



Laboratory Biosecurity *United States Regulatory Approach*

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US Policy Response to the Bioterrorist Threat

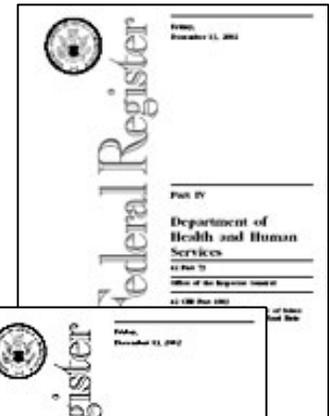
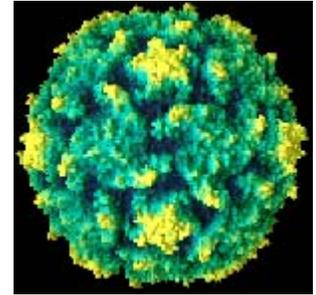
- Emerging US security regime has two sets of objectives
 - Enhance ability to respond to public and agricultural health emergencies
 - Reduce the risk that bioscience and biotechnology could be used maliciously
- Realization that bioscience facilities are potential sources of biological weapons material (viable and virulent pathogens)
- USA PATRIOT Act of 2001 – US Public Law 107-55
 - Restricted Persons
- Bioterrorism Preparedness Act of 2002 – US Public Law 107-188
 - 42 CFR 73 (Human and Overlap)
 - 9 CFR 121 (Animal and Overlap)
 - 7 CFR 331 (Plant)





US Select Agent Rule (2003)

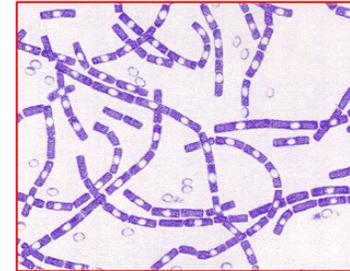
- Facility registration if it possesses one of 82 Select Agents
- Facility must designate a Responsible Official
- Background checks for individuals with access to Select Agents
- Access controls for areas that contain Select Agents
- Detailed inventory requirements for Select Agents
- Security, safety, and emergency response plans
- Safety and security training
- Regulation of transfers of Select Agents
- Extensive documentation and recordkeeping
- Safety and security inspections



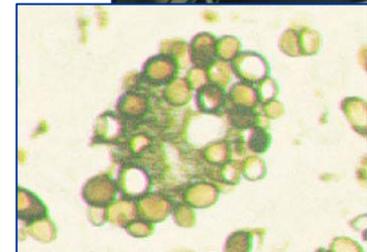
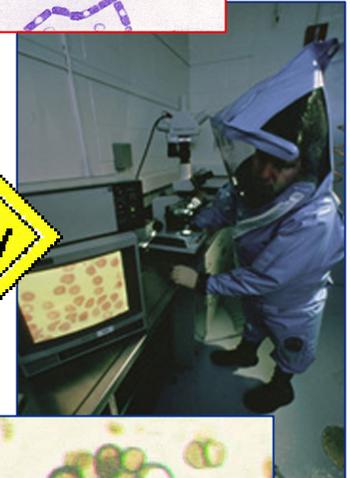


Hazardous Material Transportation Security

- Infectious substances (Class 6.2) and toxins (Class 6.1) are HazMat
- 49 CFR 172 (2003) – HM 232 – mandates security measures for the transport of some HazMat
 - Select Agents regulated under 42 CFR 73 require HazMat transport security measures
- HazMat regulated security requirements include:
 - Training
 - Security awareness training
 - Specific training as appropriate
 - Written security plan
 - Based on assessment of transportation security risks
 - Address personnel security, unauthorized access, en route security



