



Against the threat of bioterrorism, the government cracks down on lab security. But repercussions from the new laws could change the very culture of science.

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Rules, Regs, and Red Tape

The laboratory of Philippa Marrack and John W. Kappler is known among colleagues as a mecca of collaborative research, and its physical space reflects this open spirit: There are no locked doors—no doors at all, in fact—and the walls do not even reach the ceiling. People walk in and out of the lab at the National Jewish Medical and Research Center in Denver all day long. ¶ The two HHMI investigators, a husband-and-wife team that studies T cell biology, have long nurtured this collegial atmosphere because they believe there are incalculable rewards in working cooperatively. “If we stopped,” says Marrack, “it would destroy the whole ethos of the lab.” ¶ Recently, however, their research approach has come up against the realities of a world increasingly fearful of bioterrorism. Because Marrack and Kappler’s experiments often require the use of toxins made by the bacterium *Staphylococcus aureus*, they must adhere to new federal restrictions,

including sealing off their work space or an equivalent arrangement to ensure that their toxin supply is secure.

But although the researchers agree with the need for caution, they find the process as it applies to their own circumstances to be surreal because *S. aureus* is hardly a bioterrorist weapon of choice. It typically does not kill when eaten, says Kappler. “It just makes you wish you were dead.” In addition, it can be found virtually anywhere. “Every time you throw out a jar of bad mayonnaise, you are throwing out this toxin. Every time you eat a bad clam that keeps you up all night, you’ve ingested this toxin. It’s in the nose, on the skin, in your armpits, and in various other orifices. If you wanted it, you needn’t waste your time breaking into National Jewish.”

Two Stringent Laws

Marrack and Kappler are not alone in their frustration. Researchers across the country are struggling to comply with two laws aimed at preventing dozens of pathogens and toxins—so-called select agents, which include the agent that causes anthrax (*Bacillus anthracis*), botulinum neurotoxins, and the staphylococcal enterotoxins that Kappler and Marrack use—from falling into terrorist hands. The frustration arises when these laws, passed by Congress in the aftermath of September 11, 2001, are seemingly applied too broadly—whether there is a threat or not—and when adhering to them could seriously compromise researchers’ projects.

The first law, the USA Patriot Act, specifies who may work with select agents, and it can impose criminal or civil penalties for violations. The second law, the Public Health Security and Bioterrorism Preparedness and Response Act, updates existing rules that regulate the use of select agents, including the requirement that facilities register if they possess them. Previously, only facilities wishing to *transfer* select agents needed to register.

To be sure, the scientific community understands the need for the new rules. The devastating events of 9/11 and the still-unsolved case of the anthrax attacks that followed made Americans aware of their vulnerability. Thus, labs have been working hard to cooperate with the two federal agencies charged with enforcing these laws: the Centers for Disease Control and Prevention (CDC) and the Animal and Plant Health Inspection Service (APHIS), an agency of the U.S. Department of Agriculture.

But the well-intentioned laws appear to have had unintended consequences, adversely affecting U.S. biomedical scientists’ collegiality and competitiveness alike. As collaborative research ventures are being dampened, individual researchers’ productivity and professional growth, and thus their international standing, are seen to be diminished.

“I don’t think the rules are having a negative impact on the *spirit* of collegiality—the willingness of scientists to trust each other and share their ideas, data, and materials in pursuit of shared research goals,” says Julie E. Fischer, a senior associate at the Henry L. Stimson Center in Washington, D.C., who studies biological security measures and their impact on research. “But the rules have seriously altered the forms in which collaborative research can take place.”



Safe to Study

A traditional way for researchers to learn the latest techniques has been to visit a colleague’s lab for a fixed period of time. But because the new rules connect a researcher’s clearance to both an agent *and* a lab, someone deemed “safe” to study a select agent in one place cannot readily do so in another, even if the second lab and its researchers have been cleared.

