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42 CFR Part 73

Possession, Use, and Transfer of Select Agents and Toxins; Biennial Review; Final Rule

DEPARTMENT OF HEALTH AND HUMAN SERVICES

[Docket No. CDC-2011-0012]

42 CFR Part 73

RIN 0920-AA34

Possession, Use, and Transfer of Select Agents and Toxins; Biennial Review

AGENCY: Centers for Disease Control and Prevention (CDC), Department of Health and Human Services (HHS).

ACTION: Final rule.

SUMMARY: In accordance with the Public Health Security and Bioterrorism Preparedness and Response Act of 2002, the Centers for Disease Control and Prevention (CDC) located within the Department of Health and Human Services (HHS) has reviewed the list of biological agents and toxins that have the potential to pose a severe threat to public health and safety and is republishing that list. As a result of our review, we have added Chapare virus, Lujo virus, and SARS-associated coronavirus (SARS-CoV) to the list of HHS select agents and toxins. We have also removed from the list of HHS and overlap select agents and toxins, or excluded from compliance with part 73, the agents and toxins described in the Executive Summary. Further, in accordance with Executive Order 13546, "Optimizing the Security of Biological Select Agents and Toxins in the United States," HHS/CDC has designated 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; established new security requirements for entities possessing Tier 1 agents, including the requirement to conduct pre-access assessments and on-going monitoring of personnel with access to Tier 1 agents and toxins; and made revisions to the regulations to clarify regulatory language concerning security, training, biosafety, and incident response.

In a companion document published in this issue of the **Federal Register**, the United States Department of Agriculture (USDA) has made parallel regulatory changes.

DATES: *Effective Dates:* The amendments to §§ 73.1, 73.3 through 73.6, 73.9, 73.10, 73.13, 73.16, 73.17, and 73.20, of Title 42, Code of Federal Regulations are effective December 4, 2012. The remaining provisions to this final rule are effective April 3, 2013.

Applicability Dates: By December 4, 2012, all entities that possess SARS, Chapare, and Lujo viruses must provide notice to CDC regarding their possession of these viruses, and by April 3, 2013, all previously unregistered entities must meet all of the requirements of this part.

The Final Rule timelines are based on the timelines that worked effectively for the Federal Select Agent Program Interim Final Rules that were published in December 2002. If the regulated community has concerns about the established timeline, they can contact Federal Select Agent Program for technical assistance.

Comment Date: Written comments on the new information collection contained in this final rule should be received by October 15, 2012.

ADDRESSES: Please send written comments on the new information collection contained in this final rule to CDC Desk Officer, Office of Management and Budget, Washington, DC 20503 or by fax to (202) 395-5806.

FOR FURTHER INFORMATION CONTACT: Robbin Weyant, Director, Division of Select Agents and Toxins, Centers for Disease Control and Prevention, 1600 Clifton Road NE., Mailstop A-46, Atlanta, Georgia 30333. Telephone: (404) 718-2000.

SUPPLEMENTARY INFORMATION: The Preamble to this final rule is organized as follows:

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I. Executive Summary

We published an Advance Notice of Proposed Rulemaking (ANPRM) (75 FR 42363) on July 21, 2010 and a Notice of Proposed Rulemaking (NPRM) (76 FR 61206) on October 3, 2011. The NPRM solicited comments regarding (1) the appropriateness of the current HHS list of select agents and toxins; (2) whether there are other biological agents or toxins that should be added to the HHS list; (3) whether biological agents or toxins currently on the HHS list should be deleted from the list; (4) whether the HHS select agents and toxins list should be tiered based on the relative bioterrorism risk of each biological agent or toxin; and (5) whether the security requirements for select agents or toxins in the highest tier should be further stratified based on type of use or other factors. In addition, Executive Order 13546 "Optimizing the Security of Biological Select Agents and Toxins in the United States" directed the HHS Secretary 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.

We provided a 60-day comment period for written comments that ended December 2, 2011. We extended the comment period for an additional 30-day period that ended January 17, 2012.

The changes to the current regulations include:

1. Modification of the select agent and toxin list:

a. The following viruses are added to the HHS select agent list based on scientific data related to their significant public health risk: SARS-CoV, Lujo and Chapare viruses.

b. The following agents would no longer be considered HHS select agents or toxins, or would be excluded from compliance with part 73: 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 virus, *Rickettsia rickettsii*, the non-short, paralytic alpha conotoxins containing the following amino acid sequence

X₁CCX₂PACGX₃X₄X₅X₆CX₇,¹ 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 would no longer be considered an overlap select agent: 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) *Yersinia pestis*
- (7) Botulinum neurotoxin
- (8) Botulinum neurotoxin producing species of *Clostridium*

ii. Overlap select agents and toxins

- (1) *Bacillus anthracis*
- (2) *Burkholderia mallei*
- (3) *Burkholderia pseudomallei*

3. Establishing physical security standards for entities possessing Tier I select agents and toxins, including the requirement to conduct pre-access assessments and on-going 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, and incident response.

Costs of the Rule: 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 the possession, use, and transfer of select agents or toxins. In addition, the entity is required to ensure that the facility where the agent or toxin is housed has adequate biosafety and containment measures, that the physical security of the premises is adequate, that all individuals with access to select agents or toxins have the appropriate education, training, and/or experience to handle such agents or toxins, and that complete records concerning activities related to the select agents or toxins are maintained.

The final rules will further reduce or minimize the risk of misuse of select agents and toxins that have the potential to pose a severe threat to human, animal or plant health, or to animal or plant products. The USDA/Animal and Plant Health Inspection Service (APHIS) and HHS/CDC recognize that several of the required measures of the regulations may impose certain operational costs upon affected entities, particularly entities that have the newly designated Tier 1 select agents and toxins. In many cases, however, the affected entities already employ some or all of the required measures. Compliance costs actually incurred will therefore vary from one entity to the next.

While information on the specific changes that would need to occur at individual sites and the associated costs was not readily available during proposed rulemaking, some general observations regarding the potential costs were presented. These general cost observations can be found in table 2 in the Regulatory Impact Analysis located at: www.regulations.gov and at <http://www.selectagents.gov/>.

Benefits of the Rule: The objectives of the final rules are to create a means of ensuring enhanced oversight in the transfer, storage, and use of select agents and toxins; define the security procedures and suitability assessments for pre-access suitability and continual monitoring of individuals with access to Tier 1 select agents and toxins; and require that entities in possession of such agents and toxins develop and implement effective means of biosafety, information security, and physical security. The overall benefit of the amended provisions will be a reduced likelihood of the accidental or 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.

II. Changes to 42 CFR Part 73

The table below describes the changes to the current regulation.

Section No.	Current	Change
73.0	Applicability and related requirements	No change.
73.1	Definitions	Definitions added: Conotoxins; Information security; Occupational exposure; Recombinant nucleic acids; Security barrier; and Synthetic nucleic acids.
73.2	Purpose and scope	No change.
73.3	HHS select agents and toxins	Designates Tier 1 select agents and toxins; adds select agents and toxins; clarifies language; deletes from the HHS list.
73.4	Overlap select agents and toxins	Designates Tier 1 select agents and toxins; adds select agents and toxins; clarifies language; deletes from the overlap list.
73.5	Exemptions for HHS select agents and toxins.	Amends the immediate notification list to Tier 1 agents; clarifies language.
73.6	Exemptions for overlap select agents and toxins.	Amends the immediate notification list to Tier 1 agents; clarifies language.
73.7	Registration and related security risk assessments.	No change.
73.8	Denial, revocation, or suspension of registration.	No change.
73.9	Responsible Official	Adds new paragraph (a)(5); clarifies language.
73.10	Restricting access to select agents and toxins; security risk assessments.	Adds new paragraph (e); adds clarifying language.
73.11	Security	Revises regulatory text—paragraph (b), (c)(2),(g). Adds new paragraphs (c)(8), (c)(9), (c)(10), (e), (f).
73.12	Biosafety	Revises paragraphs (a) and (c)(1); replaces “url” in paragraph (c)(3); adds new paragraph (d).

¹ 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; The consensus sequence includes known toxins α-MI and α-GI (shown above) as well as α-GIA, Ac1.1a, α-CnlA, α-CnlB; X1 = any amino

acid(s) or Des-X; X2 = Asparagine or Histidine; P = Proline; A = Alanine; G = Glycine; X3 = Arginine or Lysine; X4 = Asparagine, Histidine, Lysine, Arginine, Tyrosine, Phenylalanine or Tryptophan; X5 = Tyrosine, Phenylalanine, or Tryptophan; X6 = Serine, Threonine, Glutamate, Aspartate,

Glutamine, or Asparagine; X7 = Any amino acid(s) or Des X; and “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.

Section No.	Current	Change
73.13	Restricted experiments	Clarifies language.
73.14	Incident response	Revises paragraphs (a), (b); adds new paragraphs (c) and (e).
73.15	Training	Revises paragraph (a); redesignates and revises paragraphs (b), (c); adds new paragraph (b).
73.16	Transfers	Redesignates paragraphs; adds new paragraphs (f), (h), (l).
73.17	Records	Revises paragraph (a)(1); adds new paragraph (a)(2).
73.18	Inspections	No changes.
73.19	Notification of theft, loss, or release	No changes.
73.20	Administrative review	Revises paragraphs.
73.21	Civil money penalties	No changes.

A. Modifications to the List of HHS and Overlap Select Agents and Toxins

The changes to the list of HHS select agents and toxins are based on comments received in response to the NPRM, recommendations from the Federal Experts Security Advisory Panel (FESAP) and HHS/CDC’s Intragovernmental Select Agents and Toxins Technical Advisory Committee (ISATTAC), and our review of current scientific literature.

Executive Order 13546 established the FESAP to advise the HHS Secretary on the designation of Tier 1 agents and toxins, the reduction in the number of agents on the select agent list, the establishment of appropriate practices to ensure reliability of personnel with access to Tier 1 agents, and the establishment of the appropriate practices for physical security and cyber security for facilities that possess Tier 1 agents.

The ISATTAC was established by the CDC Director and is comprised of Federal government employees from the CDC, the National Institutes of Health (NIH), the Food and Drug Administration (FDA), the Biomedical Advanced Research and Development Authority (BARDA) within the HHS Office of the Assistant Secretary for Preparedness and Response (HHS/ASPR), the USDA/APHIS, USDA/Agricultural Research Service (ARS), USDA/CVB (Center for Veterinary Biologics), the Department of Homeland Security (DHS), and the Department of Defense (DOD). The purpose of the ISATTAC is to assist CDC’s Division of Select Agents and Toxins in performing its regulatory functions under the select agent regulations, including conducting a review of the select agents and toxins list.

We received 113 comments that addressed the composition of the select agents and toxins list.

As discussed below, the final rule removes or excludes 13 select agents and toxins, added 3 select agents, and designated 11 select agents and toxins as “Tier 1” agents.

HHS Select Agents and Toxins

Addition of Chapare and Lujo Viruses

On August 19, 2009, we proposed adding the haemorrhagic fever virus Chapare, to the list of select agents (74 FR 41829). Chapare virus is a recently described New World arenavirus that is associated with fatal hemorrhagic fever syndrome and is most closely related to Sabia virus, an HHS select agent (Ref 1).

On October 3, 2011, we proposed adding the haemorrhagic fever virus Lujo to the list of select agents (76 FR 61206). According to available reports, Lujo virus (1) caused a fatal outbreak of hemorrhagic fever, (2) has a case fatality rate of 80 percent, (3) has been phylogenetically identified as an arenavirus, and (4) is related to those members of the Old World arenaviridae family (Junin, Machupo, Sabia, Guanarito, and Lassa) listed as HHS select agents that cause hemorrhagic fever and pose a significant risk to public health and safety (Ref 2).

Some commenters argued that there does not appear to be valid evidence that these viruses could be effectively utilized as terrorism agents. Another commenter recommended that all hemorrhagic arenaviruses be included in the select agent list.

We made no changes to the HHS list of select agents and toxins based on these comments. Although the literature on these newly described viruses is small and recent, both viruses have thus far produced high morbidity and mortality rates. Both Lujo and Chapare virus share other characteristics with regulated hemorrhagic fever viruses (Junin, Machupo, Sabia, Guanarito, and Lassa). As a taxonomic group, the hemorrhagic arenaviruses exhibit distinct differences in morbidity, mortality, transmissibility, and degree of pathogenicity. Therefore our consideration of whether to add a particular arenavirus to the list is made on a taxon-by-taxon basis. As more information becomes known about the public health risks of these two new hemorrhagic fever viruses, their status as select agents can be reassessed.

Individuals and entities that currently possess Chapare or Lujo virus, if they are not already registered entities, will have to either transfer the organism or genomic material to a registered entity, destroy their stocks and report the destruction to HHS/CDC, or if they choose to retain their stocks, register with HHS/CDC and comply with all applicable regulations as provided in this final rule. We also recognize that those entities that choose to become registered will need time to come into full compliance with the requirements of the regulations. This final rule will become effective on December 4, 2012. On and after that date, any individual or entity possessing, using, or transferring any listed select agent or toxin must be in compliance with the provisions of each part. However, to minimize the disruption of critical research or educational projects involving Chapare or Lujo virus that are underway as of the effective date of these regulations, we are providing that any individual or entity possessing Chapare or Lujo virus as of the effective date (current possessors) will be afforded additional time to reach full compliance with the regulations in each part. Accordingly, by December 4, 2012, all entities that possess Chapare and/or Lujo virus must provide notice to HHS/CDC regarding their possession of Chapare and/or Lujo virus, and by April 3, 2013, all previously unregistered entities must meet all of the requirements of this part.

Addition of SARS-Associated Coronavirus (SARS-CoV)

SARS-CoV is associated with one of the most significant pandemics of the 21st century. According to the World Health Organization, the 2002–2003 SARS pandemic involved 29 countries, produced over 8000 cases of disease, and resulted in 774 deaths (Ref 3). Since the end of the pandemic the majority of reported SARS-CoV infections have occurred in laboratorians, or individuals who had close contact with infected laboratorians (Ref 4–6). At least 13 (6 primary cases and 7 contacts)

individuals have contracted laboratory-associated SARS-CoV infections (Ref 7).

On July 13, 2009, we proposed the addition of SARS-CoV to the list of select agents and toxins (74 FR 33401). We received ten comments from representatives of universities, public health laboratories, commercial, and government facilities, all arguing that SARS-CoV should not be added to the select agent list. Commenters believed that further deliberation of the biosafety and biosecurity issues involved with this agent should be considered due to the implications for research and public health activities. The commenters further reasoned that adding SARS-CoV as a select agent would decrease public safety and security by preventing expert researchers from pursuing important work due to what they described as the additional costs and onerous burdens inherent with the select agent registration and compliance process.

During the public comment period for this rulemaking we received three comments from representatives from universities and a public health laboratory that recommended the addition of SARS-CoV to the list of select agents and toxins because (1) it exhibited high transmissibility and high lethality; (2) caused epidemics on four continents with significant mortality; (3) had a major economic impact; and (4) had a major psychological impact. Commenters further argued that the virus has demonstrated its ability to cause a contagious disease, has caused several laboratory infections (including one incident that led to cases in non-laboratory contacts) and is a virus which no longer circulates in nature.

We agree with the commenters who supported the addition of SARS-CoV to the list of select agents and toxins because of the significant impact of SARS-CoV on the public health system, the high degree of pathogenicity, and the lack of vaccines or proven therapeutics currently available to prevent or treat SARS-CoV infections. Additionally, we note that the virus no longer appears to be naturally circulating in humans, raising the concern that the general population does not possess a significant level of immunity.

The genome of SARS-CoV will be regulated as an HHS select agent. As a member of the *Coronaviridae* family, SARS-CoV is an enveloped virus with a positive-sense RNA genome. Positive-sense RNA viruses that utilize host polymerases contain nucleic acids, in and of themselves, that can produce infectious forms of the virus. The select agent regulations apply to nucleic acids that can produce infectious forms of any

of the select agent viruses (See section 3(c) of 42 CFR part 73, 9 CFR part 121, and 7 CFR part 331).

Based on information received from the HHS/CDC's Etiologic Agent Import Permit Program and the HHS/CDC's Office of Infectious Diseases, there are 119 entities that currently possess SARS-CoV. Of those 119 entities, 77 entities are registered with the Federal Select Agent Program; 42 entities are not registered. Of the 42 non-registered entities, only 38 may possess SARS-CoV or SARS-CoV genomic material (RNA). The 38 non-registered entities that may possess SARS-CoV or SARS-CoV genomic material (RNA) include 10 academic, 22 commercial, 5 State government, and 1 Federal government institutions.

Entities and individuals that currently possess SARS-CoV or SARS-CoV genomic material (RNA) will have to either (1) transfer the organism or genomic material to a registered entity; (2) destroy their stocks and report the destruction to CDC; or (3) register with HHS/CDC or USDA/APHIS to possess SARS-CoV and comply with all applicable regulations as provided in this final rule. We also recognize that those entities that choose to become registered with the Federal Select Agent Program will need time to come into full compliance with the requirements of the regulations. Since this final rule will become effective on December 4, 2012 and any individual or entity possessing, using, or transferring any listed agent or toxin must be in compliance with the provisions of each part on or after that date, we are providing that any individual or entity possessing SARS-CoV as of the effective date (current possessors) will be afforded additional time to reach full compliance with the regulations in each part. Accordingly, by December 4, 2012, all entities that possess SARS-CoV must provide notice to HHS/CDC regarding their possession of SARS-CoV, and by April 3, 2013, all previously unregistered entities must meet all of the requirements of this part. We are extending the effective date for these currently non-registered entities to minimize the disruption of critical research or educational projects involving SARS-CoV that are underway as of the effective date of these regulations.

Removal of Cercopithecine Herpesvirus 1 (Herpes B Virus)

We are removing Cercopithecine herpesvirus 1 (Herpes B virus) from the HHS list of select agents and toxins. We proposed the removal of Cercopithecine herpesvirus 1 (Herpes B virus) from the HHS list of select agents and toxins

because the virus is not easily transmitted to humans, the person-to-person transmission risk is small, the numbers of recorded human infections are low, and multiple licensed antiviral treatments for Herpes B infections are available. The only comments that we received on this proposal were supportive for the removal.

Removal of *Clostridium Perfringens* Epsilon Toxin

The proposed rule retained *C. perfringens* epsilon toxin on the list of select agents and toxins. The final rule removes it. Commenters questioned why *C. perfringens* epsilon toxin was listed as a select agent since its production is licensed by USDA under the Virus-Serum-Toxin Act. In addition, commenters argued that from a veterinary laboratory perspective, *C. perfringens* epsilon toxin is commonly detected in the gastrointestinal tract during routine post-mortem diagnostic testing and the quantity of toxin recovered from a positive diagnostic sample would be far below the 100 mg exclusion amount provided for in the select agent regulations. Commenters also supplied scientific data in support of removal of *C. perfringens* epsilon toxin from the select agent and toxin list (Ref 8).

Although many of the concerns raised by the commenters are addressed by the exemption and exclusion provisions in the regulations (42 CFR 73.3 and 73.5), we agree with commenters and have determined that *C. perfringens* epsilon toxin should be removed from the list of HHS select agents and toxins. *C. perfringens* epsilon toxin was originally included on the select agent list because of its relatively low (LD)₅₀ (lethal dose fifty: the amount of the toxin required to kill 50 percent of the test population) in rodents and moderate toxicity when in aerosol form. The LD₅₀ results for *C. perfringens* epsilon toxin are based on a mouse *in vivo* injection model, which does not completely mimic a natural infection, and therefore may not accurately represent the human LD₅₀. Additional significant factors in our determination to remove *C. perfringens* epsilon toxin include the absence of known human cases of disease, a lack of human or non-human primate toxicity data, and insufficient new data to indicate that *C. perfringens* epsilon toxin is a significant threat to public health and safety.

Reduction of Conotoxins on the HHS List of Select Agents and Toxins

The term "conotoxin" is used broadly to comprise a very large number of polypeptides isolated from the venom of

fish-hunting marine snails of the *Conus* genus of gastropod mollusks. Many of these molecules are neurologically active in mammals. Although we did not propose the removal for conotoxins, we did receive multiple comments that conotoxins should be removed from the list of select agents and toxins for the following reasons:

- Commenters noted that most components isolated from cone snail venom are harmless to humans; in fact, one of them (MVIIA = Ziconotide = Prialt™) is an FDA-approved commercial drug for the treatment of chronic pain. Several other conopeptides have reached clinical trials at various levels (CVID, Conantokin-G, Contulakin-G, Xe2174 and ACV1 = α conotoxin Vc1.1), and they all show extremely low levels of toxicity to humans.

