Overview of the New CDC Select Agent Rule: Title 42 C.F.R. Part 73

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Today I would like to give a very brief background on the 1996 legislation and the original Select Agent Rule of 1996. In addition, I will provide an overview of recent antiterrorism legislation that resulted in the publication of the new Select Agent Rule in December 2002. I will also review the new rule, compare some of the differences between the old and the new regulations, and provide an update on the status of the implementation of the new regulation and some of the future endeavors we are planning under the new regulation.

So, with that, travel back to 1995. In 1995, a number of events occurred that caused the federal government to review existing federal regulations restricting the acquisition of biological agents and toxins. It was noted that for certain human pathogens there were no licensing or registration requirements for entities that were transferring these agents within the United States. In addition, there was no requirement to report the transfer of these agents to the federal government, and no uniform safety standards were available for entities performing these transfers. As a result, Congress directed the Secretary of Health and Human Services (HHS) first to establish a list of biological agents and toxins that have the potential to pose a severe threat to public health and safety. Second, it required, through regulation, that HHS establish procedures for the transfer of those agents, including, among other things, ensuring that these entities have the appropriate training and skills to handle those agents safely, and that the laboratory facilities have the proper containment and destruction protocols available for those agents.

HHS delegated the Centers for Disease Control and Prevention (CDC) the responsibility for implementing the regulation. That regulation became known officially as Section 72.6 of Title 42 of the Code of Federal Regulations titled “Additional Requirements for Facilities Transferring or Receiving Select Agents.” This section was added to an existing CDC regulation that dealt with interstate shipment of etiologic agents and set minimum packaging and labeling requirements for those agents. The fundamental components of the regulation, 42 C.F.R. 72.6 were:

- A list of 38 agents included in the appendices of Part 72
- A registration requirement of facilities that intend to transfer these agents
- A requirement that each entity designate a responsible official who is required to certify that the entity meets the requirements to safely handle those agents
- The transfer requirements, specifically, the documentation of the movement of those agents on a federal government form known as CDC Form, EA-101
- Establishment of verification procedures, including the inspection of registered entities
- Onsite agent disposal requirements
- Specific research and clinical exemptions

For all practical purposes, section 72.6 (old Select Agent Rule) was superceded as of March 12, 2003 by the Interim Final Rule, 42 CFR Part 73, published on December 13, 2002 (the new Select Agent regulation). As of March 12, 2003, the Select Agent Program had 355 active registrations under the old Select Agent Rule; inspected approximately
30% of those registered entities, and received over 4,000 transfer documents.

Many changes occurred after the terrorism events of 9/11 and the bioterrorism events of October, 2001. Congress went back to the antiterrorism legislation, reviewed it, and passed new legislation. The first legislation passed was what is abbreviated as the USA PATRIOT ACT. Of relevance, is the section of the legislation that refers to a restricted person. As stated in the legislation, if an individual met the definition of a restricted person, that individual could not have access to a select agent or toxin. The Public Health Security and Bioterrorism Preparedness and Response Act of 2002 (the Act), which was signed by the President in June of 2002, authorized the regulation of the possession, use, and transfer of these agents and toxins by those who could lawfully possess them. Title 2 of the Act, specifically Subpart A, significantly changed and in fact replaced the regulatory authorities of Health and Human Services under Section 511 of the old 1996 Antiterrorism Act. Under Subpart B, the Act granted comparable regulatory authority to the Department of Agriculture (USDA) for biological agents and toxins that present a severe threat to plant/animal health or plant/animal products. It also required that the USDA and HHS coordinate activities in regard to those agents that would be regulated by both agencies. Those agents are referred to as “overlap” agents, which are zoonotic agents that have the potential to cause a severe threat to public health and safety as well as animal health and safety. The legislation actually establishes the authority to create three lists of agents: those solely regulated by HHS, those solely regulated by USDA, and those jointly regulated by both departments, referred to as “overlap agents.”