“This has made it very tough for select-agent labs to host visiting researchers, even those who have been cleared to work in other select-agent labs,” Fischer says. “Same goes, by the way, for postdocs leaving one registered select-agent lab to study the *exact* same select agent in another registered lab. I have heard a great deal of discontent from researchers who support postdocs who cannot work on the project for which they were hired for 6 months or more.”

Moreover, international collaborations could become “difficult to the point of impossible for all practical purposes when select agents are involved,” Fischer says. “I don’t think that anyone understands what the long-term implications of that might be.”

The new laws have subjected not just researchers and labs but whole institutions to unprecedented scrutiny. Many organizations have had to renovate their facilities, follow complicated and often cumbersome steps to register and transport substances that appear on the select-agents list, and submit anyone working with these materials to extensive FBI background checks.

Besides being time-consuming, these procedures are also expensive. “The increased requirements for biosecurity may, if fully implemented, completely swallow the current level of grant funding,” says Markus Schaufele, director of the safety office of the University of Chicago Hospitals. “There could be very little left to do the actual research.”

Meanwhile, the range of the research has sometimes been constrained. While scientists have always been required to notify the government each time they transfer a dangerous organism, the laws have been tightened: Researchers must seek CDC’s permission before transporting these materials and they must scrupulously document their movements.

Although Marrack and Kappler agree with the need for caution, they find the process as it applies to their own circumstances to be surreal.

Philippa Marrack and John W. Kappler (above) worry about the ethos of their lab.

These requirements already have proved problematic for scientists working on unexpected pathogen outbreaks. Last year, for example, researchers at the Wisconsin State Laboratory of Hygiene found themselves stalled in their ability to quickly investigate an outbreak of monkeypox because the virus was not among those they listed when registering with the federal government. Clinical specimens legally could not be transferred to the lab from the places where they were isolated from patients. Instead, virus samples first had to be sent to the CDC, circumventing—and delaying—the state’s response.

“Such an incident leaves us wondering how a serious health crisis involving a select agent such as anthrax might evolve in the current regulatory environment,” wrote R. Timothy Mulcahy, associate vice chancellor for research policy at the University of Wisconsin–Madison, in a November 2003 editorial in *Science* magazine.

Another constraint is researchers’ need to undergo FBI screening before being allowed to work with agents on the select list. This process can take considerable time, as the agency is currently working its way through thousands of people seeking clearance, and it can wind up reducing the pool of participating scientists.

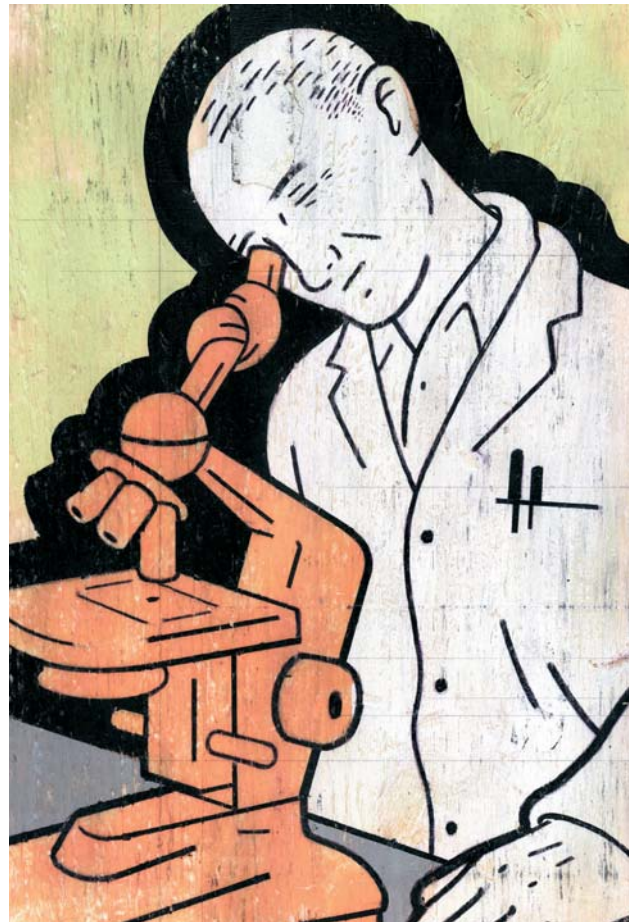
Foreign students trying to come to the United States to conduct research are having an especially tough time. “It takes our researchers longer to get into the country because of the backlog and the increased scrutiny, and obviously this slows up the research,” says Amy Wilkerson, associate vice president of research support at the Rockefeller University.