- Commenters pointed to the fact that the term “conotoxin” can be applied to several hundred thousand compounds found in *Conus* venoms that are not toxic at all to humans is evidence that this designation needs to be revised. Furthermore, the designation of “conotoxins” as select toxins imposes an enormous and unnecessary burden for the development of cone snail-based therapeutics.

Other comments included the following:

- Conotoxins have never been weaponized.
- Conotoxins must be delivered parenterally.
- Conotoxins are difficult to manufacture.
- Conotoxins are not self-replicating.

We agree, in part, with the commenters. Based upon available experimental evidence, most known conotoxins (*i.e.*, “conopeptides”) do not possess sufficient acute toxicity to pose a significant public health threat, and many are employed as useful research tools or potential human therapeutics. However, currently available data demonstrate that the sub-class of conotoxins generally called “short, paralytic alpha conotoxins,”

exemplified by α -conotoxin GI and α -conotoxin MI do possess sufficient acute toxicity by multiple routes of exposure, biophysical stability, ease of synthesis, and availability. Therefore, we have modified the type of conotoxins that are regulated to focus on those that pose a threat to public health and safety. The conotoxins that remain on the HHS list will be limited to the short, paralytic alpha conotoxins containing the following amino acid sequence $X_1CCX_2PACGX_3X_4X_5X_6CX_7$, whereas:

- (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) X_1 = any amino acid(s) or Des-X;
- (d) X_2 = Asparagine or Histidine;
- (e) P = Proline;
- (f) A = Alanine;
- (g) G = Glycine;
- (h) X_3 = Arginine or Lysine;
- (i) X_4 = Asparagine, Histidine, Lysine, Arginine, Tyrosine, Phenylalanine or Tryptophan;
- (j) X_5 = Tyrosine, Phenylalanine, or Tryptophan;
- (k) X_6 = Serine, Threonine, Glutamate, Aspartate, Glutamine, or Asparagine;
- (l) X_7 = 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.

The short, paralytic alpha conotoxins containing the following amino acid sequence $X_1CCX_2PACGX_3X_4X_5X_6CX_7$ will be considered a select toxin if the total amount (all forms) under the control of a principal investigator, treating physician or veterinarian, or commercial manufacturer or distributor exceeds 100 mg at any time (Ref 9–13). As such, we have added the definition of regulated conotoxins.

Removal of *Coccidioides Posadasii*/*Coccidioides Immitis*

We are removing *C. posadasii*/*C. immitis* from the HHS list of select agents and toxins. We proposed the removal of *C. posadasii*/*C. immitis* based on the availability of licensed treatments for *Coccidioides* infection and a lowering of our assessment of the impact of *Coccidioides* infection on human health, as indicated by the high proportion of subclinical cases observed in endemic areas (Ref 14). The only comments that we received on this issue were supportive of the removal of *C. posadasii*/*C. immitis* from the HHS list of select agents and toxins.

Removal of Flexal Virus

We are removing Flexal virus from the HHS list of select agents and toxins. We proposed the removal of Flexal virus based on the lack of severity of disease and the lack of significant outbreaks of disease associated with this virus in humans. The only comments that we received on this issue were supportive of the removal of Flexal virus from the HHS list of select agents and toxins.

Removal of the West African Clade of Monkeypox Virus

We are excluding the West African clade of Monkeypox from regulation

under this part, while retaining the Congo Basin clade of Monkeypox. We proposed the retention of Monkeypox on the list of select agents and toxins, but invited comments on removing the West African clade of Monkeypox virus from the list. Monkeypox is closely related to smallpox virus and produces a clinical syndrome similar to that seen with smallpox. Mortality rates associated with Monkeypox infections have been reported to be as high as 17 percent (Ref 15–16). Monkeypox can be separated into two genetically distinct variants called the West African and Congo Basin clades. Clinical and laboratory studies indicate that the Congo Basin clade is significantly more pathogenic to humans and animals than the West African clade (Ref 17–18). The 37 confirmed cases of human Monkeypox associated with the 2003 importation of a West African strain from Ghana into the United States were associated with no case-fatalities and no observed chain of human-to-human transmission. Clinically severe human disease associated with West African strains is rare and this virus clade has not been associated with human mortality (Ref 19). Based on this information, we are excluding the West African clade from regulation under this part, while retaining the Congo Basin clade.

One commenter disagreed with the proposed retention of Monkeypox virus, regardless of clade, as a select agent. We agreed in part with the commenter. As indicated above, we recognize that significant differences in pathogenicity exist between the West African and Congo Basin clades and have determined that viruses of only the Congo Basin clade merit regulation as HHS select agents. We also note that there are published diagnostic tests that differentiate Congo Basin from West African clades (Ref 19).

While the listing found in section 3 (HHS select agents and toxins) will continue to read “Monkeypox”, a new subparagraph (d)(5) in that same section, excludes from regulation any West African clade of the Monkeypox virus provided that an individual or entity can verify that the Monkeypox virus is the West African clade.

Removal of South American Genotypes of Eastern Equine Encephalitis Virus (EEEV)

We proposed the removal of South America EEEV genotypes from the list of HHS select agents and toxins and the final rule is consistent with the proposed rule.

One commenter believed that all strains of EEEV should be removed from

the select agent list for the following reasons:

- The commenter noted that EEEV is endemic in Florida, but does not cause human epidemics even with high prevalence in the ecosystem and evidence of natural transmission activity to sentinels.
- The commenter noted that person-to-person transmission does not occur; transmission is only through mosquito bite. An average of only 5 human cases are identified annually in the United States.
- The commenter noted that there is a vaccine available for horses that can prevent disease even if there is ongoing natural virus transmission.
- The commenter noted that states with high endemicity of EEEV often have a state public health laboratory proactive comprehensive arbovirus surveillance program to define risk of human infection. Serum-neutralization assays are an essential part of such a program and require live virus which is needed for test performance. This work is performed at BSL3 level and additional federal regulatory requirements do not add to the safety of handling or storing the virus.
- The commenter noted that genotype analysis to determine if an EEEV strain is a North American or South American genotype is not practical in a state public health laboratory, where the goal is surveillance, not research.
- The commenter noted that this agent is not stable in the environment outside of its natural host (mosquitoes, birds).

We made no changes to the list of HHS select agents and toxins based on this comment. North American EEEV (NA EEEV), genotype strains, which are the strains responsible for human and equine disease, are all genetically very similar to each other (less than 3 percent divergence at the nucleotide level) and can be easily distinguished from South American EEEV (SA EEEV) genotype strains by sequencing. NA EEEV genotype strains differ from SA EEEV by greater than 20 percent at the nucleotide level and approximately 10 percent at the amino acid level. We are aware that EEEV is endemic in Florida, that person-to-person transmission does not occur, that an equine vaccine is available, and that EEEV isn't stable outside of its natural host. Among the factors that we considered in retaining the NA EEEV genotype were that this genotype exhibits high morbidity, high mortality, and has the potential to be weaponized. We also appreciate that public health laboratories focus on surveillance and utilize assays that do not specifically determine which

subtype of EEEV is present. However, we believe that the risks posed by the NA EEEV outweigh the practical issues associated with subtype determination. Because the NA EEEV genotype strains are distinctly different from SA EEEV in their genetics, epidemiology, and pathogenicity, we believe that the two genotypes can be distinguished from each other in the laboratory.

While the listing found in section 3 (HHS select agents and toxins) will continue to read "Eastern Equine Encephalitis virus," a new subparagraph (d) (5) in that same section excludes from regulation, any South American genotypes of Eastern Equine Encephalitis virus provided that an individual or entity can verify that the Eastern Equine Encephalitis virus is one of the South American genotypes.

Rickettsia prowazekii and *Rickettsia rickettsii*

The proposed rule retained *R. rickettsii* and *R. prowazekii* on the HHS list of select agents and toxins. The final rule removes *R. rickettsii* and retains *R. prowazekii*.

Commenters argued that *R. rickettsii* and *R. prowazekii* should be removed from the select agent list based on:

- The same rationale used by HHS/CDC to propose removal of Herpes B virus from the HHS select agent list;
- *R. rickettsii* and *R. prowazekii* are readily available in nature, and can be isolated from natural sources such as ticks and flying squirrel lice;
- *R. rickettsii* and *R. prowazekii* are not contagious;
- Human infections due to these agents are capable of being treated with doxycycline, other tetracyclines, and chloramphenicol;
- The bacteria are fastidious obligate intracellular pathogens, thus propagation requires growth in cultured host cells; and
- The inclusion of these rickettsiae on the HHS select agent list will produce no significant improvements in safety for the American public.

After careful consideration of these comments, we agree with the commenters that *R. rickettsii* should be removed from the HHS list of select agents and toxins. Significant factors in our reconsideration include the poor environmental stability of this species, the lack of person-to-person transmission especially in the absence of an appropriate vector, the availability of effective antibiotic treatments, and the difficulty in growing and purifying substantial quantities of these agents *in vitro*. However, we have determined that *R. prowazekii* should be retained as a select agent. This species was

investigated as a potential weapon by multiple national offensive programs prior to the Biological Weapons Convention, and has many characteristics of a bioweapon. The infectious dose for *R. prowazekii* is unknown but has been estimated to be as little as 10 organisms (Ref 20). There are currently no licensed vaccines against *R. prowazekii* available for human use in the United States. Until additional studies can be completed to better understand the potential risk of an intentional release of this organism to the public, we have determined to retain *R. prowazekii* on the HHS Select Agent List.

Removal of Shigatoxins and Shiga-Like Ribosome Inactivating Proteins

We proposed the retention of Shigatoxins and Shiga-like ribosome inactivating proteins on the HHS list of select agents and toxins. One commenter asked us to reconsider the retention of Shigatoxins and Shiga-like ribosome inactivating proteins as a select toxin based on the following criteria:

- Introduction of Shigatoxins by the aerosol route has not been reported;
- Shigatoxins are extremely difficult to synthesize in quantities that are toxic to humans;
- Expression of toxin in bacteria is self-limiting due to inhibitory effects on bacterial cells of over-expressed toxin; and
- There are limitations to purification and concentration of Shigatoxins that make them impractical and ill-suited to methods of dispersal that would require large quantities of toxin for delivery by food, water, or air.

We have considered all of the points raised by the commenter and, after additional consultations with subject matter experts, agree that compelling data exist to support the removal of Shigatoxin and Shiga-like ribosome inactivating proteins from the HHS list of select agents and toxins. Therefore, we have decided to remove Shigatoxin and Shiga-like ribosome inactivating proteins from the HHS list of select agents and toxins. Additional significant factors considered in our determination include the difficulty in producing or administering large quantities of toxin via the aerosol route, their poor environmental stability, the lack of significant toxicity seen with oral exposure (which is the route by which an individual becomes intoxicated by Shigatoxin), and the observation that the worst effects seen with intoxication are associated with other pathogenic factors from the Shigatoxin-producing strains of *E. coli*, which are not regulated.

Reduction of *Staphylococcal* Enterotoxins on the HHS List of Select Agents and Toxins

We proposed the reduction of *Staphylococcal* Enterotoxins on the HHS list of select agents and toxins to only include *Staphylococcal* Enterotoxins A, B, C, D, and E. Commenters were concerned that the “incredible simplicity” of obtaining *Staphylococcal* species from environmental sources and screening them for the presence of enterotoxins “utterly neuters” the intent of the select agent regulations to provide security against the misuse of such agents. A commenter requested “CDC to consider alternative regulatory strategies to balance the need of legitimate scientific access to such agents so that it is not harder to use them than for a terrorist.”

We made no changes to the HHS list of select agents and toxins based on this comment. Current data based on emesis in non-human primates demonstrates that *Staphylococcal* Enterotoxins A, B, C, D, and E pose a significant threat to public health and safety. In addition, we note that these enterotoxins exhibit significant environmental stability, which contributes to their public health risk. It should be noted that this revision represents a significant reduction of the types of *Staphylococcal* enterotoxins regulated as HHS select toxins.

Reorganization of Tick-Borne Encephalitis Complex Viruses (TBEV)

We proposed the removal of TBEV Central European subtype from the HHS list of select agents and toxins because the TBEV Central European Tick-borne subtype has been shown to be less virulent in humans than the Far Eastern subtype (Ref 21). We also proposed to reorganize the listing of the TBEV to reflect the current nomenclature given by the International Committee on Taxonomy of Viruses. For TBEV proper, there are now just three recognized subtypes: Central European, Far Eastern, and Siberian. The Russian Spring and Summer Encephalitis designation is no longer recognized (Ref 22). Two other viruses on the HHS list of select agents and toxins, Kyasanur Forest Disease virus and Omsk Hemorrhagic Fever virus, are no longer classified as TBEV. In recognition of these taxonomic changes, we proposed to include these viruses on the HHS list of select agents and toxins as follows:

Tick-borne encephalitis virus
Far Eastern subtype
Siberian subtype
Kyasanur Forest disease virus
Omsk Hemorrhagic fever virus.

All comments that we received on this issue were supportive of the removal of TBEV Central European subtype from the HHS list of select agents and toxins and the reorganization of the listing of the TBEV to reflect the current nomenclature.

Retention of *Coxiella burnetii*

We proposed the retention of *C. burnetii* on the HHS list of select agents and toxins. Commenters argued that this agent should be removed because:

- This organism is ubiquitous in the United States, and can be detected in greater than 90 percent of bulk milk tank samples. Despite this, significant human consequences to infection with this agent are rare.
- The organism is readily susceptible to available antibiotics.

While perhaps easily transmitted to humans, the disease caused by this organism is generally mild and self-limiting in humans and does not have a huge economic impact in animals. It therefore does not have the potential to be an effective terrorist weapon. We made no changes to the HHS list of select agents and toxins based on these comments. We recognize that there is a low level of mortality associated with this agent; that it is present in some bulk unpasteurized milk supplies; and that antibiotics are available to treat this disease. However, treatment of chronic Q fever caused by *C. burnetii* requires antibiotic regimens that can last for periods up to several years. This long-term treatment is associated with significant adverse effects and relapse is common upon withdrawal of the treatment (Ref 23). The determination to retain *C. burnetii* on the HHS list of select agents and toxins is based on multiple factors, including its environmental stability, ease of transmission to humans, extremely low infectious dose, high morbidity, its ability to incapacitate large numbers of people, and its prior history of weaponization. Historical records indicate that extensive development occurred in the use of this agent as an incapacitating weapon.

Retention of Diacetoxyscirpenol, Saxitoxin, T-2, and Tetrodotoxin Toxins

We proposed the retention of Diacetoxyscirpenol, Saxitoxin, T-2 toxin, and Tetrodotoxin on the HHS list of select agents and toxins. One commenter recommended the removal of these toxins along with Shiga-like ribosome inactivating proteins, Shigatoxin, Conotoxins, and *C. perfringens* epsilon toxin. This commenter stated that “continuing to

include these toxins on the select agent list has unintended consequences such as the U.S. Department of Transportation (USDOT) policies regarding shipment of infectious substances that extends the list to agents, such as *E. coli* that produce these toxins, which results in limiting shipments to public health laboratories.”

Although Shigatoxin producing strains of *Escherichia coli* are not subject to the select agent regulations, the removal of Shigatoxin and Shiga-like ribosome inactivating proteins should positively address the commenter’s concern regarding the USDOT policies. We do not agree with the commenter that Saxitoxin, T-2 toxin, Tetrodotoxin, and Diacetoxyscirpenol should be removed from the list. Significant factors considered in our determination to retain these toxins are their acute human toxicity, the lack of medical countermeasures or specific antidotes, and the stability of the toxins in a variety of different matrices including foodstuffs.

With respect to the comment expressing concerns about the regulation of *E. coli* strains that produce these toxins, it should be noted that nucleic acids that encode for the functional form(s) of select toxins, if the nucleic acids can be expressed *in vivo* or *in vitro* or are in a vector or recombinant host genome and can be expressed *in vivo* or *in vitro*, are subject to the regulations (See § 73.3(c)(2)). We consider it important to regulate *E. coli* strains that have been modified to produce these materials since they are capable of producing significant quantities of select toxins. It should also be noted that *E. coli* strains that do not contain nucleic acids that encode for the functional form(s) of select toxins are not subject to these regulations.

Retention of *Yersinia pestis*

We proposed to retain *Y. pestis* on the HHS select agents and toxins list based on our scientific conclusion regarding the bacterium’s high mortality rate, ease of dissemination and production, and person-to-person transmission of *Y. pestis* infections. We received no comments regarding this proposal.

Overlap Select Agents and Toxins

Reorganization of Venezuelan Equine Encephalitis Virus (VEE)

We proposed the removal of VEE subtypes ID and IE from the list of overlap select agents and toxins, with subtypes IAB and IC being retained on the list. Commenters recommended

removing the entire VEE group from the overlap select agent list because they believe that current subtyping assays for the identification of VEE are not sensitive enough to distinguish between these subtypes. One commenter stated that the subtype IC group can arise via a single mutation in the ID group and considering VEE's high mutation rates, an IC subtype can emerge from a laboratory using subtype ID strains. Commenters also noted that there are two vaccines available for humans. In addition, commenters argued that the mortality rate associated with VEE infections via the aerosol route may be very low.

We made no changes to the overlap list of select agents and toxins based on these comments. Straightforward diagnostic molecular techniques, such as sequencing with subtype/variety specific polymerase chain reaction (PCR) primer sets or serological testing with specific monoclonal antibodies, can distinguish between enzootic and epizootic VEE. We also note that based on available data, the emergence of epidemic subtype 1C from subtype 1D is a rare event. In addition, while an equine vaccine is available for VEE, human vaccines are limited in supply and availability.

While the listing found in section 4 (Overlap select agents and toxins) will read "Venezuelan equine encephalitis virus," a new subparagraph (d)(3) in that same section excludes from regulation, any ID and IE serotypes of Venezuelan equine encephalitis virus provided that an individual or entity can verify that the Venezuelan equine encephalitis virus is either the ID or IE serotype.

Retention of *Bacillus anthracis* (Pasteur Strain)

We proposed to designate *B. anthracis* as a Tier 1 select agent. A number of commenters objected to such a blanket designation, arguing instead that the *B. anthracis* Pasteur strain should be exempted from consideration either as a Tier 1 select agent or as a select agent in general.

Commenters argued that because Laboratory Response Network (LRN) laboratories maintain live cultures of non-pathogenic *B. anthracis* Pasteur strain for use in quality control testing, designation of *B. anthracis* as a Tier 1 select agent would have the potential to impact the willingness or ability of LRN laboratories to maintain inventories of *B. anthracis* Pasteur strain due to the perceived regulatory and financial burdens associated with the possession of Tier 1 select agents and toxins. The commenters went on to state that this

situation could potentially impact national health and safety given that the potential use of *B. anthracis* spores as a bioweapon remains a viable threat. They also argued that the increased regulatory burdens, particularly on front-line diagnostic laboratories, could lead to an overall decrease in the number of laboratories that would otherwise serve to ensure the LRN has sufficient capacity to detect and respond to a deliberate release of *B. anthracis*.

Commenters stated that the *B. anthracis* Pasteur strain is analogous to the *B. anthracis* Sterne strain, which has already been excluded pursuant to section 4(e) of the select agent regulations because it was determined not to pose a severe threat to public health and safety, animal health, or animal products. The commenters argued that *B. anthracis* Pasteur strain should not be considered as a select agent given that the only way to create an agent that poses a severe threat would be to combine the Pasteur strain with a non-regulated strain. The commenters pointed out that other agents that pose little harm individually, but could be modified genetically to become harmful, are not included on the select agent list because of this potential threat.

Another commenter claimed that the designation of *B. anthracis* Pasteur strain as a select agent would not serve to prevent an authorized person from intentionally or accidentally facilitating the combination of plasmids from Sterne and Pasteur types of strains to create a wild type phenotype. The commenter stated that combining these two strains can be accomplished no matter what sort of physical security may be employed to prevent access, theft, loss, or release of the agent. The commenter concluded that more effective preventive measures can be achieved through training and educating microbiologists on how to avoid accidentally combining these two strains and by penalizing any individuals who intentionally try to combine them.