Bacillus anthracis

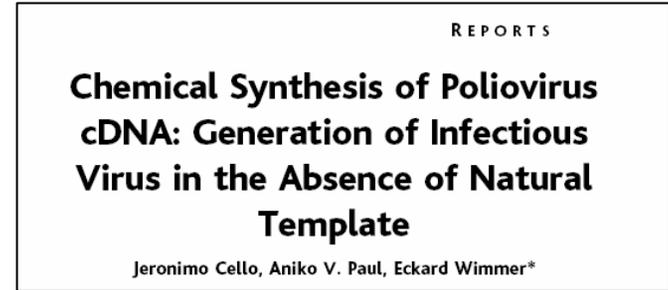


Coccidioides immitis

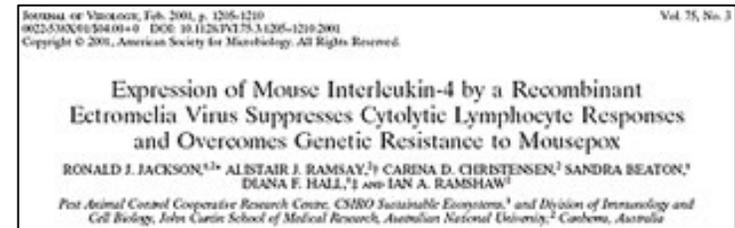


Concerns About Select Agent Rule

- Top-down security regime not tailored to laboratory realities
- No need to steal a Select Agent to perpetrate bioterrorism
- Fear that security will trump biosafety, increasing the risk of accidental release or exposure
- Security requirements increasing operational impediments and compromising research funding
- Identical protection measures for the 82 agents and toxins despite their various degrees of attractiveness to adversaries
- No protection if personnel do not understand and accept security



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Biosecurity Goes Global

The 2001 anthrax letters triggered a strong U.S. response. Now the rest of the world is starting to take biosecurity more seriously—but not necessarily by adopting the U.S. approach

Three years ago, the small number of life scientists using the term "biosecurity" were talking about ways to keep diseased crops and livestock from crossing national borders. Then came the fatal October 2001 anthrax letter attacks against several U.S. targets. In short order, thousands of U.S. scientists were confronted with an avalanche of new and often unpopular rules designed to keep potentially dangerous pathogens and toxins away from bioterrorists. Researchers who break those rules could face significant criminal penalties.

Despite these aggressive steps on the home front, U.S. officials readily acknowledged that unilateral action was insufficient and that the world needed to form a united front against increasingly sophisticated biotechnologies. But many nations were skeptical of the threat. They also doubted the value of what critics call "the guns, guards, and gates" approach to biosecurity. The result, says Reynolds Salerno, a biosecurity expert at Sandia National Laboratories in Albuquerque, New Mexico, has been "tremendous confusion and concern in the international life sciences community about biosecurity."

That confusion may be giving way to cooperation, however, as an increasingly global effort to define and implement biosecurity is gaining speed. Nations are moving to pass new biosecurity laws, while public health and security experts are hammering out voluntary biosecurity guidelines and debating "codes of conduct" for life scientists. Many countries are thinking about looser rules for less risky agents than in the United States, which critics say has imposed a one-size-fits-all approach, and few are likely to require the extensive criminal background checks carried out by U.S. agencies.

The new world order may not resemble the U.S. model. But like it or not, life scientists worldwide are about to become much more familiar with the term biosecurity.

—DAVID MALAKOFF



Spreading the word. U.K. officials are preparing to host a Bioweapons Convention-related summit in October 2005 on "codes of conduct" for life scientists who work with potentially dangerous pathogens and biotechnologies. Although few believe that such codes will deter evildoers, advocates say they can play an important role in raising awareness of biosecurity. This winter, academic and industrial scientists will gather in Washington, D.C., to sign a pledge to help prevent the misuse of biological research—a theme also stressed in a new public relations campaign (left) by the International Committee of the Red Cross (www.icrc.org). Such efforts are "a way to encourage dialogue," says Michael Moode of the Chemical and Biological Arms Control Institute, an organizer of the Washington meeting. In the meantime, the Federation of American Scientists and other groups are preparing biosecurity course materials for undergraduate and graduate students.



Whose resolve? Last April, the United Nations Security Council adopted Resolution 1540, which expresses "grave concern" about bioterrorism and directs UN members to enact tough controls on potential bioweapons. The resolution is intended to help close legal loopholes in dozens of nations—including some with growing biotech industries—with laws that don't cover all the bases. "They are now obligated to build the legal framework needed for effective biosecurity," says Barry Kellman, a law professor at DePaul University in Chicago, Illinois. Critics, however, see the measure as a U.S.-backed ploy to sidestep efforts to strengthen the Biological and Toxin Weapons Convention, which is in limbo until at least 2006.

Biocrime fighters. Interpol, the International Criminal Police Organization, has launched a 2-year effort to train police in its 181-member countries on biosecurity and fighting bioterrorism. "You'd be amazed at how little the average police chief knows about the subject," says Barry Kellman of DePaul University, who is involved in the project, which is funded by the Alfred P. Sloan Foundation. One goal: to teach investigators how to avoid lumping legitimate researchers in with the biocriminals.



