COMMENTARY

IMPLEMENTING THE SELECT AGENT LEGISLATION: PERFECT RECORD OR WRONG METRIC?

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THE ARTICLE “Transfer of Select Agents and Toxins: 2003–2013” by Shelby et al that appears in this issue describes in great detail the type and exact number of transfers of select agents, the day of the week packages were shipped, and the calendar days in transit. It also characterizes the “entities” involved in the transfers. The activities described are in response to the select agent regulations (SAR) promulgated in 1997¹ and 2003.² The Centers for Disease Control’s Division of Select Agents and Toxins³ (DSAT) and the US Department of Agriculture Select Agent Services⁴ make up the Federal Select Agent Program (FSAP), which approves and oversees transfer of agents that “pose a severe threat to public health and safety,” thereby “protecting public health and safety.”* Let’s assume for the sake of this argument that the select agent regulations were brilliantly drafted, necessary, and sufficient. Shelby et al’s article and the resources current and proposed to operate the select agent program, viewed in the shadows of an apparently increasing number of shipment errors in select agent labs, suggest that it might be time to revisit the *implementation* of the program.

*The article discussed here represents only the transfers overseen by the Division of Select Agents and Toxins, not the USDA’s counterpart organization.

INITIAL REGULATION AFTER SECURITY INCIDENTS

Scientists in high-containment labs around the world have worked safely and productively with highly pathogenic agents for decades; laboratory *safety* guidelines were first codified in the CDC publication *Biosafety in Microbiological and Biomedical Laboratories* (BMBL) in 1984 and have been regularly updated.⁵ Animal bites, minor injuries, spills, and even needle sticks occur regularly, mostly as a result of human error, but serious or fatal harm to laboratory workers has been extremely rare in the US and even globally.

In 1996 Larry Wayne Harris demonstrated an apparent intent to do harm with a pathogen isolate.⁶ Then, in 2001, the “anthrax letters”⁷ were mailed to politicians and news media figures. Those 2 events highlighted the need for a new level of *security* awareness in our infectious disease labs, and the US government quickly reacted by issuing and then strengthening the select agent regulations. Measuring effectiveness of *safety* guidelines day-to-day is much easier than measuring effectiveness of *security* regulations, because safety incidents, while typically minor, occur much more frequently than do security incidents.

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A LEGACY OF LABORATORY SAFETY

The infectious disease research community has modified, adjusted, and made continual improvements to facilities, equipment, and procedures in response to *safety* incidents. Scientists have long understood safety risks and dealt with them; they have respected the pathogens they work with and understood that, while we must continually train and always be conscious of risk, accidents can happen in any of our labs.

In our most productive and safest laboratories, the leaders have supported their biological safety professionals and encouraged safe behavior and rational implementation of safety guidelines and security regulations. In turn, the most effective safety professionals in labs worldwide support and protect personnel working with hazardous materials, engaging them with the philosophy, “How can we work together to help you accomplish your research goals safely and efficiently?”⁸ Our best laboratory leaders also take personal responsibility for the safety and security of their programs, their people, and their microbes. Regulations and oversight are necessary but not sufficient, and a healthy organizational culture, needed in all labs, greatly increases both safety and security in the laboratory.⁹ To be effective, safety and security should be primarily the responsibility of laboratory leaders and staff, not the government.

SELECT AGENT REGULATION IMPLEMENTATION AND OUTCOMES

So, what constitutes success in implementing the select agent regulations? In football, success is a winning season. In business, it is developing a product and creating wealth. In an infectious disease research laboratory, it might be production of knowledge or candidate vaccines, drugs, or useful technical tools. While safety and security are necessary in any organization, and most certainly in today’s infectious disease laboratories, they are not products.¹⁰ They are not the reason labs and scientists exist.

The CDC’s website, in describing the Division of Select Agents and Toxins, states, “This program has greatly enhanced the nation’s oversight of the safety and security of select agents...” I would argue that, for a regulatory agency, enhancing oversight is not success; it’s their job ... their mission. But is that all there is? Unless we can demonstrate a measurable reduction in laboratory accidents or malevolent use that justifies the current intensive and costly oversight, we should at least be assured that we are “do[ing] no harm” to the enterprise being regulated. Because productivity is by definition the goal of any laboratory, minimally affecting or even enhancing productivity while enforcing the select agent regulations should be a central goal—a measure of success—for organizations charged with implementing the regulations.

MEASURING SUCCESS?

Success in implementation of the regulations can be understood only if we have data on, in this case, requests for transfer of agents approved or disapproved, the timeframe of these activities, and any positive or negative perturbations to the research enterprise. Such data would provide a better view of the efficiency of this aspect of select agent regulation implementation. The Federal Select Agent Program oversees more than just pathogen transfers. It inspects and influences laboratory facilities design and construction, equipment used, procedures, and even laboratory animal housing systems.