We only agree in part with the commenters that it does not meet the Tier 1 designation, but do not agree to removing it from the select agent list altogether.

While we agree that the Pasteur strain does not meet the criteria for inclusion as a Tier 1 select agent, we believe that retaining the Pasteur strain as a select agent will allow for continued oversight of laboratories in which the accidental (or intentional) combination of this strain with the Sterne strain could occur to produce the wild type phenotype *B. anthracis de novo*. Failure to retain the

Pasteur strain as a select agent could result in an environment in which the probability of creating virulent wild type *B. anthracis* strains by the combination of non-regulated strains would be enhanced. Therefore, we have chosen not to exclude the Pasteur strain from the overlap list of select agents in this rulemaking. We will continue to evaluate exclusion requests as additional information becomes available in this area.

Retention of *Brucella abortus*, *Brucella melitensis*, and *Brucella suis*

We proposed to retain *B. abortus*, *B. melitensis*, and *B. suis* on the overlap list of select agents and toxins based on the bacteria's ease of production, high infectivity via the aerosol route, low infectious dose, and lack of brucellosis vaccines currently available for humans in the United States. We received no comments based on this proposal and will be retaining *B. abortus*, *B. melitensis*, and *B. suis* on the overlap list of select agents and toxins.

Retention of *Burkholderia mallei*

We proposed to retain *B. mallei* on the overlap list of select agents and toxins based on our determination that the bacteria can be easily produced in large quantity and transmitted via the aerosol route. In addition, the mortality rate for untreated cases of glanders is high, and given the rarity of this disease in the United States, experience in the diagnosis and treatment is limited. We received no comments based on this proposal and will be retaining *B. mallei* on the overlap list of select agents and toxins.

Retention of *Burkholderia pseudomallei*

We proposed the designation of *B. pseudomallei* as a Tier 1 select agent. Commenters stated that *B. pseudomallei* should not be a select agent based on the following criteria:

- The criteria by which *Coccidioides* were proposed by HHS/CDC to be removed from the list;
- *B. pseudomallei* is non-communicable from person-to-person;
- *B. pseudomallei* lacks a history of use or development as a successful biologic weapon (as compared with *B. mallei*, a highly pathogenic organism with which *B. pseudomallei* is inappropriately linked in the list);
- *B. pseudomallei* has a low incidence of symptomatic disease following natural infection; and
- The outcome of 99.9 percent of infections with *B. pseudomallei* is asymptomatic infection. Life-threatening illness occurs only in a few

hosts with particular risk factors, particularly renal failure and diabetes.

We disagree with the commenters that *B. pseudomallei* should be removed from the overlap list of select agents and toxins. Significant factors in our determination include the fact that *B. pseudomallei* is as virulent in animal models as *B. mallei*, *B. pseudomallei* is not endemic in the United States, *B. pseudomallei* has a low infectious dose, *B. pseudomallei* possesses robust environmental stability, and timely diagnosis may be complicated because of the rareness of disease in the United States. In addressing the comment referring to the criteria used to remove *Coccidioides*, we note the availability of licensed treatments for *Coccidioides* infection and a lowering of our assessment of the impact of *Coccidioides* infection on human health as indicated by the high proportion of subclinical cases observed in endemic areas. We do not believe that these factors apply to *B. pseudomallei*. In addition, we note that *B. pseudomallei* is not extensively endemic in the United States as are *Coccidioides* species. Therefore, we are retaining *B. pseudomallei* on the overlap list of select agents and toxins.

B. Tiering of Select Agents and Toxins

On July 2, 2010, President Obama signed Executive Order 13546 “Optimizing the Security of Biological Select Agents and Toxins in the United States” that directed the HHS Secretary to 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. In the development of the Tier 1 subset, care was used to balance risks identified in Executive Order 13546 with the Congressional mandate found in the Public Health Security and Bioterrorism Preparedness and Response Act of 2002 (42 U.S.C. 262a) to ensure the availability of select agents and toxins for research, education, and other legitimate purposes. Executive Order 13546 also established the FESAP to advise the HHS Secretary on the designation of Tier 1 agents and toxins, reduction in the number of agents on the select agent list, establishment of suitability standards for those having access to Tier 1 select agents and toxins, and the establishment of physical security and information security standards for Tier 1 select agents and toxins. Tiering of the select agents and toxins list will allow for the application of optimized security measures for those select agents or

toxins which pose a higher risk to public health and safety. A two-part risk analysis was conducted by the FESAP on each select agent and toxin on the list. First, experts in the biology of these agents and toxins evaluated their “potential for mass casualties or devastating effects to the economy, critical infrastructure, or public confidence.” This included assessments of morbidity and mortality, communicability, infectious dose, availability of countermeasures, and estimated economic impact of a potential attack. Second, each agent and toxin was assessed by experts from the DOD, DHS, and Department of Justice (DOJ) for its “risk of deliberate misuse,” including its history of weaponization and/or known interest by state or non-state adversaries. In addition, the Federal Select Agent Program also used information obtained from DHS Material Threat Determinations in making final decisions regarding their recommendations as to which select agent or toxin should be designated as Tier 1. These evaluations in combination with (1) input from public comments received in response to the NPRM, and (2) relevant findings in recent government and non-government reports, informed the deliberations on which agents should be designated as Tier 1, as well as those that should be removed from the select agent and toxin list. Agents that scored highly on both the public health and biothreat sets of criteria were judged to be those that met the criteria for Tier 1. We have determined that the following agents should be designated as Tier 1 agents: *B. anthracis*, Botulinum neurotoxins, Botulinum neurotoxin producing species of *Clostridium*, *B. mallei*, *B. pseudomallei*, Ebola virus, *F. tularensis*, Marburg virus, Variola major virus, Variola minor virus, and *Y. pestis*.

Commenters questioned why we believe that the current regulations were not sufficient to contain, secure, and protect the proposed Tier 1 select agents and toxins from theft, loss, exposure, or release. In response, we note that the absence of clearly defined, risk-based security measures in the select agent regulations raised concern both by stakeholders within the Executive Branch and outside the government. This is the focus of Executive Order 13486 (Strengthening Laboratory Biosecurity in the United States) and Executive Order 13546 (Optimizing the Security of Biological Select Agents and Toxins in the United States) that call for improvements in select agent security and risk management. The additional security requirements for those entities

possessing Tier 1 select agents and toxins will enhance physical security, personnel suitability, and information security within the affected entities.

The commenters further contended that the proposed regulatory changes failed to achieve the goal of minimizing the impact of the regulations on the legitimate uses of select agents and toxins that Executive Order 13546 notes are essential to national security. In response, we note that the overall number of select agents and toxins has been reduced, lessening the overall regulatory burden. In addition, by maintaining a performance-based approach in the regulations, we are allowing regulated entities to develop policies and procedures that meet the new requirements of the regulations while accommodating specific operational aspects of each entity.

Other commenters stated that the proposed tiering system poses significant questions as to the nature of the risk assessment process. Specifically, commenters questioned listing as Tier 1 agents bacterial diseases that are treated with licensed antibiotics, that are not commonly spread person-to-person, and that are present in the environment of the United States; while viruses that have no known therapy and that pose extreme risk to western populations are absent from the Tier 1 list. The commenters believed that the 20 criteria used for evaluation of each select agent and toxin should be made available to the regulated community for review and assessment. We note that the 20 criteria referenced by the commenters were the ones used by the FESAP in providing recommendations to the Federal Select Agent Program. Nevertheless, we agree with the commenters that it is reasonable to publish the criteria used by the FESAP in providing the tiering recommendations to the Federal Select Agent Program. These criteria are:

1. The relative ease with which a select agent or toxin might be acquired from a laboratory or commercial source;
2. The relative ease of production of a select agent or toxin;
3. The relative ease by which a select agent or toxin might be modified in order to enhance its pathogenicity, transmissibility, or ability to evade medical and non-medical countermeasures;
4. The potential for easy deliberate dissemination;
5. The potential for creating disease or illness;
6. The relative environmental stability of a select agent or toxin by itself and how well it survives in the environment

in which it is formulated or disseminated;

7. The amount of select agent or toxin necessary to induce illness;

8. The relative ease with which a particular select agent or toxin might be disseminated or transmitted from one animal or person to another or into the environment where it could produce a deleterious effect upon animal, plant, or human health;

9. Whether the target population has innate immunity to the select agent or toxin or whether immunity has been acquired from a source such as vaccines;

10. The potential for the select agent or toxin to create morbidity (*i.e.*, any non-fatal illness that renders partial dysfunction to an animal or human lasting weeks or months that will eventually resolve with medical, veterinary, and/or supportive care);

11. The burden placed on the human, veterinary, or plant health system by the deliberate release of the select agent or toxin;

12. The ability to detect a release of the select agent or toxin into the environment, food, water, or soil;

13. The ability of the human and agricultural health authorities to accurately and rapidly diagnose and treat the disease presented by a release of the select agent or toxin;

14. The existence of countermeasures to prevent, treat, or mitigate the symptoms of a disease caused by the release of a select agent or toxin and/or its spread through a population;

15. The potential for high animal, plant, or human mortality rates with delivery of medical countermeasures;

16. The potential for high animal, plant, or human mortality rates without delivery of medical countermeasures;

17. The short-term economic impact of a single outbreak of a disease or release of a toxin;

18. The human, monetary, and other resource costs of making an area, building, industrial plant, farm, or field safe for humans, animals or plants to inhabit following the release of the select agent or toxin;

19. The pathogen's ability to persist in the environment or to find a reservoir that makes its recurrence more likely; and

20. The long-term health or economic consequences caused by a single release of the select agent or toxin.

Commenters argued that if there is a "Tier 1" designation of certain select agents and toxins, there logically should be a list of designated "Tier 2" select agents and toxins. We made no changes based on this comment. In designating certain select agents and toxins as "Tier 1," the Federal Select Agent Program

considered and rejected the idea of designating the remaining agents as "Tier 2" because the establishment of the Tier 1 category is in no way intended to imply that the agents not designated as Tier 1 pose a lesser risk to public health and safety than they have previously. Further, we believe that the establishment of more varying levels of risk categories would create an increased administrative oversight burden and needless complications for regulated entities.

Various commenters argued that the following select agents should be not be listed as Tier 1 agents: *F. tularensis*, *Y. pestis*, *B. mallei*, *B. pseudomallei*, and *B. anthracis* because these bacteria are all readily found in the environment and treated effectively with antibiotics, such that additional security requirements will have little or no effect on biodefense. Commenters said they recognized that public perception must be taken into account, but they stated a belief that there is little public recognition of many of these bacteria as potential biothreat agents. Commenters stated that *F. tularensis* is not transmissible from one human to another nor does it have either the potential for major human health impact or the potential for a high mortality rate.

Based on the FESAP recommendation using the criteria identified above, we disagree with the commenters that *F. tularensis* should not be designated as a Tier I select agent. Significant factors that we considered include the low infectious dose, the robust environmental stability, and a well-documented history of weaponization associated with this agent.

Commenters stated that *B. pseudomallei* should be not be listed as Tier 1 agent because *B. pseudomallei* is non-communicable from person-to-person, lacks a history of use or development as a successful biologic weapon (as compared with *B. mallei*, a highly pathogenic organism with which *B. pseudomallei* is inappropriately linked in the list), and has a low incidence of symptomatic disease following natural infection. The outcome of 99.9 percent of infections with *B. pseudomallei* is asymptomatic infection. Life-threatening illness occurs only in a few hosts with particular risk factors, particularly renal failure and diabetes.

Based on the FESAP recommendation using the criteria identified above, we disagree with the commenters that *B. pseudomallei* should not be designated as a Tier I select agent. Significant factors in our determination include the fact that *B. pseudomallei* is as virulent in animal models as *B. mallei*, *B.*

pseudomallei is not endemic in the United States, *B. pseudomallei* has a low infectious dose, *B. pseudomallei* possesses robust environmental stability, and timely diagnosis may be complicated due to the rareness of disease in the United States. In addressing the comment referring to the criteria used to remove *Coccidioides*, we note the availability of licensed treatments for *Coccidioides* infection and a lowering of our assessment of the impact of *Coccidioides* infection on human health, as indicated by the high proportion of subclinical cases observed in endemic areas. We do not believe that this applies to *B. pseudomallei*. In addition, we note that *B. pseudomallei* is not extensively endemic in the United States as are *Coccidioides* species. Therefore, *B. pseudomallei* will be listed as a Tier 1 select agent and toxin.

Commenters stated that Botulinum toxin should not be identified as a Tier 1 agent because Botulinum toxin is a non-replicating, non-infectious chemical agent and should not be in the same category as highly contagious biological agents such as *B. anthracis* or un-treatable agents such as the Ebola virus. We made no changes based on these comments. We are aware that Botulinum toxin is a non-replicating and non-infectious toxin. However, the rule seeks to balance the regulatory oversight of agents and toxins that have the potential to pose a severe threat to public health and safety while maintaining availability of these agents and toxins for research and educational activities. Another commenter further argued that Botulinum neurotoxin quantities in excess of 500 microgram (μg) should be designated as Tier 1 toxin, but quantities of less than 500 μg should not be regulated. One commenter questioned the "logic (or science)" behind this decision, particularly when pharmaceutical production facilities possessing greater than 500 μg will be exempt from the new regulations.

We noted that the pharmaceutical production facilities possessing select agent or toxins are currently regulated under select agent regulations. However, products that are, bear, or contain listed select agents or toxins that are cleared, approved, licensed, or registered under any of the laws specified in Section 5(c) and 6(c) of the regulations are exempted from the requirements of the select agent regulations, insofar as their use is only for the approved purpose and meets the requirements of such laws. The exemption would only apply to the final product created from or containing the select agent or toxin. The amount of each toxin that could be possessed

without regulation by a principal investigator, a treating physician or veterinarian, or a commercial manufacturer or distributor was determined on the basis of toxin potency and how much one could safely possess without constituting a potential threat to public safety or raising concerns about use as a weapon that would have a widespread effect. The level specified in the rule was determined after consultation with subject matter experts on this toxin. The determination that a toxin posed a severe public health threat was based on the ability for the mass distribution of the toxin for mass casualty purposes. Therefore Botulinum neurotoxin will be placed on the HHS Tier 1 list of select agents and toxins.

Commenters stated that Ebola and Marburg viruses should be removed from Tier 1 because none of the other hemorrhagic fever viruses are in Tier 1, yet they are just as dangerous. We disagree with the commenters and note that the hemorrhagic viruses on the select agent list exhibit distinct differences in morbidity, mortality, transmissibility, and degree of pathogenicity. Therefore our consideration to designate a particular virus as Tier 1 is made on a virus-by-virus basis. Ebola virus and Marburg virus are designated as Tier 1 select agents.

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)

One commenter argued that Reconstructed 1918 Influenza virus should be a Tier 1 select agent since it is a pathogenic agent not currently present in any human population and not currently present in any natural environment. The commenter further argued this agent exhibited high transmissibility and high lethality and caused a global pandemic with massive mortality (≥ 50 million deaths; ≥ 3 percent of the human population at the time), massive economic impact, and major psychological impact when last present in human populations.

We did not propose to designate Reconstructed 1918 Influenza virus as a Tier 1 select agent and are making no changes to the HHS list of select agents and toxins based on this comment. Recent studies have increased our understanding of the public health risks associated with this agent. Current reports suggest that as much as 60 percent of the population in the United States may have some immunity to the

1918 Influenza virus. We also considered the potential availability of vaccines and antiviral treatments when considering whether to designate this virus as a Tier 1 select agent.

Although we did not designate the Reconstructed 1918 Influenza virus as a Tier I select agent, we retained this virus as a select agent. In retaining this virus as a select agent we recognize that, to the best of our knowledge, the only place the Reconstructed 1918 Influenza virus currently resides is in laboratories. Unlike other influenza viruses, the most likely source of a Reconstructed 1918 Influenza virus outbreak would be as a result of a breach or failure of a laboratory's biosafety or biosecurity program.

Diagnostic Laboratories and Tier 1 Agents

Commenters have expressed concerns about the ability of diagnostic laboratories, such as those in the LRN, to retain their ability to perform diagnostics while meeting the requirements for Tier 1 select agents and toxins. The Federal Select Agent Program recognizes the critical role of diagnostic laboratories in the early detection and response to outbreaks of disease in humans and agriculture. While all of the Tier 1 regulatory requirements will apply to laboratories that maintain permanent stocks of Tier 1 select agents and toxins, laboratories may wish to consider maintaining their proficiency in detecting Tier 1 select agents and toxins through the use of excluded attenuated strains of select agents and toxins that meet their testing requirements. Examples of excluded attenuated strains include: *B. anthracis* strains devoid of the plasmid pX02 (e.g., *B. anthracis* Sterne, pX01+pX02-) (effective 2–27–2003), *F. tularensis* subspecies holartica LVS (live vaccine strain; includes NDBR 101 lots, TSI–GSD lots, and ATCC 29684) (effective 2–27–2003), and *Y. pestis* strains (e.g., Tjiwidej S and CDC A1122) devoid of the 75 kb low-calcium response (Lcr) virulence plasmid (effective 2–27–2003). Possession of an excluded attenuated strain, so long as it has not been subjected to any manipulation that restores or enhances its virulence, would be excluded from the HHS and USDA select agent regulations. Those laboratories encountering a Tier 1 select agent or toxin in their routine work with diagnostic or proficiency testing, would still qualify for the clinical or diagnostic laboratory exemption found in sections 5(a) and 6(a) of the regulations. Should a diagnostic laboratory wish to maintain a select agent identified in a diagnostic sample longer than the seven calendar

days currently allowed by the select agent regulations, the diagnostic laboratory can request that HHS/CDC or USDA/APHIS grant additional time before the select agent is transferred or destroyed pursuant to either section 5(a) or section 6(a) of the regulations.

C. Responses to Other Proposed Changes

With respect to the remainder of the sections outlined below, the following changes are based on comments received in response to the NPRM and recommendations from the FESAP. We updated the Web address throughout the document as all information concerning the Federal Select Agent Program is now centralized on the National Select Agent Registry (NSAR) at <http://www.selectagents.gov/>. In addition, HHS/CDC and USDA/APHIS used similar language in our final rules to ensure consistency between the regulations.

Definitions

Occupational Exposure

We proposed to add a definition for occupational exposure based on the definition used in the Occupational Safety and Health Administration (OSHA) regulations found in 29 CFR 1910.1030 (Bloodborne pathogens). Commenters proposed that we not use the OSHA definition since the adoption of this definition would limit possible exposures to select agents only to bloodborne pathogens and to other potentially infectious materials as noted in that standard, but not to occupational exposure to aerosols of the agents in the select agent list. One commenter recommended “a definition, which combines the OSHA bloodborne pathogens standard and the definition of “exposure incident” found in the Bloodborne Pathogen Standard and Exposure Incident (Laboratory) from the Cal/OSHA Aerosol Transmissible Diseases (California Code of Regulations, Title 8, Section 5199), to ensure that both non-aerosol and aerosol exposure events are appropriately addressed that would state “Exposure Incident: Any event which results in (1) an individual experiencing a specific eye, mouth, or other mucous membrane, non-intact skin, or parenteral contact with a select agent or toxin; or (2) an individual experiencing a potential exposure to an aerosolized select agent without the benefit of appropriate exposure controls, and the circumstances of the aerosol exposure make the transmission of a disease sufficiently likely that the individual requires further medical evaluation by a

Physician or other licensed health care professional.” We agree with the commenters and are revising the definition to state: “Any reasonably anticipated skin, eye, mucous membrane, parenteral contact, or respiratory aerosol exposure to select agents or toxins that may result from the performance of an employee’s duties.”

