.
    b. Determine what level of interaction is desirable, which will determine the final nature of the system (a staffed call center, a computer program, etc.).
    c. Determine desired guidance produced by system for both the regulated and the regulators.
    d. Determine if the system is required or optional.
    e. Determine if the system should be accessible to laboratories not regulated by the DSAT (foreign laboratories or domestic laboratories working on pathogen components, near neighbors).
2. Choose a tier 1 pathogen to use in a pilot test of system.
3. Perform a best practices study of laboratories that work on this pathogen to identify containment measures, health surveillance measures and any other practices or measures that may reduce risk of loss of containment or infections outside of the laboratory. This study will also examine laboratory configurations and general experimental design to provide an evidence basis for the system.
4. Leveraging data on infection risks and loss of containment risks, develop a system that can identify critical control points (those that are most likely to be the proximal source of a hazard) for the pathogen given a

variety of experimental conditions and containment measures. This system is likely to employ a quantitative Fault Tree that can explore the uncertainty in a variety of parameters.

5. Establish pilot system and communicate its existence to the community of laboratories working on this pathogen.
6. Pilot test and evaluate the system for one year. Evaluate utility of interaction with the regulated community, guidance to the regulators and overall perceived and actual utility of system.
7. If system is shown to have utility, expand to other Tier 1 BSAT and re-evaluate.
8. If system continues to show value expand to other BSAT.

Deliverables:

1. Requirements study report.
2. Report on best practices and laboratory data for chosen pilot pathogen.
3. Fault trees that support the system.
4. If system is embodied as a computer program, the program itself will be delivered and will become property of the DSAT.
5. Evaluation report after pilot project.

APPENDIX J. DESCRIPTION OF THE ABSA INTERNATIONAL LABORATORY ACCREDITATION PROGRAM (TAKEN FROM WWW.ABSA.ORG, ACCESSED 15 SEPTEMBER 2016)

"ABSA International (ABSA) has developed a voluntary ABSA Laboratory Accreditation Program for BSL–2, ABSL–2, BSL-3, and ABSL-3 laboratories that are not under the jurisdiction of the U.S. Select Agent and Toxins Regulations. ABSA accreditation will provide entities recognition of excellence and compliance with high standards, while providing facilities guidance in generating processes and policies to create a safer environment for their organization, employees, research animals, and the community.

The benefits of ABSA Accreditation include recognition within the biosafety community that an institution conducts work with biohazardous agents in a safe and secure manner and assurance to the public that the institution is conducting safe science, thus protecting its employees, research animals, the public, and the environment. The entire process is confidential.

ABSA accreditation criteria are based on currently recognized guidelines and practices. The ABSA Laboratory Accreditation Program uses the CEN (*Comité Européen de Normalisation*, European Committee for Standardization) Workshop Agreement 15793, Laboratory Biorisk Management to assess the overall management of biological safety by the institution. *The Biosafety in Microbiological and Biomedical Laboratories*, 5th edition, CDC/NIH (BMBL) and the *NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules* (NIH Guidelines) are used to assess the technical aspects of the institution's biosafety program and practices.

ABSA site visitors will review documents request for pre-inspection including your institutions Risk Assessment SOPs and conduct a comprehensive on-site assessment. Their report is then reviewed by the ABSA Accreditation Board and accreditation status is determined. If deficiencies are found, they are outlined in a letter and the institution is given a period of time to correct them. Once the deficiencies are corrected, accreditation is awarded. The entire process is *completely confidential*.

After an institution earns accreditation, it must be re-evaluated every three years in order to maintain its accredited status. ABSA accreditation benefits an institution in many ways. And each time a new organization becomes accredited, it helps to raise the global benchmark for biological safety best practices.

Here are a few of the benefits of earning accreditation:

It represents quality
Organizations and companies look for ways to communicate their commitment to excellence. In the scientific community, ABSA Accreditation shows that an institution is serious about setting, achieving and maintaining high standards. ABSA offers the only volunteer accreditation for BSL–2, ABSL–2, BSL-3, and ABSL-3 laboratories that are not under the jurisdiction of the U.S. Select Agent and Toxins Regulations as a sign of quality and good science.

It promotes a safe environment
ABSA Accreditation provides entities recognition of excellence and compliance with high standards, while providing guidance in generating processes and policies to create a safer

environment for their organization, employees, research animals, and the community. ABSA Accreditation engages scientists, researchers, managers and administrators in an independent, rigorous assessment of their institution's compliance program—an assessment that ultimately results in improved research practices and outcomes.

It is a recruiting tool
ABSA accredited institutions can use their accreditation as a recruiting tool to attract the best and brightest researchers and biosafety professionals. Talented professionals look for high quality programs to support their activities. Accreditation provides recognition that the institution is dedicated to achieving the highest standards within the research, clinical, and biosafety communities confirming your lab conducts work with biohazardous agents in a safe and secure manner.

It demonstrates accountability
In today's world, companies and organizations are held to very high levels of accountability—by their own constituents and the general public. Accreditation through ABSA is voluntary and demonstrates a willingness to go above and beyond the minimums required by law. It tells the public that the institution is committed to conducting safe science, protecting employees, research animals, the public, and the environment. ABSA Accreditation can impact insurance and legal issues by providing documentation that your lab is doing all it can to minimize risks.

It provides a confidential peer-review
A team of highly qualified ABSA representatives provides an in-depth, confidential, on-site evaluation of the institution's biosafety management programs. ABSA Accreditation Inspectors are biosafety professionals who have been involved on both sides of the inspection process, always providing a healthy exchange of ideas throughout the inspection. This voluntary accreditation program can also be used as a pre-inspection readiness tool to help meet or exceed requirements (CDC Importation Permit inspection, etc.) This independent peer-review ensures that the institution's program is meeting ABSA Accreditation standards.

It stimulates continuous improvement
When an institution participates in the ABSA Accreditation program, it's committing to a process that stimulates continuous improvement. Earning and maintaining accreditation keeps an institution aware of, and engaged in, current best practices. Accreditation is a true commitment to the promotion of biological safety and shows the world that an institution is serious about ensuring a safe environment for their organization, employees, research animals, and the community."

The standards used by the ABSA International Laboratory Accreditation Program are available at: http://absa.org/pdf/ABSAlabAccreditation.pdf

DISTRIBUTION

1 Division of Select Agents and Toxins, Centers for Disease Control and Prevention
(electronic copy)
Attn: S. Edwin
Director, Division of Select Agents and Toxins
Office of Public Health Preparedness and Response
1600 Clifton Road, NE Mailstop A-46
Atlanta, GA 30329-4027

1	MS1363	Benjamin Brodsky	06824 (electronic copy)
1	MS1363	Lisa Astuto Gribble	06825 (electronic copy)
1	MS1363	Andrew W. Nelson	06826 (electronic copy)
1	MS1363	Mika Shigematsu	06820 (electronic copy)
1	MS1363	Laurie Wallis	06824 (electronic copy)
1	MS1363	Julie Wilder	06824 (electronic copy)

1	MS0899	Technical Library	9536 (electronic copy)


Sandia National Laboratories