Self-help book. Early next year, the 192-member World Health Organization (WHO) plans to unveil its first-ever set of international biosecurity guidelines. The consensus how-to guide, currently in draft form, should help "clear up a lot of confusion ... by clarifying best practices and minimum standards for keeping pathogens secure," says Brad Kay, a WHO biosecurity expert in Lyon, France.

But implementing the voluntary standards is another story. Many poorer nations won't want to divert precious public health funds to security, and WHO has meager resources to help out. It also isn't clear what would happen to labs that don't meet the standards. "WHO has no mandate to become a global enforcer," says Kay.

In the United States, meanwhile, a team of government and academic researchers is writing a new biosecurity chapter for the "bible" of lab safety, *Biosecurity in Microbiological and Biomedical Laboratories*.



Center of expertise. The United States and Europe are spending more than \$90 million annually to help Russia secure its sprawling former bioweapons complex and employ an estimated 6000 former bioweapons scientists. But efforts to attract investment from foreign biotech and drug firms have had mixed results, and some critics say more needs to be done to prevent ex-Soviet pathogens and weapons experts from leaking into the black market. "Biosecurity is about limiting the spread of expertise, too," says Amy Smithson, a nonproliferation specialist at the Center for Strategic and International Studies in Washington, D.C.



Asia alert. Asian Pacific leaders pledged last year to get tough on biosecurity—in part due to fears that their rapidly growing biotech industries could attract regional terrorist groups along with investors. "Singapore views this threat with grave concern," Deputy Prime Minister Tan Keng Yam said at a biosecurity conference held in the city-state earlier this year. China, meanwhile, has ratcheted up export controls and is examining both its biosecurity and biosecurity rules in the wake of the SARS epidemic and several lab accidents.

Lessons learned. The Republic of Georgia is on the verge of adopting biosecurity rules modeled on the U.S. approach—but with some important differences. For instance, the same agency will regulate both biomedical and agricultural scientists in the United States that job is split between the Centers for Disease Control and Prevention and the U.S. Department of Agriculture. "We're telling people that our model is often far more complicated than what they need," says a U.S. State Department official who advises other governments on biosecurity.

Building boom. Kazakhstan is the first of several nations getting new, secure laboratories to store and study dangerous pathogens. The facilities are courtesy of a U.S.-funded effort to reduce the bioterror threat in the former Soviet Union. Construction of the new Human Health Central Reference Lab and Repository in Almaty is set to begin in mid-2005, with Uzbekistan and Georgia next on the list. Meanwhile, talks are under way on long-term strategies for consolidating the 500 or more culture collections around the world that stock dangerous pathogens, with a goal of fewer, more secure facilities.



Heightened Security or Neocolonial Science?

New restrictions on federally funded research involving the world's most dangerous pathogens are hampering foreign collaborations

ALMATY, KAZAKHSTAN—Scott Weaver thought he had a green light for a great research partnership. After an expensive security upgrade of his labs and hours of paperwork, the director for tropical and emerging infectious disease research at the University of Texas Medical Branch (UTMB) in Galveston was ready to resume research on the Venezuelan equine encephalitis (VEE) virus in Colombia, Peru, and Venezuela. The mosquito-borne disease, endemic in all three countries, is not the worst of its kind: The alphavirus kills less than 1% of its human victims. But VEE's potential to incipitate has landed it on a list of "select agents": several dozen of the nastiest sorts of pathogens that the U.S. government fears could be turned into biological weapons. That designation has thrown up new hurdles for Weaver and his collaborators in South America—and for many other U.S. scientists working overseas.

In August, the U.S. National Institute of Allergy and Infectious Diseases (NIAID) informed Weaver that under the terms of his two VEE grants, the laboratories of his foreign colleagues must have procedures in place for handling select agents that are equivalent to tough U.S. regulations imposed last year. "I seriously doubt whether my collaborators in Caracas or Bogotà could ever meet U.S. standards for select-agent security," says Weaver. "These developing countries cannot afford the kinds of elaborate systems that labs in the U.S. have been required to install," such as sophisticated security and inventory systems and background checks on employees. He's since had to alter his projects to avoid isolating the VEE virus in the labs south of the border. Because the new policy may force some foreign partners to serve as mere sample exporters, it resurrects "the stereotype of the ugly American: arrogant, demanding, and insensitive," Weaver charges: "American collaborations will be unwelcome in many developing countries of the world."