Recombinant and Synthetic Nucleic Acids

We proposed to add the definitions for recombinant and synthetic nucleic acids to the regulations. One commenter stated that the broad definition has implications in all areas of synthetic biology technology, including industrial enzymes, renewable chemicals for pharmaceutical and industrial applications, biobased products, personal care products, renewable specialty chemicals, biofuels, and healthcare products. The commenter argued that the consequences of such a definition could impede the growth of sustainable products from an emerging science such as synthetic biology technology. The commenter recommended that we not adopt the new definitions of recombinant and synthetic nucleic acids as put forth in the proposed rule because the existing language of the regulation is sufficient to cover the uses of synthetic nucleic acids as currently practiced; and furthermore, that the proposed definitions utilize language that was proposed to, but rejected by, the NIH Recombinant DNA Advisory Committee (NIH–RAC). The commenter further argued that if we feel compelled to introduce a new definition, that we follow the leadership of the NIH–RAC and promulgate a simpler definition that is not focused on the underlying mechanism of production of the nucleic acids. We made no changes to the definition based on this comment. The scope of our oversight is limited by the list of select agents and toxins and therefore does not extend to all synthetic biology. We have updated the organization of the definitions of recombinant and synthetic nucleic acids upon consultation with the NIH Office of Biotechnology Activities. The definitions now read as:

- Recombinant nucleic acids. (a) Molecules that are constructed by joining nucleic acid molecules and that can replicate in a living cell (*i.e.*, recombinant nucleic acids) or (b) molecules that result from the replication of those described in (a) above.
- Synthetic nucleic acids. (a) Molecules that are chemically or by other means synthesized or amplified,

including those that are chemically or otherwise modified but can base pair with naturally occurring nucleic acid molecules (*i.e.*, synthetic nucleic acids) or (b) molecules that result from the replication of those described in (a) above.

In addition, we have separated the definition of recombinant and synthetic nucleic acids for clarity.

Restricted Person

We proposed to add the definitions for the following terms in 42 CFR 73.1, to clarify the criteria related to the identification of a restricted person: *Adjudicated as a mental defective*, *Alien*, *Committed to any mental institution*, *Controlled substance*, *Crime punishable by imprisonment for a term exceeding 1 year*, *Indictment*, *Lawfully admitted for permanent residence*, *Mental institution*, *Restricted person*, and *Unlawful user of any controlled substance*. Commenters stated that proposed definitions need to be further clarified and are overly restrictive or vague. We agree with these comments and are not including these definitions in this final rule.

Exclusions

We proposed to remove language stating that an attenuated strain of a select agent that had been granted an exclusion because it did not pose a severe threat to public health and safety would be published in the **Federal Register**. We received no comments regarding this proposal. However, one commenter requested clarification regarding previously established exclusions as currently listed on the NSAR at <http://www.selectagent.gov/Select%20Agents%20and%20Toxins%20Exclusions.html>. The commenter stated that individuals should not have to reapply and secure written approval for those attenuated strains that were previously recognized as excluded from select agent status.

In response to this commenter, we note that the language posted on the Federal Select Agent Program Web site at <http://www.selectagent.gov/Select%20Agents%20and%20Toxins%20Exclusions.html> already clarifies that once an attenuated strain of a select agent (or an inactivated select toxin) is determined not subject to the requirements of select agent regulations, the strain or toxin will only be subject to regulation if there is any modification such that virulence is restored or enhanced. Therefore, individuals are not required to reapply and seek written approval for attenuated strains or inactive toxins that have already been

determined by the Federal Select Agent Program to be excluded.

As noted earlier, we proposed the removal of the South America genotypes of EEEV and the VEEV subtypes ID and IE. We have also excluded the West African clade of Monkeypox virus. To prevent confusion on how an entity should handle samples that have been determined to be within a general taxonomic classification (*e.g.*, EEEV) but not within a particular genotype or subtype (*e.g.*, NA–EEEV), we have maintained the current general taxonomic listing of HHS and overlap select agents as opposed to listing a specific strain and added an exemption for the strains, subtypes, or pathogenicity levels which are not considered to have the potential to pose a severe threat to public health and safety. With this change, we believe we have clarified that when an agent is initially identified by taxonomic classification it is subject to the select agent regulations until further testing is accomplished to exclude the particular agent by strain, subtype, or pathogenicity level. We believe it is important that laboratories should treat these select agents and toxins as though they must comply with this part until further testing can be conducted to verify whether the agent is indeed an excluded strain, subtype, or pathogenicity level. This change should not have any impact on the exemption for diagnostic laboratories or alter the process of taking in diagnostic samples and forwarding any potentially identified select agents for further testing. It also does not change the reporting criteria for when the agent is confirmed as a select agent. Therefore, we are maintaining the listing of select agents in 42 CFR 73.3(b) to read, Monkeypox virus and Eastern Equine Encephalitis virus, and adding the following criteria to be excluded in 42 CFR 73.3(d)(5): Any South American genotypes of Eastern Equine Encephalitis virus and any West African Clade strains of Monkeypox virus. We are also amending the proposed list of select agents in 42 CFR 73.4(b) to read Venezuelan equine encephalitis virus, and adding the following criteria to be excluded in 42 CFR 73.4(d)(3): Any ID and IE subtypes of Venezuelan equine encephalitis virus.

Toxins

In 42 CFR 73.3(e) and 73.4(e), we proposed to clarify that the “inactive form of a select toxin” may be excluded from regulation since the current term, “attenuated strain of toxin” is scientifically inaccurate. We received comments that were supportive of this

proposed change and will finalize the change in this rule.

We proposed to add 42 CFR 73.3(d)(4) which would state, "An animal inoculated with or exposed to an HHS select toxin." The change allows animals injected with or exposed to a select toxin not to be considered a "select toxin." Therefore, the animals would not need to be housed in a registered space. The change eliminates an unnecessary burden on a registered entity because recovering the toxin from within an animal subject is highly difficult and such removal is unlikely to produce a reasonable yield of recovery. In addition, there is uncertainty as to whether the toxin would remain active when recovered from the animal. For these reasons, it is highly unlikely that once introduced into an animal, sufficient toxin would be able to be recovered to pose a significant hazard to public health. We received comments that were supportive of this proposed change.

One commenter recommended that we clarify that the aggregate amount in § 73.3(d)(3) is per "principal investigator, treating physician or veterinarian, or commercial manufacturer or distributor," and not per entity. We made no changes to the regulations based on this comment because the current regulatory language provides sufficient protections against the unrecognized accumulation of regulated quantities of select toxins at a given entity through multiple procurements of less than threshold amounts by multiple principal investigators within the entity. The same commenter recommended that we amend the regulatory language from "toxin" to "purified toxin." The commenter argued that since there are naturally occurring organisms that produce these toxins, unless they are purified they will pose only a low-level risk to human health. We made no changes to the regulation based on this comment since any HHS select agent or toxin that is in its naturally occurring environment, provided the select agent or toxin has not been intentionally introduced, cultivated, collected, or otherwise extracted from its natural source, is already excluded in section 73.3. The same commenter also recommended that the guidance be clarified to state that there are some select toxin-producing organisms that are not covered under this section of the regulations. Although we agree that there are indeed toxin-producing organisms that are not covered under this section of the regulations, we made no changes to the regulation based on this comment. The regulations clearly

state which agents are regulated. Guidance is also available on the select agent Web site (<http://www.selectagents.gov/SyntheticGenomics.html>) and defines the select agents that are regulated.

Due Diligence

We proposed to require that an entity transferring a toxin in amounts which would otherwise be excluded from the provisions in 42 CFR part 73 would be excluded only if the transferor: (1) Uses due diligence and documents that the recipient has a legitimate need (*i.e.*, reasonably justified by a prophylactic, protective, bona fide research, or other peaceful purpose) to handle or use such toxin; and (2) reports to HHS/CDC if they detect a known or suspected violation of Federal law or become aware of suspicious activity related to the toxin. The majority of our commenters from academic institutions argued that the proposed toxin due diligence provisions did not improve the safety and security of excluded quantities of these toxins. The commenters expressed concerns that if the toxin is being transferred to an individual employed by an entity which clearly has a bona fide research purpose, the laboratory providing the material should not have an obligation to report the transfer. Commenters further requested that the terms, "due diligence" and "legitimate need" be clarified. We made no changes to the regulation based on these comments. The proposed amended regulatory language to require due diligence and the reporting of known or suspected violations of Federal law in this case addresses concerns that an individual may be able to accumulate, unnoticed by anyone, regulated amounts of a select toxin by stockpiling shipments of unregulated amounts. We believe that commercial manufacturers and distributors already track the shipments of toxins as part of their quality management systems. We note that entities registered with the Federal Select Agent Program are already required to maintain records of internal toxin transfers. We are not defining either "due diligence" or "legitimate need" in the regulatory language because we believe both of these terms to be widely used and commonly understood. We would expect that, before transferring any amount of a select toxin, a reasonable person would satisfy themselves that the recipient had a legitimate need for a prophylactic, protective, bona fide research, or other peaceful purpose. We also note that while the transfer has to be recorded, the only report required by the new

regulatory language is a report of a transfer believed or suspected to be a violation of law.

Exemptions

Immediate Notification of the Identification of a Select Agent or Toxin Contained in a Specimen Presented for Diagnosis or Verification

We proposed to amend 42 CFR 73.5 and 73.6 to limit the immediate notification requirement to only those select agents and toxins identified as Tier 1 agents and toxins because these agents and toxins present the greatest risk of deliberate misuse with the most significant potential for mass casualties. We received comments that were supportive of this proposed change and we are finalizing this requirement in this rule.

Public Health Emergency

To eliminate an unnecessary burden on any individual or entity responding to a domestic or foreign public health emergency, we have removed the provision that the individual or entity must complete an APHIS/CDC Form 5 to request an exemption. Guidance on requesting an exemption for an individual or entity to respond to a domestic or foreign public health emergency may be found on the select agent Web site at www.selectagents.gov.

Responsible Official

Alternate Responsible Official

We proposed to add language to clarify the role of an alternate Responsible Official in order to definitively establish that an alternate Responsible Official must have the full knowledge and authority to act for the Responsible Official in his/her absence. While commenters generally agreed, one commenter argued that the proposed changes would prohibit consultants from serving as an alternate Responsible Official. We are making no changes to the regulation in response to this comment. We first note that in the absence of the Responsible Official, a person who has been designated by the entity as an alternate Responsible Official becomes the entity's Responsible Official. We believe that an individual acting as a consultant would have neither the institutional authority nor responsibility to allow them to serve as an alternate Responsible Official. This does not mean that an entity Responsible Official cannot utilize the services of a consultant in carrying out his or her duties. But the regulations were designed to require an entity to vest authority and responsibility for ensuring compliance with the select

agent regulations in one entity official so that the person can take action in the name of the entity and on behalf of the entity, and not merely provide advice or consultation.

Commenters also recommended that a provision for delegation of responsibilities to an alternate Responsible Official by the Responsible Official should be included, even with the Responsible Official present, so that an alternate Responsible Official would always be acting under the direction/oversight of the Responsible Official. Other commenters felt that it would be practical for the Responsible Official to delegate an alternate Responsible Official who is housed in the remote facility to take on the day-to-day responsibilities of the Responsible Official in that facility. We are making no changes to the regulations in response to these comments because the regulations already provide to the Responsible Official the flexibility to delegate the authority to perform certain tasks. While the regulations allow the Responsible Official as many assistants as he/she needs to ensure compliance with the regulations, the Responsible Official retains the ultimate responsibility for compliance. The regulatory provisions for the appointment of an alternate Responsible Official are in recognition of the fact that, as a practical matter, a single person cannot always be present at an entity. We believe that it is important for each entity to identify the person who has the responsibility for that entity to ensure compliance with the select agent regulations and this approach will help achieve a higher level of compliance than would be obtained from a system of shared responsibility.

Duty Station

We proposed to add a requirement that the Responsible Official's regular place of employment or principal duty station must be located in close proximity to the physical location of the registered entity entered in section 1A of APHIS/CDC Form 1 (Application for Registration for Possession, Use, and Transfer of Select Agents and Toxins). As we stated in the preamble to the proposed rule, we believed that the Responsible Official should have a physical (and not merely a telephonic or audio/visual) presence at the entity to ensure that the entity is in compliance with the select agent regulations and be able to quickly respond to on-site incidents involving select agents and toxins. Commenters generally agreed with the requirement that the Responsible Official's regular place of

employment or principal duty station must be co-located with the physical location of the registered entity entered in section 1A of APHIS/CDC Form 1. One commenter recommended that we eliminate the requirement for the definition because the Responsible Official is frequently a high-level administrator at a university, such as a Vice President for Research, and it would be infeasible in many cases for such a Responsible Official, whose duties extend beyond biosecurity, to be physically located at a registered entity; it would only add a layer of bureaucracy, which could detract from a focus on security, to require a second, on-site Responsible Official. We made no changes based on this comment. As noted above, the Responsible Official should be an individual who can perform all of the duties required for that position. The regulations were designed to place responsibility for ensuring compliance with the regulations in one position. However, some commenters requested that we clarify the provision regarding the individual's principal duty station, physical location, and "close proximity with the physical location of the registered entity." In addition, one commenter requested that we explain how quickly the Responsible Official should be able to respond to onsite incidents in terms of turnaround time. Another commenter stated that they were not persuaded that ensuring compliance and a quick response to incidents are sufficient rationale for this requirement.

In response, we are changing the language in section 73.9 to clearly state that the Responsible Official must have a physical (and not merely a telephonic or audio/visual) presence at the registered entity to ensure that the entity is in compliance with the select agent regulations and is able to quickly respond to on-site incidents involving select agents and toxins. We recognize that some entities are located on a campus with several registered laboratories situated in different buildings throughout the campus, and we believe it would be counterproductive to require that the Responsible Official be assigned to each physical laboratory listed on the entity's registration and require a set turnaround time to respond quickly to on-site incidents. However, the Responsible Official should be able to respond in a timely manner to onsite incidents in accordance with the entity's incident response plan. The regulations also contain a performance standard that the Responsible Official is physically

located on the campus to ensure day-to-day oversight and compliance with the select agent regulations and to respond to any incident in a way that limits damage and ensures that select agents and toxins are secured and safeguarded.

Responsible Official Training Requirement

We proposed to add a specific requirement that all Responsible Officials possess the appropriate training or expertise to execute their required duties. We received multiple comments and concerns about fulfilling the provisions of this proposed requirement. The breadth and variety of training and expertise available would be difficult to capture in regulatory language. Therefore, we will continue to assess the performance of the Responsible Official based on his or her efficacy in implementing the select agent and toxin regulatory requirements at the entity. As such, we have accepted these comments and have not included this provision in the final rule.

Access to Select Agents and Toxins Timeframe

We proposed to decrease the maximum length of time in which a Security Risk Assessment (SRA) will be valid from five years to three years in order to more expeditiously identify individuals who may have fallen into one of the prohibited or restricted categories. Commenters argued that our proposal to shorten this time period would increase the work load for individuals, entities, the Federal Select Agent Program, and the Federal Bureau of Investigation (FBI), and would only add bureaucratic expense for all without any source of compensation to the investigators and institutions who are endeavoring to contribute countermeasures against biothreats. Another commenter stated that it would have a significant impact on law enforcement's ability to handle the increased workload to conduct these investigations. One commenter was concerned that there would be delays in SRA approval that would negatively impact workload performance.

We are making no changes to the regulations based on these comments. On January 9, 2009, the President signed E.O. 13486 entitled "Strengthening Laboratory Biosecurity in the United States." This Executive Order established a working group co-chaired by representatives of the DOD and HHS Secretaries. The scope of working group activities pertained to the policy of the United States that facilities that possess biological select agents and toxins have

appropriate security and personnel assurance practices to protect against theft, misuse, or diversion to unlawful activity of such agents and toxins. The working group provided final recommendations through careful consideration of proposals from subgroups and comments received from select agent entities and the public. The report is available at: <http://orise.orau.gov/emi/scapa/files/biosecurity-report.pdf>.

One of the recommendations from the working group to enhance security was to perform the SRA every three years for all individuals with access to select agents and toxins instead of the existing policy of performing the SRA every five years. We concurred with this recommendation. Based on input from the FBI, we have determined that conducting SRA approvals every three years is beneficial in increasing the security of registered entities. As a policy matter, we have been processing SRAs on a three-year basis since June 1, 2011 and an increase in administrative burden has not been noted. We also did not receive any comments from the regulated community that they have experienced any additional burdens. Accordingly, we do not believe this regulatory change will result in an increased burden on registered entities.

Portability

We also proposed to amend the regulations in section 73.10 to add new provisions by which individuals may have access to select agents and toxins at entities other than the individual's "home" entity. One commenter suggested that the Responsible Official, rather than the individual as proposed, make the request to the HHS Secretary or Administrator to approve access to select agents or toxins at another registered entity for a specific period of time. Other commenters requested clarification of the process and suggested that limiting access to only one entity at the time would be appropriate.

In response to these comments, we are amending section 73.10 to provide that "a person with a valid approval from the HHS Secretary or Administrator to have access to select agents and toxins may request, through his or her Responsible Official, that the HHS Secretary or Administrator provide their approved access status to another registered individual or entity for a specified period of time."

One commenter wanted clarification that an individual would have access to select agents at multiple registered entities based on the proposed language. The revised language would allow

individuals the flexibility to have access to select agents and toxins at entities other than the individual's "home" entity. To address the commenter's concern that the SRA portability process is unclear, additional guidance has been developed and is available at <http://www.selectagents.gov>.

Security

Animals or Plants Accidentally or Intentionally Exposed to or Infected With a Select Agent

One commenter was unclear regarding whether the security plan should contain procedures concerning animals or plants accidentally or intentionally exposed to or infected with a select toxin. We made no changes to the regulations based on this comment. As we discussed in the preamble for the NPRM, we are not requiring the security plan to address procedures concerning animals exposed to toxins because it is highly unlikely that once introduced into an animal, sufficient toxin can be recovered to pose a significant hazard to public health and safety.

Another commenter wanted to know if the provision was for clinical, veterinary, or environmental laboratories performing diagnostic work to identify a select agent in humans, food or environmental samples. We made no changes to the regulation based on this comment. Any select agent or toxin that is in its naturally occurring environment (e.g., sand samples that are naturally infected with *B. anthracis* or milk samples that contain *C. burnetii*) provided the select agent or toxin has not been intentionally introduced, cultivated, collected, or otherwise extracted from its natural source is already excluded in sections 3 and 4 of the select agent regulations.

Commenters requested that we change the statement of "safeguarding of animals or plants intentionally or accidentally exposed to or infected with a select agent" to read "intentionally exposed to, or infected with, select agents." The commenters suggested that the statement would be clearer. We made no changes to the regulations based on this comment. We believe that animals or plants accidentally exposed to or infected with a select agent should be handled as a select agent and safeguarded in the same manner as an animal or plant intentionally exposed to a select agent.

Codification of Current Practices for Shipping, Receiving and Storage

We proposed to codify current practices for shipping, receiving, and

storage of select agents and toxins to ensure that regulated entities have consistent regulatory procedures for securing and monitoring the shipment, receipt, and storage of these items. Some commenters stated that codification of current practices for shipping, receiving, and storage are unnecessary and recommended that the provision be deleted. Other commenters recommended that we define and clarify the term "unexpected shipments." We made no changes to the proposed regulation based on the comments since we believe the entity's security plan should have documented processes to ensure select agents and toxins are safeguarded against theft, loss, intentional release or unauthorized access at all times, including when a select agent or toxin is (1) ready to be packaged for transportation, (2) packaged for shipment, or (3) received by a person with approval to access select agents and toxins. These procedures would serve to decrease the chance that such materials would be made available to an unauthorized individual or an individual without a legitimate use for the materials. We also believe that the term "unexpected shipments" is self-explanatory and that an entity's security plan should contain procedures for the handling of unexpected shipments (e.g., when an entity receives a shipment of a select agent that it had neither requested nor coordinated for, and therefore was not expecting).

Information Security

We proposed that the security plans of entities with select agents and toxins must include provisions for information security. Many commenters had questions or concerns regarding the additions to the security plan proposed in section 11(c)(9) of the select agent regulations. The commenters expressed concerns that the requirement represents an added regulatory burden and the impact of this requirement should be evaluated. Other commenters thought that persons having access to information about select agents should not be regulated as having access to the select agents. The commenters further expressed their belief that the proposed language is vague and lacks sufficient direction for securing the information. We agree with the commenters. The purpose of the requirement in question is to clarify section 11(c)(9)(i) of the regulation that requires the entity to have procedures in place for information systems control. This is an overarching requirement that covers electronic [information technology] and non-electronic [hardcopy] information

oversight by the regulated community. Our intent was not to regulate access to experimental data or the results of studies involving select agents and toxins but to regulate access to the select agents and toxins themselves. Therefore, we have revised the language in order to clearly indicate that the information security provisions in question should be for access to an entity's registered space and records pertaining to select agents and toxins, as identified in sections 11 and 17 of this part.