Briefly, the Act in Title 2 added the requirement that entities intending to transfer these agents would need to register with the CDC. The original 1996 legislation, which lacked this provision, dealt solely with the intent to transfer. Under the new Select Agent rule, possession was clearly added to the requirements for registration. In addition, the new rule also required the establishment of safety standards and security requirements for entities working with these agents. As part of the security requirements, the Attorney General must perform an electronic database check on those individuals identified by the entity as needing access to those agents listed in either HHS’ or USDA’s regulations. This security requirement has become known as a “Security Risk Assessment,” which is performed by the Federal Bu-
The security risk assessment is primarily for the purpose of identifying whether individuals meet one of the prohibitions under the USA PATRIOT ACT.

The Act specifically mandates what exemptions are authorized and vastly narrowed the exemptions allowed under the old legislation. The Act added a provision to protect sensitive, site-specific information received by the federal government and strengthened criminal penalties. In addition, there is a requirement for the entity to immediately notify either the USDA or HHS of a theft, loss, or release of any of these agents and a requirement on the federal government’s part to annually report any theft, loss, or release to Congress.

The Act required initial reporting of possession of a select agent or toxin. The Act established that within 30 days from signing, HHS had to provide instructions to the public on how to report possession of a select agent or toxin. Essentially, HHS had 30 days to disseminate to the public an Office of Management and Budget cleared form for data collection. Within 60 days after the dissemination of the form, the public was required to report possession of a select agent or toxin to HHS. Finally, 90 days after signage of the Act, HHS was required to have identified those in possession. To accomplish this task, extremely broad mailing lists were used. Unfortunately, large entities received multiple notification forms. In retrospect, if time would have permitted, the targeted broad mailing lists would have been narrowed to prevent the multiple notifications.

The Act mandated HHS, in coordination with USDA, to publish an Interim Final Rule within 180 days after signage of the Act and then seek public comment during the mandated 60-day period before the effective date of the regulation. One of the first steps in that coordination process was for HHS and USDA to immediately enter into a Memorandum of Understanding for dealing with the joint regulation of these “overlap” agents.

Following are some high points of the accomplishments in drafting an Interim Final Rule in 180 days.

An Interagency Workgroup was formed that consisted of technical experts from 21 federal agencies. The workgroup was established to provide recommendations and guidance such as reviewing and updating the list of agents, providing recommendations on security requirements, reviewing the list of toxins and exemption requirements for those toxins, developing a better protocol for exemptions, and updating the genetic element section from the old regulation. Shortly after the Act was signed in June 2002, professional groups were invited to address members of the Interagency Workgroup about any concerns they had about the upcoming Interim Final Rule. A key focus of the regulation was the list of agents. Though not a requirement of the Act, the recommendations provided by the Interagency Workgroup were published in a Federal Register Notice in August, 2002. Based upon 22 comments received during the comment period, the Interagency Workgroup reviewed and made final recommendations concerning the drafting of the Interim Final Rule.

By December 9, 2002, the Interim Final Rule was on display to the public. It was published in the Federal Register on Friday, December 13, 2002. Shortly after the publication, USDA and HHS/CDC held a joint public meeting in Washington, D.C. to explain the new requirements and to seek comments. The effective date was mandated as 60 days after the Interim Final Rule was published. The comment period expired on February 11, 2002. One hundred-eleven comments were received and have been placed on the CDC program web site.

A provision of the Act allowed for the establishment of time frames of implementation so that ongoing research and educational activities would not be impeded. There was also a recognition that certain requirements of the new Rule would need to be phased in, allowances not just for the public but for the federal government as well. For example, the new security requirements required developing and implementing a security plan. Likewise, allowance needed to be given for the “Security Risk Assessment” requirement being performed by the Attorney General. Full implementation was required under the Interim Final Rule on November 12, 2003.

The Interagency Workgroup provided the program with recommendations and described significant differences between the old and new regulations. Besides some deletions and few additions, the list did not significantly change compared to the old
Appendix A list. However, there were some clarifications, specifically dealing with the neurotoxins of botulinum and the shigatoxins. The list consists of 39 agents, 19 of which are “overlap” agents and regulated by both USDA and HHS.