Although his case may be one of the first, Weaver is not the only researcher feeling the

chill. According to a prominent U.S. specialist on select agents, researchers with the U.S. Centers for Disease Control and Prevention (CDC) have seen a curtailment of foreign collaborations on avian flu and viral hemorrhagic fevers. (CDC officials declined to comment.) Scientists at the U.S. Army Medical Research Institute of Infectious Diseases (USAMRIID) in Frederick, Maryland, are experiencing sim-



No picnic. Venezuelan scientists draw blood from rodents to isolate VEE virus. New NIH rules have cramped projects on this and other select agents.

ilar constraints on projects involving Congo-Crimean hemorrhagic fever and related diseases. "The important work we need to do will get done," says USAMRIID public affairs officer Carrie Vander Linden, although the details have not been worked out.

U.S. inspectors will soon be heading out to assess lab standards overseas, scientists learned at a closed-door meeting last month. Paula Strickland, acting director of NIAID's Office of International Extramural Activities, told a group at the annual meeting of the American Society of Tropical Medicine and Hygiene (ASTMH) in Miami, Florida, that security teams will include senior microbiologists from CDC's select-agents program. An interagency committee chaired by Strickland with representatives from the U.S. State and Justice departments will determine whether foreign labs "meet minimum biosafety and biosecurity requirements."

The stepped-up regulations are the latest example of the clash between scientists' cher-

ished ways of doing business and the urgent need to reduce the potential for bioterrorism, and some researchers say the rules make sense. "It would be very embarrassing for a U.S. collaborator and a U.S. agency to be funding a facility that had a major accident, or one that was involved in a bioterrorism event," says Paul Keim, an anthrax specialist at Northern Arizona University in Flagstaff.

But others fear that the tightened security could stifle cooperation. "One doesn't develop productive collaborative relationships with foreign counterparts by announcing upon arrival that 'from now on we must do things the American way,'" says UTMB arbovirus specialist Robert Tesh. "Each country has its security priorities. The U.S. cannot demand that they conform to ours."

Adds Weaver: "By inhibiting research on the ecology and epidemiology of potential biological weapons in their natural settings overseas, we will be less prepared to respond optimally to the introduction of these agents by a terrorist."

Clampdown

After letters containing powdered anthrax were mailed to members of Congress and others in the fall of 2001, the U.S. government crafted tough requirements for scientists it funds to study dangerous pathogens. In addition to tightening security at facilities in which the microbes are kept and studied, U.S. regulations now demand rigorous protocols covering security assessments, emergency response plans, training, transfers of materials, and inspections.

Under the new NIAID rules, which the institute began developing in 2003, U.S. grantees must submit a dossier on a foreign collaborating institution detailing its "policies and procedures for the possession, use, and transport of select agents." For what NIAID calls "security risk assessments," grantees "must be willing to provide the names of all individuals who will have access to the select agents."

Weaver says the new rules prompted him to drop his original plan to process field samples potentially infected with VEE virus in South America. Now, he says, he will have all the samples shipped to Galveston. "This seems to have gotten me off the hook for the time being," he says, in that his colleagues at the National Institute of Health in Bogotà and the Central University of Venezuela and the National Institute of Hygiene in Caracas now won't have to adhere to the select-agent

A Selection of Select Agents

Smallpox virus
Crimean-Congo hemorrhagic fever virus
Lassa fever virus
Central European tick-borne encephalitis
Yersinia pestis (plague)
Foot-and-mouth disease virus

Ebola viruses
Ricin
Tetrodotoxin
Bacillus anthracis (anthrax)
Venezuelan equine encephalitis virus
Botulinum neurotoxin



terms. But the change will reduce efficiency and timeliness, he says.

"Basically, the NIH [U.S. National Institutes of Health] left me with little choice," because it would have taken "months or years" to bring overseas labs into compliance, Weaver says. Already, the labs in Colombia and Venezuela store many VEE virus isolates in their freezers. Preventing the isolation of a few more strains, he says, will not deny the virus to a potential terrorist.

Although security at foreign facilities working with select agents generally has been strengthened since the 9-11 attacks, most labs would still run afoul of the new U.S. rules. Many outside the United States appear to be unaware of the regulations. "I haven't heard much," says Lev Soudalchichiev, director general of the State Research Center of Virology and Biotechnology, a former biowarfare lab near Novosibirsk, Russia, that collaborates with the United States on smallpox research.