Commenters expressed concerns that the new information security requirements in section 11(c)(9)(ii) would require registration and security risk assessments for all staff managing records pertaining to select agent work. Our response is that this would depend on the individual's duties. If an individual is able to access a select agent or toxin, the individual would need to undergo a security risk assessment. However, if the individual's duties are limited so that he or she would be prevented from accessing the select agents or toxins, then the individual would not need to undergo a security risk assessment.

We anticipate that these requirements are already being met and will merely require entities to document the systems and processes currently in place. The guidance documents developed in conjunction with this rule are, in part, a response to the questions and issues raised by the commenters. Guidance on information security may be found at www.selectagents.gov. Issues addressed in the guidance document include, but are not limited to: information technology security, network security, computer security, peripheral devices and data storage, physical security and its application to information security, risk management, and training.

Inventory Verification for Select Agents and Toxins

We proposed more specific minimum security standards for select agents or toxins that included inventory verifications for select agents and toxins. Commenters requested that section 11(e)(4)(ix) be revised to delete the word "all" and clarify that the inventory audits be conducted for only those affected Tier 1 select agents and toxins. We agree with the commenters that the intent of the proposed provision was limited to only those select agents and toxins affected by the triggering event. However, we reevaluated the proposal that would have been limited to only Tier 1 agents and toxins, and based on experience, believe that this provision needs to be applied to all select agents and toxins. Therefore, we

have revised the final regulatory language to address inventory verification for all select agents and toxins, by creating a new subparagraph (e) in section 11 which states "(e) Entities must conduct complete inventory audits of all affected select agents and toxins in long-term storage when any of the following occur:

(1) Upon the physical relocation of a collection or inventory of select agents or toxins for those select agents or toxins in the collection or inventory;

(2) Upon the departure or arrival of a principal investigator for those select agents and toxins under the control of that principal investigator; or

(3) In the event of a theft or loss of a select agent or toxin, all select agents and toxins under the control of that principal investigator."

Reference

We proposed to remove the reference in § 73.11(e), "Laboratory Security and Emergency Response Guidance for Laboratories Working with Select Agents" in *Morbidity and Mortality Weekly Report* (December 6, 2002) because we posted a security guidance document in March 2007 that supersedes this reference. We received no comments regarding the removing of this reference.

Reporting Incidents to the FBI

We proposed to add a requirement that the security plan include procedures for the Responsible Official to immediately notify the FBI of suspicious activity that may be criminal in nature and related to the entity, its personnel, or its select agents or toxins. Commenters stated that this proposal contradicts FBI guidance contained in their "Agricultural, Chemical and Petroleum Industry Terrorism Handbook" and creates a conflict within those entities that have their own recognized law enforcement agencies. Commenters requested justification for this change and clarification on the intent of the requirement. Commenters also argued that the proposed language is unclear and unnecessary. Specifically, commenters asked what constitutes a "suspicious criminal activity"; what is an "entity"; and whether the intent of this proposal is for the Responsible Official to be the designated individual to contact the FBI. We do not believe that there exists any conflict between the security requirements in section 73.11 (Security) of the select agent regulations and the guidance contained in the FBI's "Agricultural, Chemical and Petroleum Industrial Terrorism Handbook." However, where any conflict might

exist, the requirements of the federal regulations would supersede guidance. The intent of this requirement is to facilitate the involvement of antiterrorism resources which will increase the security of select agents and toxins. We also believe that the FBI field offices, which are centrally located in major metropolitan areas across the United States, can assist the entity by working closely with them on crime threats. However, we agree with the commenters that it may be appropriate that the notification of suspicious activity first go to the local law enforcement. Therefore, we have changed the language in section 73.11(c)(8) to read: "Describe procedures for how the Responsible Official will be informed of suspicious activity that may be criminal in nature and related to the entity, its personnel, or its select agents or toxins; and describe procedures for how the entity will notify the appropriate federal, state, or local law enforcement agencies of such activity." The guidance document on reporting suspicious activities may be found at www.selectagents.gov.

Intrusion Detection System

We proposed more specific minimum security standards for select agents and toxins that included intrusion detection systems. Commenters requested clarification as to what was meant by "intrusion detection system" (IDS) and asked for examples of what constitutes an IDS. They also requested clarification concerning the requirement that "personnel monitoring the IDS must be capable of evaluating and interpreting the alarm." We have made no changes in response to this comment. We believe that the terms are self-explanatory and these types of alarms need to be monitored by personnel who are capable of responding appropriately. However, we are removing the words "prescribe and/or" to clarify the intent of the provision. We have developed guidance that describes IDS as a sensor device or devices which triggers an alarm when a security breach occurs and notifies a response force (e.g., police, guards, etc.) capable of addressing any threat that may be present. This guidance also provides examples of various types of IDS. The guidance document may be found at www.selectagents.gov.

Submission of Security Plans

We proposed to amend § 73.11 to require that the entity security plan be submitted for initial registration and renewals of registration. Commenters recommended that we eliminate the proposed requirement, and stated that

this requirement would delay the renewal process and place entities in a “regulatory bind,” that the requirement would compromise the “need to know” status of the security plans, and that these documents should remain a protected document made available for review during the site visit only. We made no changes to the regulations based on these comments. Section 11 already has a provision that “the security plan must be submitted upon request.” The requirement in question merely codifies our long-standing policy of requesting the security plans for initial registration and the renewal process. We also note that, in practice, the submission of security plans for initial registration and registration renewals has not created a delay in either process.

Security for Tier 1 Select Agents and Toxins

Access Controls to Tier 1 Agents

We proposed specific minimum security standards for access controls to Tier 1 agents in section 11(4)(iii) of the regulations. One commenter stated that these provisions would be difficult for laboratories co-located with other entities. We made no changes to the proposed standards based on this comment. Based on our experience with over 350 entities in a ten-year period, we observed that registered entities have been successful in meeting the current regulatory requirements in a co-located situation, and we have no reason to believe that this will not continue.

Back-Up Power for Tier 1 Select Agents and Toxins

We proposed more specific minimum security standards for Tier 1 agents that included the provision of back-up power. Commenters requested clarification regarding whether the back-up power requirement would only apply to registered spaces or whether it would include the entire entity or building that houses the registered space. Commenters recommended adding the phrase “for the registered space” into this section. We agree with the commenters and have revised the language accordingly.

Another commenter stated that the provision should remain a recommendation not a requirement. Although we believe back-up power for information security networks is an essential component for the safeguarding of Tier 1 agents against unauthorized access, theft, loss, or release during power outages, further consideration led us to alter the nature of this requirement. Rather than

focusing on power/electricity alone, we have clarified the requirement in order to address the importance of having comprehensive back-up procedures in the event of a system failure. These procedures may include, but are not limited to, provisions for back-up power.

Security Enhancements for Tier 1 Select Agents and Toxins

We proposed specific minimum security standards for Tier 1 select agents or toxins. Commenters requested guidance and a timetable of when the security upgrades need to be addressed. In this final rule, we have included a phase-in period for the effective date for certain requirements which should allow entities sufficient time to comply without causing disruption or termination of research or educational projects. As noted in the “Effective Dates” portion of this document, one hundred and eighty days after the publication of the final rule, entities will need to be in compliance with new provisions outlined in section 11 (Security). In addition, we have developed guidance to assist entities with security enhancements for Tier 1 agents.

Other commenters stated that the proposed rule included more specific minimum security standards for Tier 1 select agents and toxins and requested that we identify criteria for stratifying security requirements, making them risk-based and considering the type of work performed at the facility. The commenters also argued that the additional regulations for Tier 1 agents and toxins will create more responsibilities for the entity and require more resources to meet these requirements. While we are in general agreement with these concerns, we note that entities possessing Tier 1 agents and toxins are already meeting these requirements. In addition, we have developed guidance to assist entities with security enhancements for Tier 1 agents, which may be found at www.selectagents.gov. Therefore, we are making no changes to the minimum security standards as proposed in the NPRM.

Suitability Assessment for Access to Tier 1 Select Agents and Toxins

We proposed specific minimum security standards, including personnel suitability assessments, for access to Tier 1 select agents and toxins. Many commenters had questions or concerns regarding these additional requirements, as described in section 11(f) of the proposed rule. Specific additions addressed by the commenters included:

Pre-access suitability assessments, ongoing suitability assessments, and self- and peer-reporting of incidents or conditions that could affect an individual’s ability to safely have access to or work with Tier 1 select agents and toxins. Commenters generally divided into two groups in their response to the proposed additions. Some felt that the requirements were too vague to prove useful and the requirements created administrative burden without improving the overall security of Tier 1 select agents and toxins. Others felt that the requirements could or would require entities to behave in a manner contrary to local laws, privacy laws, or union contracts. Commenters also felt that the proposed language, “individuals with access approval to select agents and toxins are trustworthy and behaving in a manner that upholds public health and safety, security, and the integrity of the scientific enterprise” were subjective standards that would be difficult to enforce. We agreed with the commenters and revised the language in the final rule to read that the security plan must contain procedures that will limit access to a Tier 1 select agent or toxin to only those individuals who are approved by the HHS Secretary or Administrator, following a security risk assessment by the Attorney General, have had an entity-conducted pre-access suitability assessment, and are subject to the entity’s procedures for ongoing suitability assessment.

We anticipate that these requirements are already being met at many registered entities and will merely require those entities possessing a Tier 1 select agent or toxin to formalize and document the systems and processes currently in place. Therefore, we do not believe the registered entities possessing a Tier 1 select agent or toxin will endure additional significant costs for suitability assessments. We believe that many of the specific concerns raised by commenters regarding potential violation of laws or union contracts arose as a result of the commenters’ examination of the FESAP November 2, 2010 document entitled “Recommendations Concerning the Select Agent Program.” As a matter of clarification, the Federal Select Agent Program considered the FESAP recommendations as well as recommendations from other sources (e.g., the National Science Advisory Board for Biosecurity, the National Research Council, and the EO 13486 Working Group), in developing the proposed rule provisions addressing personnel suitability. While we have created specific guidance regarding this

section of the revised rule, we are leaving the regulations in their broadly-written state in order to provide entities with flexibility in meeting these requirements. Given our experience with the select agent regulations and the wide variety of regulated entities those regulations cover, we have found this to be the most effective approach. The personnel suitability guidance document developed in conjunction with this rule is, in part, a response to the questions and issues raised by the commenters. Issues addressed in the guidance document include, but are not limited to:

- (1) Understanding the potential for insider threat;
- (2) Understanding the needs for suitability assessments;
- (3) Delineating the roles and responsibilities of individuals to ensure optimal security;
- (4) Requesting information about individuals in a standardized manner and assessing individuals in the context of safety and security;
- (5) Responding to reports in a consistent, prompt, and confidential manner;
- (6) Providing training for recognizing and reporting suspicious behavior.

Full guidance on suitability assessments may be found at www.selectagents.gov.

One commenter requested an exclusion or exemption clause for entities that are registered to possess Tier 1 select agents or toxins, but do not possess them. We made no changes to the regulations based on this comment. Entities that are registered to possess, use or transfer select agents and toxins must meet all of the regulatory requirements, regardless of whether or not they actually possess these materials.

Security Training for Access to Tier 1 Select Agents and Toxins

We proposed specific minimum security standards, including security training, for those individuals who would have access to Tier 1 select agents or toxins. Commenters requested clarification whether training of “all entity employees” mentioned in section 11(e)(2)(ii) meant everyone in the facility or those “Security Risk Assessment-approved employees.” We agree with the commenters and have revised the language in the regulations to clarify that the training is for employees with access to Tier 1 select agents and toxins.

Three Barriers for Tier 1 Select Agents and Toxins

We proposed specific minimum physical security standards for Tier 1 select agents or toxins that included a requirement for three barriers protecting access to these materials. Commenters requested clarification regarding what was meant by “barrier” and asked for examples of what constitutes as a barrier. They also requested clarification concerning the word “delay” since, according to the commenters, the word does not seem to describe the needed function.

We agree with the commenters that the word barrier needed further explanation and, in the definitions section in § 73.1, we have defined the term “Security barrier” as a physical structure that is designed to prevent entry by unauthorized persons. In addition, we have revised the language in this section to more clearly articulate that entities possessing Tier 1 select agents and toxins must have a minimum of three security barriers where each security barrier adds to the delay in reaching secured areas where select agents and toxins are used or stored. One of those security barriers must be monitored in such a way as to detect intentional and unintentional circumventing of established access control measures under all conditions (day/night, severe weather, etc.). The final barrier must limit access to the select agent or toxin to personnel approved by the HHS Secretary or Administrator, following a security risk assessment by the Attorney General.

Other commenters believed that the proposed requirement represents an added expense. Although we agree that there are expenses associated with the implementation of security measures, we do not anticipate that significant additional expenditures will be necessary for registered entities already possessing Tier 1 select agents or toxins. We have developed guidance to assist entities with the security barrier requirement, which may be found at www.selectagents.gov.

Response Time for Tier 1 Select Agents and Toxins

We proposed specific minimum security standards, including a response time for security forces or local police that could not exceed 15 minutes from the time of an intrusion alarm or report of a security incident in section 73.11(e)(4)(viii), for possessors of Tier 1 select agents and toxins. Commenters questioned why a 15 minute response time was chosen. Commenters also inquired whether there would be any

penalties if local law enforcement exceeds 15 minutes with their response time. In addition, commenters stated that the proposed definition of response time is unclear. One commenter recommended that we revise the provision to read “Response time for security forces or local police must not exceed 15 minutes from the time of alerting the designated force.”

Based on the comments received, we have modified the language of this section. While retaining a 15-minute response time goal for security forces or local police, we have provided flexibility for entities to develop systems in line with the optimal achievable response time in their area by revising the language to read: “The entity must: (A) Determine that the response time for security forces or local police will not exceed 15 minutes or (B) Provide security barriers that are sufficient to delay unauthorized access until the response force arrives in order to safeguard the select agents and toxins from theft, intentional release, or unauthorized access. The response time is measured from the time of an intrusion alarm, or report of a security incident, to the arrival of the responders at the first security barrier.”

Our selection of the 15 minute response time metric is based on DOD and DHS standards for high value assets (e.g., MD Number 11046 (Open Storage Area Standards for Collateral Classified Information), Department of Homeland Security Management Directive System MD) and also on our analysis of incident response plans provided by registered entities since 2003. The response time is measured from the time of an intrusion alarm, or report of a security incident, to the arrival of the responders at the first security barrier. A response is a force capable of interrupting a threat and may be unarmed guards, armed guards, or local law enforcement.

Security Requirements for Variola Major Virus or Variola Minor Virus

In recognition of the special public health risks associated with Variola major virus and Variola minor virus, we proposed to require additional physical security measures over and above those proposed for Tier 1. Commenters were concerned about listing the Variola major virus (smallpox virus) as a Tier 1 agent, given the stringent conditions already in place for its handling and tracking. The commenters recommended an alternative approach might be to designate the smallpox virus as a pathogen with very special handling requirements, given that smallpox has been officially eradicated worldwide.

We made no changes to the regulations based on the comment. We believe that setting up a different special class of standards for one pathogen would needlessly increase the complexity of the regulatory provisions without any benefit of increased security. The requirements designated for Tier 1 agents were meant for 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 such, Variola major virus and Variola minor virus meet that criterion. We also note that Variola major virus is a special case and that there are additional, specific requirements for Variola major virus in addition to the Tier 1 requirements. These specific requirements for Variola major virus and Variola minor virus do not apply to the other Tier 1 agents.

One commenter requested clarification that requirements are not applicable to diagnostic laboratories that may identify Variola major virus or Variola minor virus during the course of routine work, but would not otherwise “possess” these agents. We made no changes to the regulations based on this comment. We note that the clinical and diagnostic laboratory exemption found in section 5 of the regulations, including all of the reporting and safeguarding requirements, remains in effect.

Since the publication of the proposed rule, we became concerned that the proposed requirement for all persons with access to the Variola major or Variola minor virus to have a Top Secret clearance would have the unintended effect of preventing HHS/CDC researchers from being able to participate in collaborative work with international colleagues, such as representative of the World Health Organization. To address this concern, we have decided to modify the requirement to require only personnel with independent unescorted access to Variola major or Variola minor virus to have a Top Secret security clearance. The requirements that any access to Variola major or Variola minor would require approval from HHS/CDC and the approval of the Federal Select Agent Program would remain in effect.

Biosafety Plan

One commenter was concerned that specifying the “Biosafety in Microbiological and Biomedical Laboratories” (BMBL) (Ref 28) publication in the regulatory text would in effect incorporate the document by reference and therefore the BMBL should be published in the **Federal**

Register for public comment. We made no changes to the regulations based on this comment. The BMBL has not been incorporated by reference. The regulation clearly states that an individual or entity should “consider” the BMBL when developing a site specific biosafety plan. The BMBL is listed in the regulations because it provides useful guidance for how to work safely with a variety of pathogens. It also describes standard and special microbiological practices, safety equipment, and facilities (constituting Biosafety Levels 1–4). It is the document that is generally recognized as the national biosafety standard in the United States.

Another commenter recommended that we clarify features of containment infrastructure intended to facilitate biosafety of workers dealing with these materials. The commenter recommended the regulatory language read “The biosafety plan must contain sufficient information and documentation to describe the biosafety, physical and operational containment requirements for working with the select agent or toxin including any animals or plants intentionally or accidentally exposed to or infected with a select agent.” We made no changes to the regulations based on this comment since we believe the proposed language is clear and sufficient.

Another commenter recommended we remove the statement: “The occupational health program may also be made available to individuals without access to Tier 1 select agents and toxins.” We agree with the commenter and have eliminated that portion of the regulatory text.

Occupational Health Program

We also proposed that the biosafety plan must include provisions for the implementation of an occupational health program for individuals with access to Tier 1 select agents and toxins. Many commenters had questions and/or concerns regarding the addition of a requirement for an occupational health program. Commenters generally divided into two categories in their comments. Some commenters felt that the requirement was too vague to prove useful and that the requirement created an administrative burden without improving the overall biosafety of Tier 1 select agents and toxins. Other commenters indicated that the requirement could or would require entities to behave in a manner contrary to Health Insurance Portability and Accountability Act of 1996 (HIPAA). Commenters also felt that a preventive health and post-exposure program is

already available at registered entities and should not be a requirement in the regulations. We made no changes based on these comments.

While the select agent regulations do not supersede HIPAA, HIPAA does not prevent the requirement of the establishment of an occupational health program to address biosafety concerns for those handling select agents and toxins.

We anticipate that this requirement is already being met and will merely require those entities possessing a Tier 1 select agent or toxin to codify and document the systems and processes currently in place. Therefore, we do not believe registered entities possessing a Tier 1 select agent or toxin will endure significant additional costs associated with an occupational health program. While we have created specific guidance regarding this section, we are leaving the specifics of the occupational health program as performance-based standards in order to provide entities with flexibility in meeting these requirements. We have found this to be the most effective approach given the wide variety of regulated entities these regulations cover. Full guidance on an occupational health program may be found at www.selectagents.gov.

Restricted Experiments

We proposed to add language in order to expand the “restricted experiment” approval requirement to include all experiments involving the creation of drug resistant select agents that are not known to acquire that resistance naturally, if such acquisition could compromise the control of disease agents in humans, veterinary medicine, or agriculture regardless of the method or technology used to create the resistance. Previously, the restricted experiment language concerned only those experiments involving recombinant nucleic acids.

The restricted experiment definition currently covers the “deliberate transfer of a drug resistance trait to select agents that are not known to acquire the trait naturally, if such acquisition could compromise the use of the drug to control disease agents in humans, veterinary medicine or agriculture.” We have removed the phrase “use of the drug” and modified the language in the last sentence to read “deliberate transfer of a drug resistance trait to select agents that are not known to acquire the trait naturally, if such acquisition could compromise the control of disease agents in humans, veterinary medicine or agriculture.” We made this change because while the introduction of a drug resistance trait would normally

eliminate that drug as a therapeutic option to control the disease, there may be alternative drugs available to control the disease. Therefore, the new definition reads as follows: Restricted experiments are defined as: “(1) experiments that involve the deliberate transfer of, or selection for, a drug resistance trait to select agents that are not known to acquire the trait naturally, if such acquisition could compromise the control of disease agents in humans, veterinary medicine, or agriculture;” and “(2) experiments involving the deliberate formation of synthetic or recombinant nucleic acids containing genes for the biosynthesis of select toxins lethal for vertebrates at an LD₅₀ < 100 ng/kg body weight.”