Under the old regulation (42 C.F.R. 72.6), there was a research exemption for toxins based on the potency or LD-50 value of the toxin. Since there are problems associated with basing exemptions solely on the potency of the toxin, the Interagency Workgroup provided the following recommendation based on the amount of the toxin as well as its potency. The recommendation was to base the exemption with respect to public health concerns, not concerns of whether this could be misused to harm one or two individuals, but if the toxin could be used to harm a large number of individuals based on currently available information. The threshold amount was structured so that an individual responsible for the control of that toxin possessed less than the threshold amount, then it would be excluded from the requirements of the regulation. The recommended threshold amounts of toxin based upon the potency of the toxin are provided in Table 1.

The difficulties experienced with the old rule language for recombinant and genetic elements were factors associated with disease and trying to define the genetic elements that met the requirement. The Interagency Workgroup developed language which was adopted in the new regulation: Genetic Elements, Recombinant Nucleic Acids, and Recombinant Organisms. The intent was to identify genetic elements that were in a system or in a vector system that are either capable of expressing a live virus or potentially expressing a functional toxin. In other words, an attempt was made to try to recognize the risk and concern for those individuals working with the viable agent, and if those individuals were extracting the nucleic acid of that agent and sending it, for instance, to another institution for sequencing work, that nucleic acid, in and of itself, did not meet the statute’s requirement of posing a severe threat to public health and safety, unless that nucleic acid was placed back into some sort of expression system that would allow for replication of competent forms of any of the select agent viruses.

In reviewing the bacteria, the Interagency Workgroup tried to identify what factors would be associated with disease and, consistently, what the Workgroup identified were those nucleic acids that encoded for the listed toxins. The recommendation was that only the genetic elements of the bacteria that encode for a functional form of the toxin would be adopted into the regulation as it is either in an

<table>
<thead>
<tr>
<th>Toxin</th>
<th>Amount</th>
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<tbody>
<tr>
<td>Botulinum neurotoxins</td>
<td>0.5 mg</td>
</tr>
<tr>
<td>Staphylococcal enterotoxins</td>
<td>5 mg</td>
</tr>
<tr>
<td>Abrin</td>
<td>100 mg</td>
</tr>
<tr>
<td>Clostridium perfringens epsilon toxin</td>
<td>100 mg</td>
</tr>
<tr>
<td>Conotoxins</td>
<td>100 mg</td>
</tr>
<tr>
<td>Ricin</td>
<td>100 mg</td>
</tr>
<tr>
<td>Saxitoxin</td>
<td>100 mg</td>
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<tr>
<td>Shigatoxin</td>
<td>100 mg</td>
</tr>
<tr>
<td>Shiga-like ribosome inactivating proteins</td>
<td>100 mg</td>
</tr>
<tr>
<td>Tetrodotoxin</td>
<td>100 mg</td>
</tr>
<tr>
<td>Diacetoxyacridone</td>
<td>1,000 mg</td>
</tr>
<tr>
<td>T-2 toxin</td>
<td>1,000 mg</td>
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expression system or in a vector. As advised by the Interagency Workgroup, the transfer or possession of a nucleic acid of a toxin, in and of itself, does not meet the threshold of being a threat to public health and safety. However, if the whole genome of botulinum neurotoxin was placed into a plasmid creating a system that, with the addition of a promoter, could express the fully functional toxin, then it would be subject to our regulation. In addition, the genetically modified select agent section was retained.

The Office of Biotechnology Activity at the National Institutes of Health (NIH) had concerns over two experiments described in the NIH Recombinant Guidelines that entities receiving federal funds be prohibited from performing those experiments until they received NIH approval. However, if an entity was not receiving federal funds, it was not required to follow these guidelines. NIH proposed the adoption of that language from its Recombinant Guidelines into the new rule. The language was adopted in the new rule. If an entity intending to work with a select agent that meets one of those two restricted experiment provisions, under the old NIH Recombinant Guidelines, the entity is now required, under the Select Agent Rule, to receive federal government approval through the Select Agent Program before those experiments can be conducted.