Foreign researchers say they hope to find a way to continue working with U.S. counterparts because it would bolster security in their home countries. "If collaborations will continue, that will inevitably bring the standards up," says Bakyt Atshabar, director of the Kazakh Science Center for Quarantine and Zoonotic Diseases in Almaty, Kazakhstan, which specializes in studying endemic plague with Pentagon funding (*Science*, 17 December, p. 2021).

ASTMH and other societies intend to lobby for a relaxation of the rules. "The approach to this will not be easy," says Peter Weller, an immunologist at Harvard Medical School in Boston and ASTMH's most recent past president. For one, many agencies will want to weigh in on any change of policy. Second, Weller says, "the facile reply is that you scientists gave the Pakistanis nuclear secrets; how do we trust you on these issues?" In an e-mail response to questions from *Science*, NIAID officials say they expect no change to the select-agent terms "in the immediate future."

But some experts such as Keim say raising global security levels to U.S. standards makes sense. "We should not allow U.S. researchers to avoid regulatory oversight by going abroad. This would certainly apply to human subjects in clinical trials and animal-care standards in animal protocols. Why not security of dangerous pathogens?"

Earthquake Preparedness

Some Countries Are Betting That A Few Seconds Can Save Lives

Japan, Mexico, and Taiwan are investing in early warning systems that can offer precious seconds of warning before a major tremor

Tokyo—What would you do with 5 to 50 seconds' warning of a major earthquake?

It's not an academic question. Systems that can detect earthquakes near their source and issue warnings before the shaking starts are in place or being deployed in Mexico, Taiwan, and Japan and are being studied for locales from southern California to Istanbul. Enthusiasts are convinced that short-term warnings can save lives by stopping trains before they pass over damaged track, emptying out elevators, and alerting rescue units. "It is an epoch-making advance in earthquake safety," says Masato Motozaka, a Japanese earthquake engineer at Tohoku University in Sendai.

Not everyone agrees, however. Skeptics note that warning systems don't provide enough time to reduce casualties close to the epicenter of an earthquake. They also worry that such systems could divert spending from earthquake preparedness, which they say has the potential to do much greater good. "Warnings only help in some cases," says Robert Oshinsky, an urban planner at the University of Illinois, Urbana-Champaign. "Investing too much of one's

agent, with colleagues in Thailand and Australia will be subject to such oversight. Month fears that U.S. researchers might be held criminally responsible for violations by collaborators. When he raised this issue with Strickland at the ASTMH meeting, he says, it was apparent that "NIH had neither thought about this nor had any clear response."

NIAID officials say they are simply in step with the times; later they plan to adopt standards being developed by the World Health Organization. "We will do what we can to ensure that every possible avenue has been pursued that will allow our NIH-funded researchers to be able to conduct their research safely and securely," the officials say. Much of that work, it appears, may well have to be done inside U.S. borders.

—RICHARD STONE

money and hopes in a short-term warning system is a distraction from the hard and less sexy work, such as upgrading older structures, that is really needed to improve seismic safety."

Faster than a speeding S wave

Early warning systems are not forecasts. Instead, they detect actual quakes near their source and issue warnings to automated systems and humans up to several hundred kilometers away. They work because electronic signals transmitted through wires or air travel faster than seismic waves moving through the earth. Warning schemes also take advantage of the two types of seismic waves that are generated when a fault ruptures. The first—and faster moving—primary (P) waves



On alert. Newcast stations are being installed across Japan.

radiate directly outward from the epicenter. The secondary (S) waves, which cause the oscillating motions responsible for the most damage, lag by tens of seconds over a distance of a few hundred kilometers. "The P waves carry information; the S waves carry energy," explains Hiroo Kanamori, a seismologist at the California Institute of Technology (Caltech) in Pasadena. Unfortunately,