Is It Worth It?

To be registered and certified, labs must undergo inspection by either the CDC or APHIS, depending on the agents involved. Often, this is not an easy process for the researchers, who see much of it as nit-picking and intrusive. “If you change the floor plan or move a piece of equipment,” says David W. Drummond, director of the safety department at the University of Wisconsin–Madison, “you have to record this with the controlling agency.”

This can be especially maddening when the institution leaders believe they have already done their homework. Drummond insists that the university’s security experts scoured the facilities looking for vulnerable areas and putting new measures into place, including high-security locks and key controls where select agents are stored. Nevertheless, federal regulators continue to review Wisconsin’s registration application, submitted more than a year ago, in March 2003. In November 2004, the university received a list of questions with a 10-day response deadline. And until that registration is approved, he says, “there’s a cloud of uncertainty hanging over our heads. It’s difficult for researchers to do business—they have grants with deadlines, they need to show progress, and they need to hire personnel. Meanwhile, new staff can’t start work until they are cleared by the FBI as required by the USA Patriot Act. Our researchers estimate that current procedures nearly double the time needed to conduct their research. We believe we are complying with the rules and conducting research in a safe and secure manner, but we won’t know whether our procedures are adequate until we receive decisions on our registration. We hope and trust that the federal agencies will work together to streamline processes and reduce delays because so much of this research is critical to national security.” [In February 2005, Wisconsin received word that its registration had been finalized.]

For its part, the CDC, unaccustomed to its new enforcement role, acknowledges that it still is finding its way. “This is new ground for us,” says Von Roebuck, a CDC spokesman. The CDC has fully registered 313 facilities since November 12, 2004, according to Roebuck, but there are hundreds more to go. “We are trying to keep pace,” Roebuck says.



Exempt SARS?

Fearing a slowdown in what they described as the “astounding pace” of advances, an international group of 13 researchers met in San Francisco last spring at the Positive Strand RNA Virus symposium and drafted a letter urging the U.S. government not to add the coronavirus that causes SARS (severe acute respiratory syndrome) to the list of select agents. They were concerned that drug and vaccine development would be hurt if scientists in the United States were burdened with requirements that could stall international scientific collaboration.

“The huge success in the identification and characterization of coronavirus as the

etiologic agent of SARS required unprecedented global cooperation,” says Kathryn V. Holmes, a coronavirus expert at the University of Colorado Health Sciences Center. “If select-agent status is given to this virus, it will restrict the action of U.S. scientists with others and delay the free and easy collaboration that has characterized this landmark research so far. Vaccine and drug therapy are coming very quickly now—we think it would be a bad time to inhibit research.”

Officials at the U.S. federal agencies responsible for the select-agents list, including the CDC, have been discussing the possibility of adding the SARS coronavirus to the list; at this time, however, no final decision has been made, according to CDC spokesman Von Roebuck.

Not everybody in the scientific community, however, subscribes to the view that the rules are having a chilling impact on the conduct of scientific research.

“Concerns that the select agent rule would prevent laboratories and researchers from performing select-agents research have proved unfounded—utterly unfounded,” says Richard H. Ebright, an HHMI investigator at the Waksman Institute at Rutgers, the State University of New Jersey. “The numbers speak for themselves. The number of select-agents grants, laboratories, and researchers has increased by more than a factor of 10.”