The exclusions and exemptions provisions of the Interim Final Rule will now be reviewed. A listed select agent may be modified in a form that no longer meets the definition under the statute of posing a severe threat to public health and safety or the amount of toxins may not meet the threshold criteria to be a threat to public health and safety. Also, the new rule allows for the public to request that the government consider attenuated strains of select agents to be excluded from the requirements of the regulation. Some excluded attenuated strains were published in the December 13, 2002 Interim Final Rule. Additional requests for exclusion have been received and after the review of those requests if the attenuated strains of select agents were determined to not pose a severe threat to public health and safety, those attenuated strains were posted on both the CDC and USDA/APHIS web sites. The new rule also recognizes that organisms that have been treated so that they are no longer able to replicate, through gamma irradiation or other means, in other words rendered nonviable, are not subject to the Select Agent Rule unlike under the old rule.

The exemptions mandated in the Act are listed in Figure 2.

Under the new rule, the same fundamental principles were adopted as described under the old rule. It requires registration, in addition to transfers, for possession of the listed select agents. Again, the new rule adopted the provision of having the entity identify a single point of contact to represent that entity, which is referred to as the “Responsible Official.” The Act requires the owners, the Responsible Official, and the individuals who need access to these agents to undergo a “Security Risk Assessment” by

**Figure 2**

**OVERVIEW OF REGULATION**

42 C.F.R. Part 73

- Exemptions:
  - Clinical or Diagnostic Laboratories
  - Agents used only for diagnosis, verification, or proficiency testing (no reference or retention allowed)
  - Transferred or destroyed after identification
  - Notify federal and state authorities
  - Products approved under a Federal Act
  - Investigational products (must apply for exemption)
  - Public health or agricultural emergency (must apply for exemption)

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the Attorney General. This function has been delegated by the Attorney General to the FBI.

With respect to maintaining inventories for toxins, it should be feasible to maintain records of toxin inventory. However, for viable agents, there is a limited practicality to inventorying viable agents. Therefore, the new rule emphasizes for the viable agents that accountability records be maintained for those individuals who have access to the area where those agents are either used or stored. Also, the maintenance of the EA-101 transfer forms is required, although now with a prior approval requirement. Entities must establish emergency response plans. And again, the statute requires entities to report theft, loss, or release of an agent.

Several areas have arisen that need clarification. One of those areas is defining access. The Webster's Dictionary version of what “access” means is “the freedom or ability to obtain or make use of.” In other words, if you are able to get your hands on a select agent or toxin, you have access to that agent or toxin, and you are required to have a security risk assessment performed before you can have access. We provided, in the Interim Final Rule, two mechanisms to prevent access. The first is the obvious—the physical barrier. You can either lock the door or you can lock the container, the refrigerator/freezer, where the agent is stored. We allowed another mechanism of creating a physical barrier and that was by providing for the allowance that somebody who already has authorization from the entity and has received a security risk assessment approval, can act as an escort, provided he or she continually monitors that unauthorized person in that area where the select agent is located. The authorized individual must be present at all times and is the human, physical barrier preventing that unauthorized person (e.g., maintenance or cleaning personnel) from having access to the agent. Again, we deliberately tried to build in some flexibility for entities to have various approaches on how to restrict access to the select agent or toxin.

The penalties have been strengthened and are listed in Table 2.

I also mentioned that there are, per the statute, requirements for coordination with USDA. In regards to “overlap” agents, the statute gives the public the opportunity to submit their application to either agency. Therefore, the entity has the choice of submitting the application for an “overlap” agent to either USDA or HHS. Those two agencies are required to coordinate, behind the scenes, the review of that registration packet, and the processes involved with that registration, and require concurrence of the other agency regardless of where the application was sent.

In the Act, the Attorney General was delegated the responsibility for performing the “Security Risk Assessment” (electronic database checks of individuals and owners of entities that possess select agents or intend to use them and the individuals who would be authorized to use them). Within the Department of Justice, the Federal Bureau of Investigation, Criminal Justice Information Services Division (CJIS) was identified as having responsibility for implementing this provision and performing those electronic database checks, providing that information, depending on who the lead agency is, to either HHS or USDA, whichever is responsible for the final approval and sending that final approval to the entity.