International Perspectives

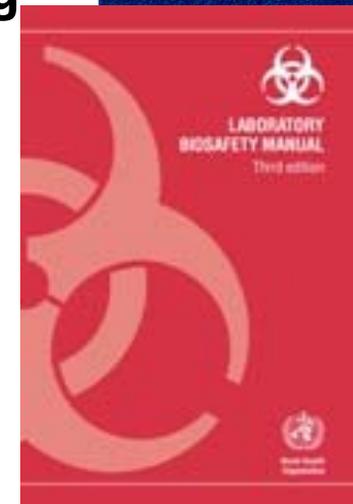
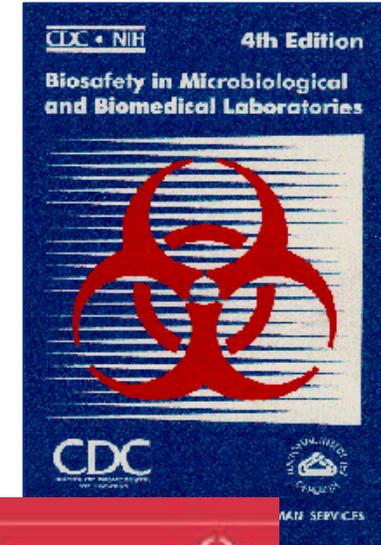
- **Bioterrorism not perceived as a serious threat in much of the world**
- **Apprehension that US biosecurity methods, or international regulatory regime, would hinder advances in basic biomedical research**
- **Acknowledgement that dangerous pathogens have intrinsic value and need to be protected globally**
- **Member States to the BWC have acknowledged the importance of national implementation of laboratory biosecurity**
- **Ultimately, success will depend on willing implementation by the international scientific community and internationally available resources**