To evaluate its work, we need to understand how helpful and responsive the Federal Select Agent Program is to inquiries regarding the way forward when laboratories seek approvals to do their work. Inspections of any kind are disruptive to any activity. The Division of Select Agents and Toxins has performed more than 1,800 laboratory inspections in the past 10 years.¹¹ What was the impact, positive and negative, on research? Did it make the work and the nation safer or more secure?

I was personally responsible for a high-containment laboratory when the 1997 select agent regulations¹ were put in place. After a 3-month administrative halt in agent transfers between our lab and others, a small CDC team inspected our facilities and procedures and certified the institute to be part of the program. The law was implemented efficiently with minimal slowing of our work. What I hear from colleagues responsible for select agent laboratories today is quite a different story.

COMMENTS FROM THE FIELD

First, I’m told that simple approvals for select agent transfers—what most people believe to be the role of the Federal Select Agent Program—do happen quickly, usually within a week or so. That’s very reasonable.

However, select agent program inspections are costly and time-consuming to program managers, individual investigators, and institutions. And they are not the only inspections undertaken in select agent labs. Organizations routinely experience multiple separate inspections each year. Each inspection typically involves 3 to 15 or more government inspectors and requires the full-time involvement of several laboratory and support staff members over the course of a visit.

The Department of Army Inspector General (DAIG) and Army MEDCOM[†] are also involved in DoD laboratory inspections. I happened to visit one such laboratory in 2014 at the outset of a 2-week combined inspection by 31

[†]The US Army Medical Command (MEDCOM) provides [Bio]Surety Management Reviews (SMRs) of Department of Defense laboratories.

inspectors from the CDC, USDA, and the DAIG. (There have been attempts, some successful, to combine inspection teams, which is a good thing and conserves valuable time for all parties.)

In addition, each individual select agent user must dedicate time to prepare for the inspection and be available as the inspectors examine the inventory of their stocks. They must also be available for questions and participate in an exit briefing. One large facility reported attempting to reduce PI agent administrative load by naming fewer than 10 “select agent managers” to take responsibility for all long-term storage of select agents and serve as the interface with inspectors. Most laboratories report that, despite all the time devoted to the preparation for and execution of select agent regulations inspections, they often wait months for a written report of findings. Often, the report for the last inspection barely arrives before the next inspection occurs.

While the inventory requirements for “agent accountability” put in place as part of surety programs¹² after September 11 and the anthrax letter mailings of 2001 have been modified somewhat, they are still onerous. One lab reports employing 2 full-time staff simply to keep track of the vials. Furthermore, because of concerns about administrative loss of a vial, investigators routinely discard samples from animals infected with select agents before a thorough analysis is done solely to get the vials off the books.

Strict accountability of all vials containing select agents projects an illusion of security when in fact it only makes diversion of such materials slightly more difficult. In any active laboratory dealing with such agents, there are many sources for infectious materials, including tissue culture flasks used to grow virus, infected animal excrement, and discarded pipette tips, to name only a few. (Select agents are also, of course, available in nature.¹³) A knowledgeable insider with malicious intent likely would not steal an accountable vial; rather he or she might sample any of these intrinsically unaccountable sources. Given the multiple levels of access control and physical security for select agent labs, it is also unlikely that anyone other than an insider would ever gain access to these accountable materials. Agent accountability may be an example of a “feel good” exercise—at least for those sufficiently unacquainted with working with replicating agents in a laboratory. What is important to the nation is scientific progress, and while accountability is in principle a very good thing, regulators seem to want more and more control; there appears to be, as one responsible individual stated, “no end to mission creep.”

Regarding the threat from the outside, 2 laboratories that are required to employ armed guards report the cost is more than \$3 million per year, more than 10% of the operating budget for one of the labs and 20% to 26% of operating budget for the other.

The greatest negative impact on research progress described to me appears to be the arbitrary requirements placed on labs by inspectors—some of whom have relatively little relevant experience—without a proper risk assessment or a

means to appeal. These requirements are sometimes termed “best practices” by inspectors even when there is no industry standard. I heard a number of examples of costly facility modifications and procedures (for safety) that also resulted in months or years of delays—requirements that had no basis in historical precedent and for which a decades-long accepted and proven protocol was suddenly found unacceptable by Federal Select Agent Program inspectors.[#]

The only recourse in these cases seems to be to submit data validating a protocol to the inspection team and wait months for approval—or not. One laboratory official told me, “They have not told us to shut down, but they have not given us the full go-ahead either.” Some of the new requirements requested by Federal Select Agent Program inspectors may be driven by the inadvertent releases of infectious materials from the CDC in 2014, but those were most likely a consequence of human failure to comply with established protocols rather than failure of the procedures themselves.

Finally, there appears to be no appeal process for the labs when new, seemingly arbitrary requirements are placed on them. Typically, appeals can only be made to the Federal Select Agent Program inspector—the person interpreting the rules.