As mentioned, timeframes for implementation were estimated and set forth in the Interim Final Rule. It was recognized that by the November 12, 2003 deadline, a significant number of individuals

<table>
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<tr>
<th>Civil Money</th>
<th>Criminal</th>
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<tr>
<td>Up to $250,000 for an individual for each violation</td>
<td>Imprisonment for up to 5 years, a fine, or both for:</td>
</tr>
<tr>
<td>Up to $500,000 for an organization for each violation</td>
<td>➢ Transfer of a select agent to an unregistered person</td>
</tr>
<tr>
<td></td>
<td>➢ Possession of a select agent by an unregistered person</td>
</tr>
<tr>
<td></td>
<td>➢ Knowingly making a false statement</td>
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would not have received security risk assessments fully processed by CJIS. The primary reason was that the information received by CJIS—either the fingerprint cards or the information packet, the FD 961 form—lacked the required information. Either the whole document was missing or certain information was missing on it. That hampered CJIS’s ability to fully process these Security Risk Assessments in a timely manner. As a result, APHIS, CDC, and CJIS worked very aggressively, prior to the November 12, 2003 deadline, to alert those entities of the need to provide CJIS with the complete information. On November 3, 2003, APHIS and CDC jointly published another Interim Final Rule, which provided that if the complete Security Risk Assessment information was received by CJIS as of November 12, 2003, and an entity or individual otherwise met all of the requirements of Part 73, then an entity was eligible for a provisional registration, or an individual who was required to have access to the agents, a provisional granting of access until the final security risk assessment is performed.

Some of the statistics as of November 12, 2003 are shown in Figure 3. As noted, the vast majority of applications received by both APHIS and CDC had “overlap” agents.

As of November 12, 2003, full or provisional registrations were issued to approximately 400 entities, of which approximately 81% were CDC-lead entities and 19% were USDA/APHIS-lead entities.

The CDC-lead entities are identified in Figure 4 by the entity types.

Under the old regulation, academic institutions were the predominate type of entity registered. The reason for the decrease is due to the toxin exclusion component, recognizing that extremely minute amounts of toxins did not constitute a public health threat. On another note, the nonfederal government labs drastically increased compared to the old regulation because of the statutory mandate that clinical diagnostic labs that retain a select agent cannot be treated any differently than any other entity that possesses a select agent. Therefore, those state and local public health labs that retain select agents are now required to register.

To wrap up, the November 12, 2003 deadline was met. As I mentioned, there was an Interim Final Rule that allowed for provisional registrations and provisional grants of access. As CJIS completes those security risk assessments, the provisionals are being updated. CDC received 111 comments to the Interim Final Rule. Those comments are being re-
Figure 4

Types of CDC Lead Entities Registered
(N = 323)

Private
9%
Commercial
11%
Gov (non-Fed.)
30%
Gov (Fed.)
18%
Academic
30%
Other
2%

Figure 5

FOR MORE INFORMATION

• CDC Select Agent Program
  ➢ Phone 404-498-2255
  ➢ Fax 404-498-2265
  ➢ E-mail lrsat@cdc.gov
  ➢ Web site http://www.cdc.gov/od/sap
• USDA/APHIS
  ➢ Phone 301-734-3277
  ➢ Fax 301-734-3652
• FBI
  ➢ Phone 304-625-4900
  ➢ Fax 304-625-5393
  ➢ Web site http://www.fbi.gov/hq/cjis/cjis.htm
viewed in anticipation of publishing the Final Rule in coordination with USDA/APHIS. The anticipated date for the publication of the Final Rule, which will be published both by APHIS and by CDC, is by the end of this year 2004. In addition, an electronic application is being developed through a secure web system so that an application could be sent electronically to either APHIS or CDC.

Lastly, outreach is being provided to the public to explain the requirements and the process and alerting the public to any changes (for instance, the electronic database submission, once that gets implemented). One of these initiatives is a half-day workshop provided by the Select Agent Program on Sunday, May 23, 2004, just before the ASM general meeting. It is a training session on the requirements of the Select Agent Rule.

Figure 5 is the contact information for the federal partners involved in the regulation of these biological agents and toxins.