It should be noted that restricted experiments are not prohibited experiments. However, an entity must seek permission prior to the initiation of a restricted experiment and receive approval from the Administrator or HHS Secretary. Approval for the performance of a restricted experiment or the possession of a product of a restricted experiment may involve meeting additional safety and/or security requirements as prescribed by the Federal Select Agent Program. Many experiments that involve the deliberate transfer of a drug resistant trait do not meet the definition of a restricted experiment because the drug is not used to control disease in humans, veterinary medicine, or agriculture. The Federal Select Agent Program encourages anyone who intends to conduct a select agent experiment utilizing drug resistance markers to submit that experiment for review so that they can be advised on whether the experiment would be considered a restricted experiment and require approval prior to its initiation.

One commenter stated that “denial of restricted experiments is an obstacle to the development of countermeasures instead of promoting real biosecurity.” We made no changes based on this comment. As mentioned previously, many experiments that involve the deliberate transfer of a drug resistant trait to a select agent do not meet the definition of a restricted experiment because the drug is not used to control disease in humans, veterinary medicine, or agriculture. The rationale for requiring a heightened review of experiments that involve introduction of a drug resistant trait to a select agent for therapeutically useful antibiotics is ultimately out of concern that what is made in the laboratory might not always remain in the laboratory and therefore present a public health or agricultural risk. For experimental protocols

utilizing transient drug resistant traits, it should be noted that mutants possessing those traits can be maintained without removal of the trait and therefore pose a potential risk to public health or agriculture. We therefore consider these protocols to fall under the restricted experiment section of the regulations.

Commenters also suggested aligning the restricted experiment language with the “NIH Guidelines for Research Involving Recombinant DNA Molecules” (NIH Guidelines) language that restricts and requires approval for experiments with pathogens involving drug resistance for therapeutically useful agents against that pathogen. We made no changes based on these comments. The definition of a restricted experiment is aligned with the NIH Guidelines and reads as “* * * select agents that are not known to acquire the resistance naturally, if such acquisition could compromise the control of disease agents in humans, veterinary medicine, or agriculture.” We have not expanded the definition to include the introduction of all drug resistant traits to a select agent but only to those traits used to control disease in humans, veterinary medicine, or agriculture.

Incident Response

One commenter argued that since the incident response plan must fully describe the entity’s response policies or procedures for failure of intrusion detection or alarm system, the Federal Select Agent Program should provide clarification as to what was meant by an intrusion detection system (IDS) and examples of what constitutes IDS. We have developed guidance that describes IDS as a sensor device or devices which triggers an alarm when a security breach occurs and notifies a response force (e.g., police, guards, etc.) capable of addressing any threat that may be present. This guidance also provides examples of various types of IDS. The guidance document may be found at www.selectagents.gov.

One commenter recommended that instead of using the word “etc.” in section 14(b) they recommended that the section state, “* * * and emergencies such as fire, gas leak, explosion, power outage, and other natural and man-made events.” We agreed with the commenter and revised the language.

While we did not propose any changes to section 73.14 (c)(6), a commenter recommended that the language regarding planning and coordination with local emergency responders be amended. Specifically, the commenter believed that biosafety, as opposed to biosecurity needs, would

be better addressed if this provision read as follows: “* * * emergency responders, including local public health authorities.” We made no changes to the section based on the comment since the proposed language would limit the concept to only public health authorities and not agricultural health. Emergency responders can also include police, fire and rescue service, and emergency medical service.

Training

We proposed to specify that the Responsible Official ensure maintenance of training records since there was no particular person designated as the entity’s required record keeper, only that a training record must be kept. We received no comments regarding this proposal.

We proposed to amend the regulations in 42 CFR 73.15 that contain provisions of mandatory training for staff and visitors who work in or visit areas where select agents or toxins are handled or stored to provide security awareness and incident response training. Commenters requested clarification concerning the required annual insider threat awareness briefings for those entities possessing a Tier 1 select agent or toxin as proposed in section 15(b) of the select agent regulations. The commenters asked that the content of these threat awareness briefings be made available to public health laboratories so that it could then be specifically customized for various regions of the country and include what are the minimum requirements, who the intended audience is, and what documentation will be needed to satisfy the requirement.

While we have created specific guidance regarding this section of the revised regulations, the guidance does not take the form of a prescriptive program. Given our experience with the select agent regulations and the wide variety of entities those regulations cover, we have found a broader approach to be most effective. The guidance documents developed in conjunction with this rule are, in part, a response to the questions and issues raised by the commenters. The document regarding annual insider threat awareness briefings includes a designated person to manage the assessment of laboratory personnel, laboratorian involvement in threat mitigation, and behaviors of concern as specific examples of best practices that we believe entities would be well served in adopting. Full guidance on this and other issues may be found at www.selectagents.gov.

One commenter proposed that the requirements for incident response training should remain as currently written to only include safety incident training via annual blood-borne pathogens, general safety, biological hygiene, chemical hygiene, and lab specific select agent training. We made no changes to the proposed requirement based on this comment because we believe that incident response training needs to be expanded so that personnel are trained in how to safeguard select agents and toxins during natural emergencies and man-made disasters.

Commenters requested clarification that refresher training would only be mandated when substantive changes are made to the plans including what level of retraining would be required and whether retraining would only be required for those areas of the plan that have been amended. We made no changes to the proposed requirements based on these comments. We believe that the regulatory language clearly states that training will need to be provided when significant processes are changed in the plan and that training will need to be provided to those individuals who are affected by these changes in the plan.

One commenter recommended that we consider the staff time it will take for visitor training. We made no changes to the proposed requirement based on this comment. First, we believe that it is very important that visitors receive the appropriate incidence response and security awareness training to protect their personal safety while in registered areas. We do not believe that the staff time needed to fulfill this requirement will cause a significant increase in time and effort when integrated into the current visitor training program.

One commenter requested clarification on the refresher training of escorted personnel and visitors because the commenter believed that refresher training is only required once a year, but does not happen with visitors or escorted personnel. We agreed with the commenter and have revised the language to read: "Refresher training must be provided annually for individuals with access approval from the HHS Secretary or Administrator or at such time as the registered individual or entity significantly amends its security, incident response, or biosafety plans."

Transfers

We proposed to clarify when "transportation in commerce" begins and ends to better allow registered entities to adequately address those situations when a select agent or toxin

is (1) ready to be packaged for transportation, (2) packaged for shipment, or (3) received and handled by a person with approval to access select agents and toxins. One commenter stated that the security of the package between steps (2) packaged for shipment and (3) received and handled by a person with approval to access select agents and toxins should be the sole responsibility of the courier. We made no changes to the language based on this comment. As stated in the preamble to the proposed rule, "transportation in commerce" begins when the select agent(s) or toxin(s) are packaged for shipment and ready for receipt by a courier and ends when the package is received by the intended recipient who is an individual approved by the HHS Secretary or Administrator to have access to select agents and toxins, following a security risk assessment by the Attorney General.

Commenters believed that the new provision outlined in section 16(f) meant that all transfers must be made by an individual approved by the HHS Secretary or Administrator to have access to select agents and toxins, following a security risk assessment by the Attorney General. We agreed with the commenters and revised the language to state that after authorization is provided by USDA/APHIS or HHS/CDC, the packaging of the select agent(s) and toxin(s) is performed by an individual approved by the HHS Secretary or Administrator to have access to select agents and toxins and is in compliance with all applicable laws concerning packaging.

Records

We proposed to clarify the current language that an accurate, current inventory needs to be maintained for each select agent that the entity possesses including synthetic select agent organisms and any animals or plants intentionally or unintentionally exposed to or infected with a select agent (including number and species, location, and appropriate disposition). Commenters argued that counting individual vials of replicating biological agents is costly, burdensome, and a major source of frustration for investigators. They further claimed that there is widespread concern that both counting vials and measuring volumes of individual vials are not effective means of increasing security and wondered if there was another way to account for inventory. Other commenters noted that animals infected with a select agent are part of ongoing experimentation and are thus part of working stocks rather than current

inventory and requested clarification on whether or not the term "animal" also included "arthropods."

We are making no changes to the regulations based on these comments. While we are aware of the burden resulting from the requirement to maintain an accurate and current inventory of each select agent and toxin held in long-term storage, we believe this is an essential element to establish security of select agents or toxins. We recognize that it may still be possible for an insider to steal a sample of an agent either from working stock or from an inventory without being detected. However, if an entity has a robust inventory management system, such incidents have a better chance of being detected. To assist registered entities in meeting the requirements for accurate inventories of materials in long term storage, we have developed guidance that may be found at www.selectagents.gov.

It should be noted that while the volume measurements the commenter references are required for inventories of select toxins, they are not required in the case of inventory of select agents held in long-term storage due, in part, to the points raised by the commenter. However, we disagree with the commenter's assessment that measuring volume in the case of select toxins and counting vials in general, as part of required inventory tracking of both select agents and toxins for registered entities, is not necessary.

We recognize that there has been some confusion between those infected animals (including arthropods) and plants considered to be "working stock" and those considered to be "inventory held in long term storage." To that end, we have developed specific guidance that will enable entities to better differentiate between these two categories. This guidance is available at www.selectagents.gov.

In order to clarify our intent regarding "working stock" and "inventory held in long term storage," as it relates to infected animals and plants, we are revising paragraph (a)(2) in section 17 of the select agent regulations to require an accurate, current accounting of any animals or plants intentionally or accidentally exposed to or infected with a select agent (including number and species, location, and appropriate disposition) instead of an accurate, current inventory of those animals or plants.

One commenter had concerns about tracking nucleic acids for laboratories, which generate bacterial mutants and perform reverse genetics. The commenter believed that this would be

incredibly time consuming, overly burdensome, and of no value. The commenter argued that the theft of viral genetic elements would be less useful to a person without scientific expertise and unnecessary for the individual with the skills.

We made no changes to the regulations based on this comment. It should be noted that not all recombinant material is regulated. The scenarios described by this commenter would not involve regulated nucleic acids. For example, bacterial genomes and viral genomes not determined to be infectious are not subject to these regulations. Additional guidance on this topic is available at www.selectagents.gov.

Administrative Review

We proposed to amend the regulations in 42 CFR 73.20 that addresses the administrative review of an individual or entity's denial, revocation, or suspension of registration or access approval. Specifically, we proposed to modify the current regulations in order to allow individuals more time to gather the necessary components of their appeal following the denial, limitation, or revocation of access approval. In addition, we proposed to remove the provision "Where the denial, revocation, or suspension of an individual's access approval is based upon identification by the Attorney General, the request for review will be forwarded to the Attorney General" to provide clarification that the decision regarding the appeal is determined by the HHS Secretary. We received comments supporting these proposed changes.

Guidance Documents

In the proposed rule, we specifically requested comment from the regulated community and any other interested persons on the need for and desirability of guidance documents that would serve to assist regulated entities in meeting the requirements of regulations. We were particularly interested in public comment regarding Web sites, articles, or other sources that may be useful in developing such guidance documents. We received a number of comments on the issue of guidance which are discussed below. As these comments pertain to the development of guidance documents and not to the regulations themselves, we have made no regulatory changes as a result. Guidance documents may be found at www.selectagents.gov.

Commenters stated that further sources of information, apart from interaction with Federal Select Agent

Program inspectors, should be made available to assist regulated entities in implementing the additional requirements. Other commenters urged that we develop guidance as a collaborative effort with a variety of subject matter experts both inside and outside the government.

We agreed with these comments and consulted with a wide variety of contributors including HHS and USDA subject matter experts, a National Science Advisory Board for Biosecurity report entitled "Enhancing Personnel Reliability among Individuals with Access to Select Agents" (Ref 24), the National Academies Committee on Laboratory Security and Personnel Reliability Assurance Systems for Laboratories Conducting Research on Biological Select Agents and Toxins report entitled "Responsible Research with Biological Select Agents and Toxins" (Ref 25), the Report from the Executive Order 13486 Working Group on Strengthening Laboratory Security in the United States (Ref 26), and a report from the Defense Science Board Task Force on Department of Defense Biological Safety and Security Program (Ref 27).

There exist a variety of ways for regulated entities to obtain information from the Federal Select Agent Program. HHS/CDC and USDA/APHIS may be contacted via email at lrsat@cdc.gov or Agricultural.Select.Agent.Program@aphis.usda.gov, respectively. Guidance is also available at www.selectagents.gov. The Federal Select Agent Program issues periodic email updates, which are sent to Responsible Officials and alternate Responsible Officials at all registered entities. We also hold workshops on various topics of concern to the regulated community. Examples of past workshops have discussed personnel reliability programs, security plans, preparing a registration package, and the inspection process.

Miscellaneous

Coordination Between USDA/APHIS and HHS/CDC

One commenter expressed general support for the harmonization of APHIS and CDC select agent regulations. The commenter stated that such coordination could be further achieved via joint inspections of registered entities. We are making no changes as a result of this comment since it is outside the scope of this rulemaking.

The commenter further stated that language and definitions used in the USDA/APHIS and HHS/CDC regulations should be consistent, citing HHS/CDC's

use of the term "biosafety" in 42 CFR 73.12 as compared to the term "biocontainment" found in USDA/APHIS's regulations in 7 CFR 331.12.

Since the Federal Select Agent Program is jointly administered by USDA/APHIS and HHS/CDC, we make every effort to achieve congruence between our various regulations. In certain cases, as a result of the differences between plant, animal and human select agents and toxins, the terminology employed must necessarily differ. The term "biocontainment" is found in the USDA/APHIS regulations in 7 CFR 331.12 relating to Plant Protection and Quarantine (PPQ) select agents and toxins while the term "biosafety" is found in the USDA/APHIS regulations in 9 CFR 121.12 relating to Veterinary Services (VS) select agents and toxins. "Biosafety" is the accurate term to describe procedures relating to humans or animals. However, the term "biocontainment" is more appropriate for describing procedures necessary to contain plant pathogens.

Animals or Plants Exposed to or Infected With Select Agents or Toxins

We proposed to require that security, biosafety, and incident response plans include provisions to address the safeguarding of animals or plants accidentally or intentionally exposed to or infected with select agents against unauthorized access, theft, loss or release. Commenters requested clarification about whether this requirement would be limited to experimental plants and animals that are possessed by and controlled by the registered entity. We made no changes to the requirement based on these comments. An entity's security, biosafety, and incident response plans should address any plants or animals within the entity that may be exposed to a select agent, regardless of whether or not the exposure was intentional or accidental.

Another commenter requested clarification on whether the term "animal" included arthropods. We made no changes based on this comment as the term "animal" does include arthropods.

Cost

Commenters requested that we consider the indirect consequences of continuing to include agents and toxins on the select agent list, the negative effect of the proposed rule changes on the potential workforce for select agent research, and the possibility that additional regulations concerning Tier 1 select agents and toxins will mandate more federal oversight and institutional

compliance requirements, resulting in increased costs to taxpayers both directly and indirectly through reduced research efficiency. Commenters requested that a full financial and scientific impact of these added requirements be carefully assessed prior to implementation, especially the increased costs to academic institutions with no associated funding, and the increased burden on investigators already having difficulty finding time for research and experimentation. The commenters also stated that the timeline for implementation of the new requirements should be considered and disclosed to affected entities.

A cornerstone of the Federal Select Agent Program is to establish and enforce safety and security measures to prevent access to select agents and toxins for use in domestic or international terrorism or for any other criminal purpose. An equally important function of the Federal Select Agent Program is to allow for the appropriate availability of biological agents and toxins for research, education, and other legitimate purposes. To achieve both requires the balancing of the need for continuing biological research with requiring a level of safety and security commensurate with the risks posed by these biological agents and toxins. We understand that safety and security requirements cost money and that money in the area of biological research is often a scarce commodity. However, we are also aware that a lack of adequate safety and security requirements could result in damages measured both in dollars and in human lives. It is our determination, based on the information available to us, that the additional requirements would not constitute a significant economic or recordkeeping burden on the regulated entities. We also believe that in many cases these regulations serve to codify systems and procedures already in use by a majority of regulated entities.

To achieve regulatory flexibility, we have included a phase-in period for the effective date for certain requirements of the revised regulations which should allow entities to comply without causing disruption or termination of research or educational projects. As noted in the "Effective Dates" portion of this document, sixty (60) days from the publication of the final rule, entities will need to be in compliance with sections 1–10, 13, 16, and 20. One hundred and eighty days after the publication of the final rule, entities will need to be in compliance with sections 11 (Security), 12 (Biosafety), 14 (Incident response), and 15 (Training).

Request for a Letter of Interpretation Policy

One commenter suggested that the Federal Select Agent Program should augment guidance documents with a letter of interpretation policy. Specifically, the commenter recommended that select agent registrants should be able to submit written requests detailing a compliance issue and receive back a written letter of interpretation from the Federal Select Agent Program in a similar manner as employers can submit requests for interpretation to the Department of Labor Occupational Safety and Health Administration. We are making no changes to the select agent regulations based on this comment because it is outside the scope of this rule.

III. Required Regulatory Analyses

A. Executive Orders 12866 and 13563

Executive Orders 12866 and 13563 direct agencies to assess all costs and benefits of available regulatory alternatives and, if regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety effects, distributive impacts, and equity). Executive Order 13563 emphasizes the importance of quantifying both costs and benefits, of reducing costs, of harmonizing rules, and of promoting flexibility.

Under Executive Order 12866, HHS must determine whether a regulatory action is "significant." A "significant regulatory action" under Executive Order 12866 is defined as (1) an action that is likely to result in a rule that may have an annual effect on the economy of \$100 million or more, or adversely and materially affects a sector of the economy, productivity, competition, jobs, the environment, public health or safety, or state, local or tribal governments or communities (or an economically significant action); (2) creates a serious inconsistency or otherwise interferes with an action taken or planned by another agency; (3) materially alters the budgetary impact of entitlements, grants, user fees or loan programs or the rights and obligations of recipients; or (4) raises novel legal or policy issues. Because this rulemaking proposes changes to how a subset of select agents and toxins is protected, this rule has been determined to be "significant" under Executive Order 12866 and, therefore, has been reviewed by the Office of Management and Budget (OMB).

We have prepared an economic analysis for this rule. The economic

analysis provides a cost-benefit analysis, as required by Executive Order 12866, and a final regulatory flexibility analysis (See Section III.B. of this Preamble) that examines the potential economic effects of this rule on small entities, as required by the Regulatory Flexibility Act. The economic analysis is summarized below. Copies of the full analysis are available on www.regulations.gov, Docket CDC–2012–0012, at www.selectagents.gov or by contacting the person listed under **FOR FURTHER INFORMATION CONTACT**.

Summary of the Regulatory Impact Analysis

The Public Health Security and Bioterrorism Preparedness and Response Act of 2002 (Pub. L. 107–188) provides for the regulation of certain biological agents and toxins that have the potential to pose a severe threat to human, animal, or plant health, or to animal or plant products. The Animal and Plant Health Inspection Service (APHIS) and the Centers for Disease Control and Prevention (CDC) have primary responsibility for implementing the provisions of the Act within the Department of Agriculture and the Department of Health and Human Services, respectively. Within APHIS, Veterinary Services (VS) select agents and toxins are those that have been determined to have the potential to pose a severe threat to animal health or animal products, and Plant Protection and Quarantine (PPQ) select agents and toxins are those that have been determined to have the potential to pose a severe threat to plant health or plant products. HHS select agents and toxins are those that have been determined to have the potential to pose a severe threat to human health. USDA/APHIS and HHS/CDC coordinate regulatory activities for overlap select agents and toxins that have been determined to pose a severe threat to human and animal health or animal products.

Sections 201 and 212(a)(2) of the Act require a biennial review and republication of the select agent and toxin list, with revisions as appropriate in accordance with this law. These final rules will implement the recommendations of the third biennial review, and incorporate risk-based tiering of the select agent and toxin lists, as required by Executive Order 13546, "Optimizing the Security of Biological Select Agents and Toxins in the United States." In addition, the APHIS and CDC final rules will codify several amendments to the regulations, including the addition of definitions and clarification of language concerning security, training, biosafety/

biocontainment, and incident response. These changes will improve the applicability and effectiveness of the select agent regulations and provide for enhanced program oversight.