“As of November 2004, more than 300 laboratories and more than 12,000 persons had been registered for access to select agents. These numbers are disturbingly high. Most citizens would be astonished—and alarmed—to learn that more than 12,000 persons had access to—and ability to release, distribute, or sell—fully virulent live bioweapons agents.”

For clearance, much depends on the results of a rigorous facility inspection and the kind of changes needed if some systems are deemed insecure. This process at Rockefeller, according to Wilkerson, went relatively smoothly. The CDC site-visit team was “very professional and collegial,” she says. “They were here for a day and a half, and things went pretty much as expected. We were told to expect a report in 4 to 6 weeks, and there were no surprises.”

Marrack and Kappler at National Jewish, however, had a very different experience. Told they could use no more than 5 milligrams of staph-produced toxins per investigator at any one time unless they rebuilt their labs to be highly secured, the two researchers decided instead to reduce the amount of toxin they store to below federal limits. To comply, they had to destroy 27 milligrams of toxin worth \$5,000. One side effect, Marrack says, is that the lab will have to time its experiments carefully to be sure it does not run out of toxins.

Ultimately, however, Kappler says, “we probably will look for another way to do these experiments. There are other proteins around that aren’t on the list that work similarly. But it means having to retool our experiments, and sometimes start from the beginning. That would be a big deal, but we

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Richard Ebright (below) doesn’t believe new regulations have had a chilling impact.

are seriously considering it, just to get out from under these regulations.”

Similarly, other scientists are wondering whether the bureaucratic hassle is worth it. “I’ve heard numerous stories of facilities simply getting rid of the select agent rather than go through the extensive registration and inspection process,” says Jay T. Skarda, manager of safety at National Jewish.

Karen VanDusen, director of environmental health and safety at the University of Washington in Seattle, has seen a similar reaction among researchers. “We sit down with researchers and ask, Are you aware of the

requirements you will have to meet in order to do this kind of research? We talk to them about security additions to their labs, hiring practices, background checks—and some have said, ‘I don’t think I’m going to bother.’”

Room for Improvement

Of course, the scientific community does not want to compromise national security, but what is particularly troubling to many is that their research is being compromised without necessarily improving national security. They argue that the regulations fail to distinguish among agents as to the degree of risk. Instead of allowing institutions to make performance-based decisions, scientists must live with a one-size-fits-all set of regulations.

“I’m not saying that rules aren’t needed,” notes W. Emmett Barkley, HHMI’s director of the office of laboratory safety. “I am saying there is room for developing different levels of control, depending on the risk.” Not all laboratory procedures merit the extraordinary security measures being imposed at this time. And in some cases, these measures are not only disruptive for the researchers, but could constitute, in effect, a Maginot Line for the country. “There is a great deal of fear that the source of materials [used in a future bioterrorism attack] will be obtained from laboratories,” says Barkley, “when in fact they are virtually anywhere you’d want to find them. We are in a situation where the fear and the security concerns are themselves controlling the debate on what is risky and what is not risky,” as opposed to a scientific assessment of risk.

Some researchers are concerned that the current intense and inflexible regulatory climate will lead to disturbing changes in the very nature of biological research and to its core values of conduct. “We are in the beginning of a massive cultural shift,” says VanDusen. “We have to tell researchers, ‘Don’t leave your lab doors open. It’s not OK to come and go.’ It just can’t be that way anymore.”

Barkley, too, sees a cultural shift. “The most successful labs have this wonderful desire to be open, to be collaborative, to share materials and stimulate new directions of research,” he says. “And now they are being constrained.”

Yet this system need not change, at least not by much. The Stimson Center’s Fischer, for one, hopes the federal government will engage with the research and safety communities in a frank dialogue about the real costs and benefits of the select-agent rules. “This is critical if we are to achieve something more than a false sense of security,” she says, “and avoiding hampering those who strive to better understand diseases, whether they occur naturally or deliberately.”