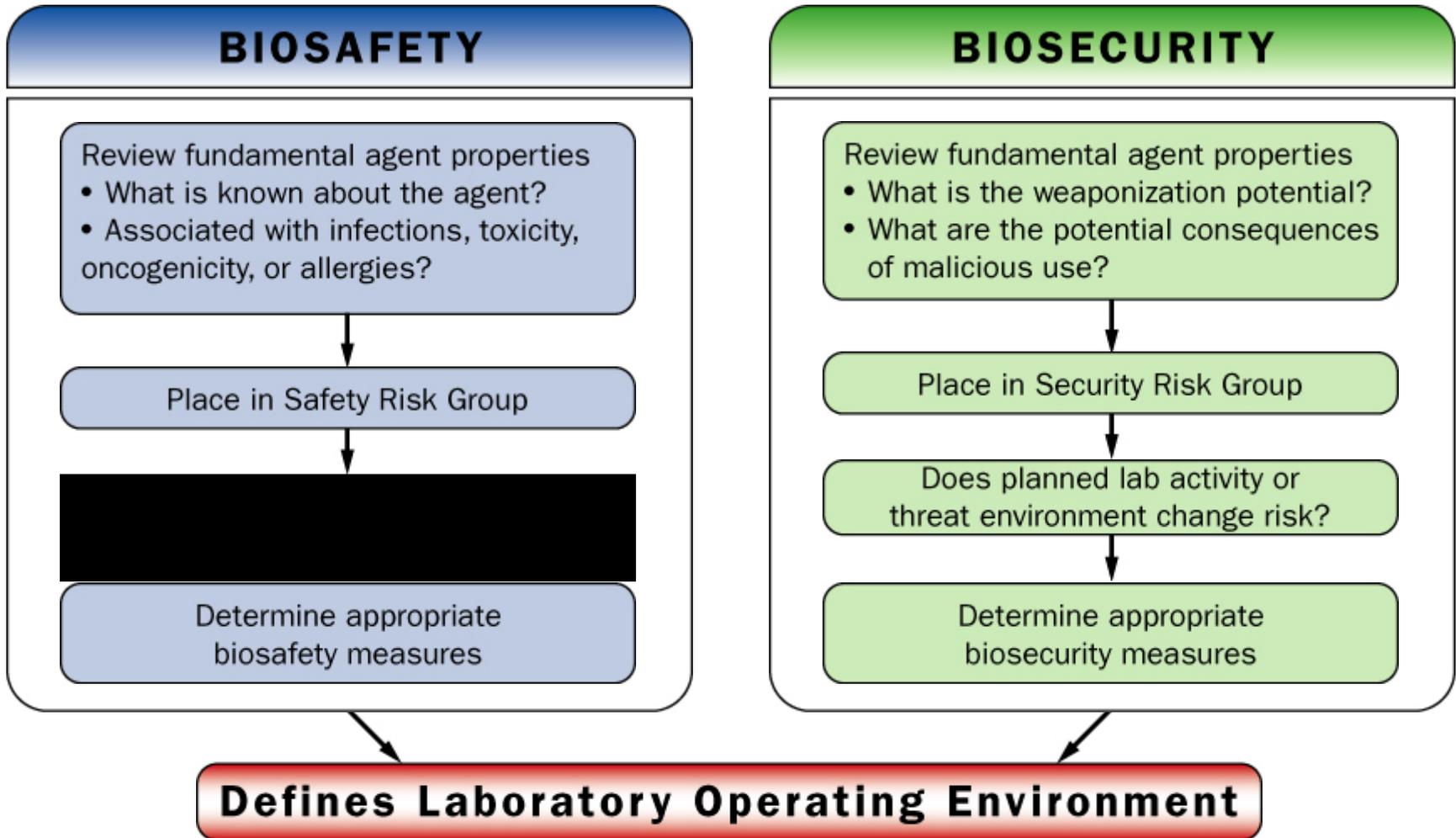
Anticipated Developments

- **Select Agent Final Rule still forthcoming**
- **Next edition of BMBL will include a chapter on biosecurity in addition to a revised Appendix F**
- **WHO/FAO/OIE developing joint international biosecurity guidelines**
- **OECD has expressed interest in establishing biosecurity guidelines**
- **Hopefully, these initiatives will**
 - **Avoid conflicting recommendations**
 - **Promote the concept of integrated biosafety and biosecurity**
 - **Introduce a tiered system of protection**





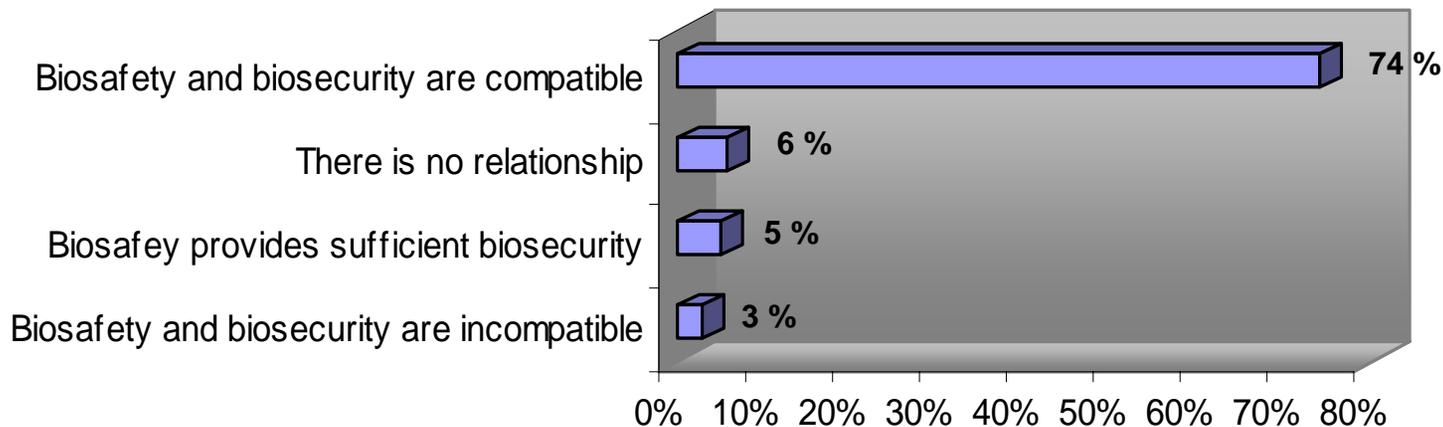
Biological Agent Risk Assessments





Sandia Biosafety/Biosecurity On-Line Survey

- **360 respondents so far**
 - **51% Select Agent facilities, 49% non-Select Agent facilities**
 - **43% universities, 18% industry, 16% clinical/diagnostic, 15% government**
 - **27% lab directors/managers, 22% biosafety officers, 16% PI's, 12% technicians, 8% RO's**



- **“A biosecurity program should be designed to incorporate both activities (biosafety and biosecurity) into a daily regime that allows for productive work as well as safety and security.”**



Summary

- **Biosecurity regulations, guidelines, and implementation methodologies are evolving**
- **The “internationalization” of laboratory biosecurity practices is an important development**
 - **Securing dangerous pathogens in one or a few countries is insufficient to mitigate the threat of bioterrorism or biological weapons proliferation**
- **However, the US Select Agent Rule is not universally applicable**
 - **Laboratory biosecurity guidelines and requirements need to reflect local and national concerns and priorities**