Based on information obtained through site-specific inspections, we believe most registered entities already have in place many of the information security requirements set forth in the final rules, and compliance costs of the rules are therefore expected to be minimal. Entities more likely to be affected will be laboratories and other institutions conducting research and related activities that involve the use of select agents and toxins categorized as Tier 1. These entities will be required to conduct a pre-access suitability assessment of individuals with access to a Tier 1 select agent or toxin, as well as enroll these individuals in an occupational health program.

The rules would reduce the period that FBI background checks are valid from five to three years. This increased frequency would effectively increase the cost of background checks by 67 percent. Based on the current number of individuals required to have the background checks, we estimate that the present value of these government-borne costs over five years will increase by \$1.96 million across all registered

entities. The annual increase in costs will total about \$432,000.

While we expect few if any of the registered entities to incur significant compliance costs, required documentation of measures already regularly performed with respect to biocontainment/biosafety, incident response, information security, and ongoing suitability assessment may require additional time of personnel. We estimate additional recurring costs related to information security, such as for software updates, could total about \$2 million per year, or about \$5,500 per entity, in the unlikely event that none of the entities already uses equivalent information security measures. As noted, many of these costs are already currently borne by entities in their conduct of generally recognized best practices. For entities possessing a Tier 1 agent or toxin, the costs of pre-access suitability assessments and occupational health programs are estimated to total between \$2.8 million and \$4.4 million, or between about \$9,600 and \$15,100 per entity, on average. Again, actual costs incurred are unlikely to reach these maximum cost ranges; we expect that many of the entities with a Tier 1 agent or toxin already conduct assessments and have

health programs similar or equivalent to those required by the final rules.

The benefits of strengthened safeguards against the unintentional or deliberate release of a select agent or toxin greatly exceed compliance costs of the rules. As an example of losses that can occur, the October 2001 anthrax attacks caused 5 fatalities and 17 illnesses, disrupted business and government activities (including \$2 billion in lost revenues for the Postal Service), and required more than \$23 million to decontaminate one Senate office building and \$3 billion to decontaminate postal facilities and procure mail-sanitizing equipment. Deliberate introduction greatly increases the probability of a select agent becoming established and causing wide-ranging and devastating impacts to the economy, other disruptions to society, and diminished confidence in public and private institutions.

The amended regulations will enhance the protection of human, animal, and plant health and safety. The final rules will reduce likelihood of the accidental or intentional release of a select agent or toxin. Benefits of the rules will derive from the greater probability that a release will be prevented from occurring.

SUMMARY OF THE ESTIMATED MAXIMUM ADDITIONAL COSTS ATTRIBUTABLE TO THE FINAL RULES FOR THE FEDERAL GOVERNMENT AND AFFECTED ENTITIES ¹

	Unit cost	Number of units	Total additional cost
Added Annual Cost for the Federal Government			
Increased frequency of FBI/CJIS background checks.	\$240 per person	13,488 approved SRAs; checks valid for three years.	\$432,000 per year ² .
Added Recurring Costs for Affected Entities ³			
Submission of Security Plan	\$4.95 per submission	Estimated 130 annual renewals.	\$643.50 per year.
Information Security ⁴			
network connectivity monitoring (encryption software).	\$24–\$37 per license	365 registered entities	\$8,760–\$13,505 per licensing period.
network connectivity monitoring (firewall software).	\$79–\$199 per license	365 registered entities	\$28,835–\$72,635 per licensing period.
malware software ⁴ (intrusion detection) ...	\$15 per computer	365 registered entities	\$5,475 per software update.
malware software (antivirus)	\$80 per user per year	13,488 approved SRAs	\$1,079,040 per year.
system software updates (dedicated time for IT Specialist).	\$2,400 per year	365 registered entities	\$876,000 per year.
Total ⁵	approximately \$2 million annually, or on average about \$5,500 per registered entity.		
Added Costs for Entities that have a Tier 1 Select Agent or Toxin ^{3,6}			
Pre-suitability Assessment	\$100–\$120 per person	13,488 approved SRAs	\$1.35–1.62 million.
Occupational Health Program	\$107–\$204 per person	13,488 approved SRAs	\$1.44–2.75 million.

SUMMARY OF THE ESTIMATED MAXIMUM ADDITIONAL COSTS ATTRIBUTABLE TO THE FINAL RULES FOR THE FEDERAL GOVERNMENT AND AFFECTED ENTITIES ¹—Continued

	Unit cost	Number of units	Total additional cost
Total ⁷	approximately \$2.8 million–\$4.4 million, or on average about \$9,600–\$15,100 per entity with a Tier 1 agent or toxin		

¹ The costs for registered entities summarized in this table are the estimated maximum additional expenditures that would be incurred, if none of the entities currently meets any of the additional security requirements set forth in the final rules. In addition, there will be the opportunity cost of additional time required to modify biosecurity and incident response plans and to conduct audits. Entities will be required to conduct complete inventory audits of all select agents and toxins in long-term storage upon the physical relocation of a collection or inventory of select agents or toxins, upon the departure or arrival of a principal investigator for those select agents or toxins, or in the event of a theft or loss of a select agent or toxin. Time costs are noted qualitatively in the Benefits and Costs section of this analysis.

² The annual additional cost estimate assumes a uniform distribution of the 13,488 background checks over three years.

³ Based on site inspections, many of the entities currently have provisions in place similar or equivalent to those required.

⁴ Several of the recurring costs are associated with technological updating of information security, such as firewall and malware software updates. Estimated costs across all entities are uncertain as information is unavailable regarding the number of computers per affected entity. The estimates assume a single computer per entity is used for covered work.

⁵ Assumes costs of licensing and software updates are incurred annually.

⁶ Estimated costs are likely overstated as not all SRA-approved individuals will have access to Tier 1 select agents and toxins.

⁷ Average cost per entity is based on 292 entities that are registered to possess a Tier 1 agent or toxin.

B. Regulatory Flexibility Act

The Regulatory Flexibility Act (RFA) (5 U.S.C. 601 *et seq.*) requires an agency to consider the potential impact of its regulations on small entities, including small businesses, small governmental units, and small not-for-profit organizations. We have prepared an economic analysis for this rule. The economic analysis provides a cost-benefit analysis, as required by Executive Order 12866, and a final regulatory flexibility analysis that examines the potential economic effects of this rule on small entities, as required by the Regulatory Flexibility Act. Based on the economic analysis, which is available at www.selectagents.gov, we do not expect the rule to have a significant economic impact on small entities. In the absence of significant economic impacts, we have not identified alternatives that would minimize such impacts.

C. Paperwork Reduction Act of 1995

In accordance with section 3507(d) of the Paperwork Reduction Act of 1995 (44 U.S.C. 3501 *et seq.*), the information collection or recordkeeping requirements included in this final rule will be reviewed by the Office of

Management and Budget (OMB) as a revision to existing OMB Control Number 0920–0576, expiration 10/31/2014.

USDA/APHIS and HHS/CDC are asking OMB to approve, for 3 years, the use of these information collections, associated with its efforts to more closely regulate select agents or toxins that could be used to commit acts of domestic or international terrorism. We are soliciting comments from the public (as well as affected agencies) concerning this information collection activity. USDA/APHIS and HHS/CDC need this outside input to help accomplish the following:

- (1) Evaluate whether the proposed information collection is necessary for the proper performance of our agency's functions, including whether the information will have practical utility;
- (2) Evaluate the accuracy of our estimate of the burden of the proposed information collection, including the validity of the methodology and assumptions used;
- (3) Enhance the quality, utility, and clarity of the information to be collected; and
- (4) Minimize the burden of the information collection on those who are

to respond (such as through the use of appropriate automated, electronic, mechanical, or other technological collection techniques or other forms of information technology; *e.g.*, permitting electronic submission of responses).

Estimate of burden: Public reporting burden for this collection of information is estimated to average 2.3187883 hours per response.

Respondents: Researchers, universities, research and development organizations, commercial manufacturers, non-profit institutions, diagnostic laboratories and other interested parties who possess, use, or transfer agents or toxins deemed a severe threat to human, animal or plant health, or to animal or plant products.

Estimated annual number of respondents: 386.

Estimated annual number of responses per respondent: 12.

Estimated annual number of responses: 4,721.

Estimated total annual burden on respondents: 10,947 hours. (Due to averaging, the total annual burden hours may not equal the product of the annual number of responses multiplied by the reporting burden per response.)

Section	Form name	Number of respondents	Number of responses per respondent	Average burden per response (in hours)	Total burden hours
9 CFR 121.5 and 6, 7 CFR 331.5, 43 CFR 73.5 and 6.	Report of Identification of a Select Agent or Toxin.	161	3	1	299
§ 121.7, § 331.7, § 73.7	Application for Registration	7	1	5	35
§ 121.7, § 331.7, § 73.7	Amendment to a Certificate of Registration.	380	7	1	2,660
§ 121.11, § 331.11, § 73.11	Security Plan	380	1	5	1,900
§ 121.12, § 331.12, § 73.12	Biosafety/Biocontainment Plan	380	1	8	3,040
§ 121.13, § 331.13, § 73.13	Request Regarding a Restricted Experiment.	160	1	2	320
§ 121.14, § 331.14, § 73.14	Incident Response Plan	380	1	5	1,900
§ 121.15, § 331.15, § 73.15	Training	380	1	1	380

Section	Form name	Number of respondents	Number of responses per respondent	Average burden per response (in hours)	Total burden hours
§ 121.16, § 331.16, § 73.16	Request to Transfer Select Agents and Toxins.	290	1	2	580
§ 121.17, § 331.17, § 73.17	Records	295	1	0.5	148
§ 121.19, § 331.19, § 73.19	Notification of Theft, Loss, or Release.	195	1	2	390

Copies of this information collection may be obtained by calling the CDC Reports Clearance Officer at (404) 639-5960 or sending an email to omb@cdc.gov. HHS/CDC is requesting continued OMB approval to collect this information through the use of five updated forms. These forms are: (1) Application for Registration, (2) Transfer of Select Agent or Toxin Form, (3) Facility Notification of Theft, Loss, or Release Form, (4) Clinical and Diagnostic Laboratory Reporting Form, and (5) Request for Exemption.

D. Executive Order 12988: Civil Justice Reform

This rule has been reviewed under Executive Order 12988, Civil Justice Reform. Once the final rule is in effect: (1) All State and local laws and regulations that are inconsistent with this rule will be preempted; (2) no retroactive effect will be given to this rule; and (3) administrative proceedings will not be required before parties may file suit in court challenging this rule.

E. Executive Order 13132: Federalism

This rule has been reviewed under Executive Order 13132, Federalism. The review reveals that this regulation will not have substantial and direct effects on Tribal governments and will not have significant Tribal implications.

F. Plain Writing Act of 2010

Under Public Law 111-274 (October 13, 2010), HHS has attempted to use plain language in promulgating the rule consistent with the Plain Writing Act guidelines.

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24. National Science Advisory Board for Biosecurity report: “Enhancing Personnel Reliability among Individuals with Access to Select Agents” (<http://oba.od.nih.gov/biosecurity/meetings/200905T/NSABB%20Final%20Report%20on%20PR%205-29-09.pdf>).
25. Responsible Research with Biological Select Agents and Toxins, Committee on Laboratory Security and Personnel Reliability Assurance Systems for Laboratories Conducting Research on Biological Select Agents and Toxins, National Research Council of the National Academies (<http://www8.nationalacademies.org/cp/projectview.aspx?key=49097>).
26. Report of the Working Group on Strengthening the Biosecurity of the United States, Executive Order 13486 Working Group (<http://edocket.access.gpo.gov/2009/pdf/E9-818.pdf>).
27. Defense Science Board Task Force on Department of Defense Biological Safety and Security Program (<http://www.acq.osd.mil/dsb/reports/ADA499977.pdf>).
28. *Biosafety in Microbiological and Biomedical Laboratories* (<http://www.cdc.gov/biosafety/publications/bmbl5/index.htm>).

List of Subjects in 42 CFR Part 73

Biologics, Packaging and containers, Penalties, Reporting and recordkeeping requirements, Transportation.

Dated: September 28, 2012.

Kathleen Sebelius,
Secretary.

For the reasons stated in the preamble, the Centers for Disease Control and Prevention, United States Department of Health and Human Services, amends 42 CFR part 73 as follows:

PART 73—POSSESSION, USE, AND TRANSFER OF SELECT AGENTS AND TOXINS

■ 1. The authority citation for part 73 continues to read as follows:

Authority: 42 U.S.C. 262a; sections 201–204, 221 and 231 of Title II of Public Law 107–188, 116 Stat. 637 (42 U.S.C. 262a).

■ 2. Add § 73.0 to read as set forth below.

§ 73.0 Applicability and related requirements.

All individuals and entities that possess SARS-CoV, Lujo virus, or Chapare virus must provide notice to CDC regarding their possession of SARS-CoV, Lujo virus, or Chapare virus on or before November 5, 2012. Currently registered individuals and entities possessing SARS-CoV, Lujo virus, or Chapare virus must meet all the requirements of this part by December 4, 2012. All previously unregistered individuals and entities possessing SARS-CoV, Lujo virus, or Chapare virus must meet all of the requirements of this part by April 3, 2013.

■ 3. Section 73.1 is amended by adding, in alphabetical order, definitions of *Conotoxins*, *Information security*, *Occupational exposure*, *Recombinant nucleic acids*, *Security barrier*, and *Synthetic nucleic acids* to read as set forth below.

§ 73.1 Definitions.

* * * * *

Conotoxins means short, paralytic alpha conotoxins containing the following amino acid sequence X₁CCX₂PACGX₃X₄X₅X₆CX₇, whereas:

- (1) C = Cysteine residues are all present as disulfides, with the 1st and 3rd Cysteine, and the 2nd and 4th Cysteine forming specific disulfide bridges;
- (2) The consensus sequence includes known toxins α-MI and α-GI (shown above) as well as α-GIA, Ac1.1a, α-CnIA, α-CnIB;
- (3) X₁ = any amino acid(s) or Des-X;
- (4) X₂ = Asparagine or Histidine;
- (5) P = Proline;
- (6) A = Alanine;
- (7) G = Glycine;
- (8) X₃ = Arginine or Lysine;
- (9) X₄ = Asparagine, Histidine, Lysine, Arginine, Tyrosine, Phenylalanine or Tryptophan;

- (10) X₅ = Tyrosine, Phenylalanine, or Tryptophan;
- (11) X₆ = Serine, Threonine, Glutamate, Aspartate, Glutamine, or Asparagine;
- (12) X₇ = Any amino acid(s) or Des X; and
- (13) “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.

* * * * *

Information security means protecting information and information systems from unauthorized access, use, disclosure, disruption, modification, or destruction in order to provide—

(1) Integrity, which means guarding against improper information modification or destruction, and includes ensuring information authenticity;

(2) Confidentiality, which means preserving authorized restrictions on access and disclosure, including means for protecting personal privacy and proprietary information; and

(3) Availability, which means ensuring timely and reliable access to and use of information.

Occupational exposure means any reasonably anticipated skin, eye, mucous membrane, parenteral contact, or respiratory aerosol exposure to select agents or toxins that may result from the performance of an employee’s duties.

* * * * *

Recombinant nucleic acids means:

(1) Molecules that are constructed by joining nucleic acid molecules and that can replicate in a living cell or

(2) Molecules that result from the replication of those described in paragraph (1) of this definition.

* * * * *

Security barrier means a physical structure that is designed to prevent entry by unauthorized persons.

* * * * *

Synthetic nucleic acids means:

(1) Molecules that are chemically or by other means synthesized or amplified, including those that are chemically or otherwise modified but can base pair with naturally occurring nucleic acid molecules (*i.e.*, synthetic nucleic acids) or

(2) Molecules that result from the replication of those described in paragraph (1) of this definition.

* * * * *

■ 4. Section 73.3 is amended as follows:

■ a. By adding a sentence to the end of paragraph (a) to read as set forth below.
■ b. By revising paragraph (b) to read as set forth below.

■ c. In paragraph (c) introductory text, by adding the phrase “and/or Synthetic” after the word “Recombinant” each time it appears.

- d. In paragraph (c)(2) introductory text, by adding the phrase “and/or synthetic” after the word “Recombinant.”
- e. By revising paragraph (d)(3) to read as set forth below.
- f. By adding a new paragraph (d)(4) to read as set forth below.
- g. By adding a new paragraph (d)(5) to read as set forth below.
- h. By revising paragraph (e) to read as set forth below.
- i. In paragraph (f)(3)(i), by removing the words “Lassa fever virus” and “South American Haemorrhagic Fever virus (Junin, Machupo, Sabia, Flexal, Guanarito)” and by adding, after “Botulinum neurotoxins,” the term “Botulinum neurotoxin producing species of *Clostridium*.”

§ 73.3 HHS select agents and toxins.

(a) * * * The select agents and toxins marked with an asterisk (*) are designated as Tier 1 select agents and toxins and are subject to additional requirements as listed in this part.

(b) 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 X₁CCX₂PACGX₃X₄X₅X₆CX₇)
- 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 (subtypes A–E)
- T–2 toxin
- Tetrodotoxin
- Tick-borne encephalitis virus

- Far Eastern subtype
- Siberian subtype
- Kyasanur Forest disease virus
- Kyasanur haemorrhagic fever virus
- Variola major virus (Smallpox virus) *
- Variola minor virus (Alastrim) *
- Yersinia pestis* *

* * * * *

(d) * * *

(3) Except as required in § 73.16(l), the aggregate amount of the toxin under the control of a principal investigator, treating physician or veterinarian, or commercial manufacturer or distributor does not, at any time, exceed the following amounts: 100 mg of Abrin; 0.5 mg of Botulinum neurotoxins; 100 mg of Conotoxins (Short, paralytic alpha conotoxins containing the following amino acid sequence X₁CCX₂PACGX₃X₄X₅X₆CX₇); 1,000 mg of Diacetoxyscirpenol; 100 mg of Ricin; 100 mg of Saxitoxin; 5 mg of Staphylococcal enterotoxins (subtypes A–E); 1,000 mg of T–2 toxin; or 100 mg of Tetrodotoxin.

(i) The amounts are transferred only after the transferor uses due diligence and documents that the recipient has a legitimate need (*i.e.*, reasonably justified by a prophylactic, protective, bona fide research, or other peaceful purpose) to handle or use such toxins. Notwithstanding the provisions of paragraph (d) of this section, the HHS Secretary retains the authority to, without prior notification, inspect and copy or request the submission of the due diligence documentation to the CDC.

(ii) Reports to CDC if they detect a known or suspected violation of Federal law or become aware of suspicious activity related to a toxin listed in this part.

(4) An animal inoculated with or exposed to an HHS select toxin.

(5) Any South American genotypes of Eastern Equine Encephalitis Virus and any West African Clade of Monkeypox virus provided that the individual or entity can verify that the agent is within the exclusion category.

(e) An attenuated strain of a select agent or an inactive form of a select toxin may be excluded from the requirements of this part based upon a determination by the HHS Secretary that the attenuated strain or inactivated toxin does not pose a severe threat to public health and safety.

(1) To apply for exclusion, an individual or entity must submit a written request and supporting scientific information. A written decision granting or denying the request will be issued. An exclusion will be effective upon notification to the

applicant. Exclusions will be listed on the National Select Agent Registry Web site at <http://www.selectagents.gov/>.

(2) If an excluded attenuated strain or inactivated toxin is subjected to any manipulation that restores or enhances its virulence or toxic activity, the resulting select agent or toxin will be subject to the requirements of this part.

* * * * *

■ 5. Section 73.4 is amended as follows:

- a. By adding a sentence to the end of paragraph (a) to read as set forth below.
- b. By revising paragraph (b) to read as set forth below.
- c. In paragraph (c) introductory text, by adding the phrase “and/or Synthetic” after the word “Recombinant” each time it appears.
- d. In paragraph (c)(2) introductory text, by adding the phrase “and/or synthetic” after the word “Recombinant.”
- e. By adding a new paragraph (d)(3) to read as set forth below.
- f. By revising paragraph (e) to read as set forth below.
- g. In paragraph (f)(3)(i), by removing the words “*Brucella melitensis*, Hendra virus, Nipah virus, Rift Valley fever virus, and Venezuelan equine encephalitis virus” and adding, after “*Bacillus anthracis*”, the terms “*Burkholderia mallei*” and “*Burkholderia pseudomallei*” in their place.