We know from the above examples and others¹⁴ that the program has slowed research at home. In addition, my international colleagues tell me it is now nearly impossible to exchange pathogens with their collaborators here, resulting also in a degree of isolation of US scientists from collaborating on international investigations of potentially important emerging infectious diseases.

OTHER REAL AND INTANGIBLE COSTS

It appears that the Division of Select Agents and Toxins employs more than 150 people.¹⁵ In FY2015, the select agent program received an estimated \$16.6 million, not including working capital fund expenses and other associated costs. For 2016, the program will ask for an additional \$10 million “to improve and increase regulation and oversight of select agents and toxins” and plans to increase the number of annual inspections and surprise visits for what are termed “high-risk facilities” by 25%.¹¹ Will expanding this program make us safer or more secure? Or will it further slow progress in domestic infectious disease

[#]In June 2012, Division of Select Agents and Toxins inspectors stated that nonhuman primates infected with Ebola virus held in a modern BSL-4 lab would now require individual primary containment. After many months and an NIH Office of Biotechnology Activities meeting of all North American BSL-4 laboratory directors, their safety officers, and veterinary staff, the Division still denied approval to use legacy caging and protocols. Only in the face of the West African Ebola epidemic did they grant approval—2 years after the initial demand.

research while nature continues to challenge our countermeasures? Will future potential experts making career choices move to other less regulated fields? Will the center of gravity in global infectious disease research continue to shift toward our international competition?

MEASURING BENEFITS OF THE PROGRAM

Those are some of the costs to the nation's enterprise. What are the benefits? Shelby et al's report summarizes data regarding 4,402 HHS and overlap (with USDA) transfers involving some 5,305 individual agents in just over 10 years. It documents a routine activity, but it says little about impact on safety or security and nothing about impact on research progress—positive or negative—in the entities being regulated. It is analogous to an annual report from a laboratory stating that the scientific team accomplished 30,000 diagnostic assays, sequenced 300 genomes, or evaluated 30 antiviral drug candidates, full stop. What was the quality of the work? What did it cost? Did the outcomes solve a public health or other problem? Is the work sustainable? What are the societal impacts?[‡]

The information regarding agent transfers provided in this report isn't very helpful in evaluating efficacy or efficiency of select agent regulations implementation. The article concludes with a discussion of 1 agent shipment package that was believed to have been lost, and was never found, but the FBI "concluded that the package was most likely damaged by the commercial carrier and discarded." That particular incident may have occurred with or without the select agent regulations' existence or implementation. The authors also state, "There were no reports of theft or release associated with biological select agents or toxins." Is this a perfect record or are we using the wrong metric?

How many safety or security incidents were avoided because of the program? We know that the select agent regulations did not stop the anthrax letters in 2001, the potential anthrax exposures or the mistaken shipment of virulent bird flu virus by the CDC in 2014, or the 2015 discovery of mistaken shipments of viable anthrax spores to several labs by the army. We know what we didn't stop with the select agent regulations, but the article says nothing about what we did stop.

The CDC does report that the Division of Select Agents and Toxins "restricted 264 persons from accessing select agents and toxins,"¹¹ apparently referring to individuals flagged by the FBI's Criminal Justice Information Program's Security Risk Assessment.¹⁶

[‡]Furthermore, the article doesn't mention the "mission creep" in agent transport security that has occurred in this zero-defects atmosphere. Shipping a few vials of virus via FedEx, which in the not too distant past cost under \$100, has for a few organizations using the new "Custom Critical FedEx" service, jumped to about \$5,000 per shipment.

What was implemented 15 to 20 years ago as a result of perceived *security* risks has become an extremely bureaucratic approach to oversight of laboratory *safety* by government. Assuring safety and security remotely from "inside the beltway" is impossible.** Perhaps it is time that we revisit the implementation of the select agent regulations and carefully consider their measureable and nonmeasureable impacts on our infectious diseases research programs, our public and agricultural health and safety, and our national security.

One very specific place to begin might be to carefully examine the real costs and benefits of attempting to account for individual vials of select agents. We might also consider establishing an appeal process and appointing a balanced, expert national advisory board to oversee the implementation of these important regulations. Finally, we must address the very fundamental problem of micromanaging laboratory directors remotely from inside the beltway. We must once again balance responsibility with appropriate authority and reward enlightened leadership and healthy professional cultures in our research labs.

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**Numerous government reports have concluded that *laboratory culture* is very important in assuring both safety and security, yet little has been done to reward enlightened leaders or laboratories in which personal and corporate responsibility is exemplary.^{9(pp38-41)}

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Editor's Note: On July 17, 2015, the CDC Deputy Director received word from the FedEx Express Corporate Safety Department that "under direction by FedEx Executive Management, Select Agents are no longer acceptable for transport by FedEx Express."