Summary of 2012 changes to the HHS Select Agent Regulations 42 CFR Part 73

Karen Angel, Jacinta Smith, Robbin Weyant, and Denise Gangadharan
Centers for Disease Control and Prevention, Office of Public Health Preparedness and Response, Division of Select Agents and Toxins

Abstract

In October 2012, the Departments of Health & Human Services (HHS) and Agriculture (USDA) published final rules to amend the Select Agent Regulations (42 CFR Part 73, 7 CFR Part 331, 9 CFR Part 121). The following poster will address only the amendments to the HHS Select Agent regulations found in Part 73 of Title 42 of the Code of Federal Regulations (42 CFR Part 73). Those amendments include: (1) designation of those select agents and toxins that present the greatest risk of deliberate misuse with the most significant potential for mass casualties or devastating effects to the economy, critical infrastructure; or public confidence as "Tier 1" agents; (2) description of new security requirements for entities possessing Tier 1 agents and toxins, including the requirement to conduct pre-access assessments and on-going monitoring of personnel with access to these materials; and (3) clarification of regulatory language concerning security, training, biosafety, restricted experiments, and incident response. Guidance documents developed by the Federal Select Agent Program in support of these regulatory changes will also be presented.

Introduction

The Public Health Security and Bioterrorism Preparedness and Response Act of 2002 authorized HHS and USDA to regulate the possession, use, and transfer of biological agents and toxins that have the potential to pose a severe threat to public health and safety, animal or plant health, or animal or plant products. These agents are called select agents and toxins. HHS and USDA delegated the authority to promulgate regulations to implement the Act to the Centers for Disease Control and Prevention (CDC) Division of Select Agents and Toxins (DSAT) and the USDA-Animal and Plant Health Inspection Service's Agricultural Select Agent Program (APHIS). DSAT and APHIS, in partnership with the Federal Bureau of Investigation Criminal Justice Information Services (FBI/CJIS), comprise the Federal Select Agent Program (FSAP).

On July 2, 2010, President Barack Obama signed Executive Order 13546, "Optimizing the Security of Biological Select Agents and Toxins in the United States," that directed HHS and USDA to: (1) Designate a subset of the select agents and toxins list (Tier 1) that presents the greatest risk of deliberate misuse with the most significant potential for mass casualties or devastating effects to the economy, critical infrastructure; or public confidence; (2) Explore options for graded protection for these Tier 1 agents and toxins to permit tailored risk management practices based upon relevant contextual factors; and (3) Consider reducing the overall number of agents and toxins on the select agents and toxins list.

E.O. 13546 also established the Federal Experts Security Advisory Panel (FESAP) to advise the HHS and USDA on the designation of Tier 1 agents and toxins, reduction in the number of agents on the select agent lists, establishment of appropriate practices to ensure reliability of personnel with access to Tier 1 agents and toxins, and establishment of physical security and information security standards for Tier 1 select agents and toxins.

To fulfill this statutory mandate, the CDC DSAT initiated its biennial review process, which included consultation with CDC's Intragovernmental Select Agents and Toxins Technical Advisory Committee (ISATTAC) which is comprised of Federal government subject matter experts from the CDC, the National Institutes of Health, the Food and Drug Administration, APHIS, USDA/ Agricultural Research Service, USDA Center for Veterinary Biologics, the Department of Homeland Security, the Department of Defense, and the Biomedical Advanced Research and Development Authority within the Office of the Assistant Secretary for Preparedness and Response in HHS.

Background

The Public Health Security and Bioterrorism Preparedness and Response Act of 2002 requires the biennial review and republication of the select agents and toxins list. On July 21, 2010, HHS published an advanced notice of proposed rulemaking and request for comments in the Federal Register requesting public comment on: (1) the appropriateness of the current select agents and toxins list, (2) whether there are other agents or toxins that should be added to the list, (3) whether agents or toxins currently on the list should be deleted from the list, (4) whether the list should be tiered based on the relative bioterrorism risk of each agent or toxin, and (5) whether the security requirements for agents in the highest tier should be further stratified based on type of use or other factors. On October 3, 2011, a notice of proposed rulemaking (NPRM) that proposed specific changes to the regulations was published in the Federal Register. The purpose of the NPRM was to seek public comment on the proposed changes which included the reorganization of the select agent list into a tiered list, requirement that entities with Tier 1 agents describe procedures in their security plans for conducting a pre-access suitability assessment of persons who will have access to a Tier 1 select agent and toxin, and the establishment of appropriate practices for physical and cyber security for facilities that possess these agents.

Summary of Major Changes

1. Modification of the select agent and toxin list (Figure 1):
   a. The following viruses have been added to the HHS select agent list based on scientific data related to their significant public health risk: SARS-associated coronavirus (SARS-CoV), Lujo and Chapare viruses.
   b. The following agents have been removed, effective 60 days after the publication date of the final rule, from the select agent list: Cercopithecine Herpesvirus 1 (Herpes B virus), *Clostridium perfringens* epsilon toxin, *Coccidioides posadasii/Coccidioides immitis*, Eastern Equine Encephalitis virus (South American type only), Flexal virus, West African clade of Monkeypox viruses, *Rickettsia rickettsii*, the non-short, paralytic alpha conotoxins containing the following nucleic acid sequence $X_1CCX_2PACGX_3X_4X_5X_6CX_7$[1], Shigatoxins, Shiga-like ribosome inactivating proteins, Staphylococcal Enterotoxins (non-A, non-B, non-C, non-D, and non-E subtypes) and Tick-borne encephalitis complex viruses (Central European subtype).
   c. The following agent has been removed, effective 60 days after the publication of the final rule, from the Overlap select agent list: Venezuelan Equine Encephalitis Virus (subtypes ID and IE).
2. Tiering of the select agent and toxin list:
   a. Tier I agents:
      i. HHS select agents and toxins
         1. Ebola virus
         2. *Francisella tularensis*
         3. Marburg virus
         4. Variola major virus
         5. Variola minor virus
         6. *Yersina pestis*
         7. Botulinum neurotoxin
         8. Toxin-producing strains of *Clostridium botulinum*
      ii. Overlap select agents and toxins
         1. *Bacillus anthracis* (excluding Pasteur strain)
         2. *Burkholderia mallei*
         3. *Burkholderia pseudomallei*
3. Establishes physical security standards for entities possessing Tier 1 select agents and toxins, including the requirement to conduct pre-access suitability assessments and on-going reliability monitoring of personnel with access to Tier 1 agents and toxins;
4. Miscellaneous revisions to the regulations to clarify regulatory language concerning security, training, biosafety, restricted experiments, and incident response.

[1]

a) C = Cysteine residues (indicated in bold) are all present as disulfides, with the 1st and 3rd Cysteine, and the 2nd and 4th Cysteine forming specific disulfide bridges;
b) The consensus sequence includes known toxins α-MI and α-GI (shown above) as well as α-GIA, Ac1.1a, α-CnIA, α-CnIB
c) X1 = any amino acid(s) or Des-X;
d) X2 = Asparagine or Histidine;
e) P = Proline;
f) A = Alanine;
g) G = Glycine;
h) X3 = Arginine or Lysine;
i) X4 = Asparagine, Histidine, Lysine, Arginine, Tyrosine, Phenylalanine or Tryptophan;
j) X5 = Tyrosine, Phenylalanine, or Tryptophan;
k) X6 = Serine, Threonine, Glutamate, Aspartate, Glutamine, or Asparagine;
l) X7 = Any amino acid(s) or Des X;and
m) "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.

HHS AND USDA SELECT AGENTS AND TOXINS
7 CFR Part 331, 9 CFR Part 121, and 42 CFR Part 73

HHS SELECT AGENTS AND TOXINS

Abrin
Botulinum neurotoxins*
Botulinum neurotoxin producing species of *Clostridium**
Conotoxins. Short, paralytic alpha conotoxins containing the following amino acid sequence $X_1CCX_2PACGX_3X_4X_5X_6CX_7$
Coxiella burnetii
Crimean-Congo haemorrhagic fever virus
Diacetoxyscirpenol
Eastern Equine Encephalitis virus
Ebola virus*
*Francisella tularensis**
Lassa fever virus
Lujo virus
Marburg virus*
Monkeypox virus
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

USDA SELECT AGENTS AND TOXINS

African horse sickness virus
African swine fever virus
Avian influenza virus
Classical swine fever virus
Foot-and-mouth disease virus*
Goat pox virus
Lumpy skin disease virus
Mycoplasma capricolum
Mycoplasma mycoides
Newcastle disease virus[1]
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] 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.

Conclusions

The entities that will be affected by the final rules include research and diagnostic facilities; Federal, State and university laboratories; and private commercial and non-profit enterprises. The regulations require registering for the possession, use, and transfer of select agents or toxins. The changes to the select agents or toxins list were made to improve the FSAP's ability to help ensure that select agents and toxins are secured according to level of risk. The tiering of the select agents and toxins list will allow the application of more optimized security measures for those select agents or toxins, which may pose a higher risk to public health and safety should they be stolen or otherwise misused. The reduction of agents from the list will reduce the regulatory burden on entities. The establishment of a suitability assessment and physical security and information security standards is required only for the Tier 1 select agents and toxins and will reduce the regulatory burden on entities by focusing the highest level of security on those entities that possess the most dangerous agents. In many cases the affected entities already employ some or all of the required measures.

The overall benefit of the amended provisions will be a reduced likelihood of an intentional release of a select agent or toxin and the avoidance of costs associated with such a release. The goal of the amended regulations is to enhance the protection of human, animal, and plant health and safety.

For More Information

Guidance documents have been developed in the following areas to assist regulated entities to maintain compliance with the new regulations:

- Physical Security
- Suitability Assessment
- Occupational Health
- Responsible Official Duties
- Training
- Information Security
- Long Term storage

These documents, and other resources are available at the FSAP Website
http://www.selectagents.gov

U.S. Department of Health and Human Services
Centers for Disease Control and Prevention

CS235606

E-mail: cdcinfo@cdc.gov Web: www.cdc.gov