§ 73.4 Overlap select agents and toxins.

(a) * * * The select agents and toxins marked with an asterisk (*) are designated as Tier 1 select agents and toxins and are subject to additional requirements as listed in this part.

(b) 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

* * * * *

(d) * * *

(3) Any subtypes of Venezuelan equine encephalitis virus except for Subtypes IAB or IC provided that the individual or entity can verify that the agent is within the exclusion category.

(e) An attenuated strain of a select agent or an inactive form of a select toxin may be excluded from the requirements of this part based upon a determination by the HHS Secretary or Administrator that the attenuated strain

or inactivated toxin does not pose a severe threat to public health and safety, to animal health or to animal products.

(1) To apply for exclusion, an individual or entity must submit a written request and supporting scientific information. A written decision granting or denying the request will be issued. An exclusion will be effective upon notification to the applicant. Exclusions will be listed on the National Select Agent Registry Web site at <http://www.selectagents.gov/>.

(2) If an excluded attenuated strain or inactivated toxin is subjected to any manipulation that restores or enhances its virulence or toxic activity, the resulting select agent or toxin will be subject to the requirements of this part.

* * * * *

■ 6. Section 73.5 is amended as follows:

■ a. By amending paragraph (a)(3)(i) to remove the words "Lassa fever virus" and "South American Haemorrhagic Fever viruses (Junin, Machupo, Sabia, Flexal, Guanarito)" and by adding, after "Botulinum neurotoxins," the term "Botulinum neurotoxin producing species of *Clostridium*."

■ b. By revising paragraph (e) to read as set forth below.

§ 73.5 Exemptions for HHS select agents and toxins.

* * * * *

(e) The HHS Secretary may temporarily exempt an individual or entity from the requirements of this part based on a determination that the exemption is necessary to provide for the timely participation of the individual or entity in response to a domestic or foreign public health emergency. With respect to the emergency involved, the exemption may not exceed 30 calendar days, except that one extension of an additional 30 calendar days may be granted.

■ 7. Section 73.6 is amended as follows:

■ a. By amending (a)(3)(i) to remove the words "*Brucella melitensis*, Hendra virus, Nipah virus, Rift Valley fever virus, or Venezuelan equine encephalitis virus" and adding, after "*Bacillus anthracis*", the terms "*Burkholderia mallei*" and "*Burkholderia pseudomallei*" in their place.

■ b. By revising paragraph (e) to read as set forth below.

§ 73.6 Exemptions for overlap select agents and toxins.

* * * * *

(e) The HHS Secretary may temporarily exempt an individual or entity from the requirements of this part based on a determination that the exemption is necessary to provide for

the timely participation of the individual or entity in response to a domestic or foreign public health emergency. With respect to the emergency involved, the exemption may not exceed 30 calendar days, except that one extension of an additional 30 calendar days may be granted.

* * * * *

■ 8. Section 73.9 is amended as follows:

■ a. In paragraph (a)(4), by removing the word "and."

■ b. By redesignating paragraph (a)(5) as paragraph (a)(6).

■ c. By adding a new paragraph (a)(5) to read as set forth below.

■ d. By revising the first sentence of paragraph (b) to read as set forth below.

■ e. In paragraph (c)(1), by removing the words "*Brucella melitensis*," "Hendra virus," "Lassa fever virus," "Nipah virus," "Rift Valley fever virus," "South American Haemorrhagic Fever viruses (Junin, Machupo, Sabia, Flexal, Guanarito)," and "Venezuelan equine encephalitis virus" and adding, after "Botulinum neurotoxins," the terms "Botulinum neurotoxin producing species of *Clostridium*, *Burkholderia mallei*, *Burkholderia pseudomallei*".

§ 73.9 Responsible Official.

(a) * * *

(5) Have a physical (and not merely a telephonic or audio/visual) presence at the registered entity to ensure that the entity is in compliance with the select agent regulations and be able to respond in a timely manner to onsite incidents involving select agents and toxins in accordance with the entity's incident response plan, and

* * * * *

(b) An entity may designate one or more individuals to serve as an alternate Responsible Official, who acts for the Responsible Official in his/her absence.

* * * * *

* * * * *

■ 9. Section 73.10 is amended as follows:

■ a. By redesignating paragraphs (e) through (j) as paragraphs (f) through (k) respectively.

■ b. By adding a new paragraph (e) to read as set forth below.

■ c. In newly redesignated paragraph (j), by removing the word "five" and adding in its place "three".

§ 73.10 Restricting access to select agents and toxins; security risk assessments.

* * * * *

(e) A person with a valid approval from the HHS Secretary or Administrator to have access to select agents and toxins may request, through his or her Responsible Official, that the

HHS Secretary or Administrator provide their approved access status to another registered individual or entity for a specified period of time.

* * * * *

■ 10. Section 73.11 is amended as follows:

■ a. By revising paragraph (b) to read as set forth below.

■ b. By revising paragraph (c)(2) to read as set forth below.

■ c. By adding new paragraphs (c)(8), (c)(9), and (c)(10) to read as set forth below.

■ d. By redesignating paragraphs (e) and (f) as paragraphs (g) and (h), respectively and by revising newly redesignated paragraph (g) to read as set forth below.

■ e. By adding new paragraphs (e) and (f) to read as set forth below.

§ 73.11 Security.

* * * * *

(b) The security plan must be designed according to a site-specific risk assessment and must provide graded protection in accordance with the risk of the select agent or toxin, given its intended use. A current security plan must be submitted for initial registration, renewal of registration, or when requested.

(c) * * *

(2) Contain provisions for the control of access to select agents and toxins, including the safeguarding of animals, including arthropods, or plants intentionally or accidentally exposed to or infected with a select agent, against unauthorized access, theft, loss or release.

* * * * *

(8) Describe procedures for how the Responsible Official will be informed of suspicious activity that may be criminal in nature and related to the entity, its personnel, or its select agents or toxins; and describe procedures for how the entity will notify the appropriate Federal, State, or local law enforcement agencies of such activity.

(9) Contain provisions for information security that:

(i) Ensure that all external connections to systems which manage security for the registered space are isolated or have controls that permit only authorized and authenticated users;

(ii) Ensure that authorized and authenticated users are only granted access to select agent and toxin related information, files, equipment (e.g., servers or mass storage devices) and applications as necessary to fulfill their roles and responsibilities, and that access is modified when the user's roles and responsibilities change or when

their access to select agents and toxins is suspended or revoked;

(iii) Ensure that controls are in place that are designed to prevent malicious code (such as, but not limited to, computer virus, worms, spyware) from compromising the confidentiality, integrity, or availability of information systems which manage access to registered spaces in § 73.11 or records in § 73.17;

(iv) Establish a robust configuration management practice for information systems to include regular patching and updates made to operating systems and individual applications; and

(v) Establish procedures that provide backup security measures in the event that access control systems, surveillance devices, and/or systems that manage the requirements of section 17 of this part are rendered inoperable.

(10) Contain provisions and policies for shipping, receiving, and storage of select agents and toxins, including documented procedures for receiving, monitoring, and shipping of all select agents and toxins. These provisions must provide that an entity will properly secure containers on site and have a written contingency plan for unexpected shipments.

* * * * *

(e) Entities must conduct complete inventory audits of all affected select agents and toxins in long-term storage when any of the following occur:

(1) Upon the physical relocation of a collection or inventory of select agents or toxins for those select agents or toxins in the collection or inventory;

(2) Upon the departure or arrival of a principal investigator for those select agents and toxins under the control of that principal investigator; or

(3) In the event of a theft or loss of a select agent or toxin, all select agents and toxins under the control of that principal investigator.

(f) In addition to the requirements contained in paragraphs (c) and (d) of this section, the security plan for an individual or entity possessing a Tier 1 select agent or toxin must also:

(1) Describe procedures for conducting a pre-access suitability assessment of persons who will have access to a Tier 1 select agent or toxin;

(2) Describe procedures for how an entity's Responsible Official will coordinate their efforts with the entity's safety and security professionals to ensure security of Tier 1 select agents and toxins and share, as appropriate, relevant information; and

(3) Describe procedures for the ongoing assessment of the suitability of personnel with access to a Tier 1 select

agent or toxin. The procedures must include:

(i) Self- and peer-reporting of incidents or conditions that could affect an individual's ability to safely have access to or work with select agents and toxins, or to safeguard select agents and toxins from theft, loss, or release;

(ii) The training of employees with access to Tier 1 select agents and toxins on entity policies and procedures for reporting, evaluation, and corrective actions concerning the assessment of personnel suitability; and

(iii) The ongoing suitability monitoring of individuals with access to Tier 1 select agents and toxins.

(4) Entities with Tier 1 select agents and toxins must prescribe the following security enhancements:

(i) Procedures that will limit access to a Tier 1 select agent or toxin to only those individuals who are approved by the HHS Secretary or Administrator, following a security risk assessment by the Attorney General, have had an entity-conducted pre-access suitability assessment, and are subject to the entity's procedures for ongoing suitability assessment;

(ii) Procedures that limit access to laboratory and storage facilities outside of normal business hours to only those specifically approved by the Responsible Official or designee;

(iii) Procedures for allowing visitors, their property, and vehicles at the entry and exit points to the registered space, or at other designated points of entry to the building, facility, or compound that are based on the entity's site-specific risk assessment;

(iv) A minimum of three security barriers where each security barrier adds to the delay in reaching secured areas where select agents and toxins are used or stored. One of the security barriers must be monitored in such a way as to detect intentional and unintentional circumventing of established access control measures under all conditions (day/night, severe weather, etc.) The final barrier must limit access to the select agent or toxin to personnel approved by the HHS Secretary or Administrator, following a security risk assessment by the Attorney General.

(v) All registered space or areas that reasonably afford access to the registered space must be protected by an intrusion detection system (IDS) unless physically occupied;

(vi) Personnel monitoring the IDS must be capable of evaluating and interpreting the alarm and alerting the designated security response force or law enforcement;

(vii) For powered access control systems, describe procedures to ensure that security is maintained in the event of the failure of access control systems due to power disruption affecting registered space;

(viii) The entity must:

(A) Determine that the response time for security forces or local police will not exceed 15 minutes or

(B) Provide security barriers that are sufficient to delay unauthorized access until the response force arrives in order to safeguard the select agents and toxins from theft, intentional release, or unauthorized access. The response time is measured from the time of an intrusion alarm, or report of a security incident, to the arrival of the responders at the first security barrier.

(5) Entities that possess Variola major virus and Variola minor virus must have the following additional security requirements:

(i) Require personnel with independent unescorted access to Variola major or Variola minor virus to have a Top Secret security clearance;

(ii) Require Variola major or Variola minor virus storage locations to be under the surveillance of closed circuit television that is monitored;

(iii) After hours access procedures for Variola major or Variola minor virus must require notification of the entity's security staff prior to entry into the Variola laboratory and upon exit;

(iv) Require that observation zones be maintained in outdoor areas adjacent to the physical barrier at the perimeter of the entity and be large enough to permit observation of the activities of people at that barrier in the event of its penetration;

(v) Provide for a minimum of four barriers for the protection of the Variola major or Variola minor virus, one of which must be a perimeter fence;

(vi) Require a numbered picture badge identification subsystem to be used for all individuals who are authorized to access Variola major or Variola minor without escort;

(vii) Require the use, at all times, of properly trained and equipped security force personnel able to interdict threats identified in the site specific risk assessment;

(viii) Identify security force personnel designated to strengthen onsite response capabilities, and that will be onsite and available at all times to carry out their assigned response duties;

(ix) Provide for security patrols to periodically check external areas of the registered areas to include physical barriers and building entrances;

(x) Require that all on-duty security force personnel shall be capable of

maintaining continuous communication with support and response assets by way of security operations center;

(xi) Require that Variola major and Variola minor material in long term storage be stored in tamper-evident systems;

(xii) Require that all spaces containing working or permanent Variola major or Variola minor stocks be locked and protected by an intrusion alarm system that will alarm upon the unauthorized entry of a person anywhere into the area;

(xiii) Require that alarms required pursuant to this section annunciate in a continuously manned security operations center located within the facility; and

(xiv) Require that the security operations center shall be located within a building so that the interior is not visible from the perimeter of the protected area.

(g) In developing a security plan, an individual or entity should consider the document entitled, "Security Guidance for Select Agent or Toxin Facilities." The document is available on the National Select Agent Registry Web site at <http://www.selectagents.gov/>.

* * * * *

■ 11. Section 73.12 is amended as follows:

■ a. By revising paragraph (a) to read as set forth below.

■ b. By revising paragraphs (c)(1), (2), and (3) to read as set forth below.

■ c. By redesignating paragraph (d) as paragraph (e).

■ d. By adding a new paragraph (d) to read as set forth below.

§ 73.12 Biosafety.

(a) An individual or entity required to register under this part must develop and implement a written biosafety plan that is commensurate with the risk of the select agent or toxin, given its intended use. The biosafety plan must contain sufficient information and documentation to describe the biosafety and containment procedures for the select agent or toxin, including any animals (including arthropods) or plants intentionally or accidentally exposed to or infected with a select agent.

* * * * *

(c) * * *

(1) The CDC/NIH publication, "Biosafety in Microbiological and Biomedical Laboratories." This document is available on the National Select Agent Registry Web site at <http://www.selectagents.gov/>.

(2) The Occupational Safety and Health Administration (OSHA) regulations in 29 CFR parts 1910.1200

and 1910.1450. This document is available on the National Select Agent Registry Web site at <http://www.selectagents.gov/>.

(3) The "NIH Guidelines for Research Involving Recombinant DNA Molecules," (NIH Guidelines). This document is available on the National Select Agent Registry Web site at <http://www.selectagents.gov/>.

* * * * *

(d) The biosafety plan must include an occupational health program for individuals with access to Tier 1 select agents and toxins, and those individuals must be enrolled in the occupational health program.

* * * * *

■ 12. Section 73.13 is amended as follows:

■ a. In paragraph (a), add the phrase " , or possess products (i.e., select agents that are not known to acquire the resistance naturally, if such acquisition could compromise the control of disease agents in humans, veterinary medicine, or agriculture, or recombinant and/or synthetic nucleic acids containing genes for the biosynthesis of select toxins lethal for vertebrates at an LD[50] < 100 ng/kg body weight) resulting from," after the word "conduct" both times it appears.

■ b. By revising paragraph (b) to read as set forth below.

§ 73.13 Restricted experiments.

* * * * *

(b) Restricted experiments:

(1) Experiments that involve the deliberate transfer of, or selection for, a drug resistance trait to select agents that are not known to acquire the trait naturally, if such acquisition could compromise the control of disease agents in humans, veterinary medicine, or agriculture.

(2) Experiments involving the deliberate formation of synthetic or recombinant nucleic acids containing genes for the biosynthesis of select toxins lethal for vertebrates at an LD[50] < 100 ng/kg body weight.

* * * * *

■ 13. Section 73.14 is amended as follows:

■ a. By revising paragraph (a) to read as set forth below.

■ b. By revising paragraph (b) to read as set forth below.

■ c. By redesignating paragraphs (c) and (d) as paragraphs (d) and (f) respectively.

■ d. By adding a new paragraph (c) to read as set forth below.

■ e. By adding a new paragraph (e) to read as set forth below.

§ 73.14 Incident response.

(a) An individual or entity required to register under this part must develop and implement a written incident response plan based upon a site specific risk assessment.² The incident response plan must be coordinated with any entity-wide plans, kept in the workplace, and available to employees for review.

(b) The incident response plan must fully describe the entity's response procedures for the theft, loss, or release of a select agent or toxin; inventory discrepancies; security breaches (including information systems); severe weather and other natural disasters; workplace violence; bomb threats and suspicious packages; and emergencies such as fire, gas leak, explosion, power outage, and other natural and man-made events.

(c) The response procedures must account for hazards associated with the select agent or toxin and appropriate actions to contain such select agent or toxin, including any animals (including arthropods) or plants intentionally or accidentally exposed to or infected with a select agent.

* * * * *

(e) Entities with Tier 1 select agents and toxins must have the following additional incident response policies or procedures:

(1) The incident response plan must fully describe the entity's response procedures for failure of intrusion detection or alarm system; and

(2) The incident response plan must describe procedures for how the entity will notify the appropriate Federal, State, or local law enforcement agencies of suspicious activity that may be criminal in nature and related to the entity, its personnel, or its select agents or toxins.

* * * * *

■ 14. Section 73.15 is revised to read as follows:

§ 73.15 Training.

(a) An individual or entity required to register under this part must provide information and training on biosafety, security (including security awareness), and incident response to:

(1) Each individual with access approval from the HHS Secretary or Administrator before that individual has such access to select agents and toxins. The training must address the particular needs of the individual, the work they will do, and the risks posed by the select agents or toxins; and

²Nothing in this section is meant to supersede or preempt incident response requirements imposed by other statutes or regulations.

(2) Each individual not approved for access to select agents and toxins by the HHS Secretary or Administrator before that individual enters areas where select agents or toxins are handled or stored (e.g., laboratories, growth chambers, animal rooms, greenhouses, storage areas, shipping/receiving areas, production facilities, etc.). Training for escorted personnel must be based on the risk associated with accessing areas where select agents and toxins are used and/or stored.

(b) Entities with Tier 1 select agents and toxins must conduct annual insider threat awareness briefings on how to identify and report suspicious behaviors.

(c) Refresher training must be provided annually for individuals with access approval from the HHS Secretary or Administrator or at such time as the registered individual or entity significantly amends its security, incident response, or biosafety plans.

(d) The Responsible Official must ensure a record of the training provided to each individual with access to select agents and toxins and each escorted individual (e.g., laboratory workers, visitors, etc.) is maintained. The record must include the name of the individual, the date of the training, a description of the training provided, and the means used to verify that the employee understood the training.

■ 15. Section 73.16 is amended as follows:

■ a. By redesignating paragraphs (f), (g), (h), and (i) as paragraphs (i), (j), (k), and (g) respectively.

■ b. In newly redesignated paragraph (g), by removing the words “packaging and”.

■ c. By adding a new paragraph (f) to read as set forth below.

■ d. By adding a new paragraph (h) to read as set forth below.

■ e. By adding a new paragraph (l) to read as set forth below.

§ 73.16 Transfers.

* * * * *

(f) After authorization is provided by APHIS or CDC, the packaging of the select agent(s) and toxin(s) is performed by an individual approved by the HHS Secretary or Administrator to have access to select agents and toxins and is in compliance with all applicable laws concerning packaging.

* * * * *

(h) Transportation in commerce starts when the select agent(s) or toxin(s) are packaged for shipment and ready for receipt by a courier transporting select agent(s) or toxin(s) and ends when the package is received by the intended recipient who is an individual approved by the HHS Secretary or Administrator to have access to select agents and toxins, following a security risk assessment by the Attorney General.

* * * * *

(l) A registered individual or entity transferring an amount of a HHS toxin otherwise excluded under the provisions of § 73.3(d) must:

(1) Transfer the amounts only after the transferor uses due diligence and documents that the recipient has a legitimate need (i.e., reasonably justified by a prophylactic, protective, bona fide research, or other peaceful purpose) to handle or use such toxins.

(2) Report to CDC if they detect a known or suspected violation of Federal law or become aware of suspicious activity related to a toxin listed in § 73.3(d) of this part.

■ 16. Section 73.17 is amended as follows:

■ a. By revising paragraph (a)(1) introductory text to read as set forth below.

■ b. By redesignating paragraphs (a)(2) through (a)(6) as paragraphs (a)(3) through (a)(7) respectively.

■ c. By adding a new paragraph (a)(2) to read as set forth below.

§ 73.17 Records.

(a) * * *

(1) An accurate, current inventory for each select agent (including viral genetic elements, recombinant and/or synthetic nucleic acids, and organisms containing recombinant and/or synthetic nucleic acids) held in long-term storage (placement in a system designed to ensure viability for future use, such as in a freezer or lyophilized materials), including:

* * * * *

(2) An accurate, current accounting of any animals or plants intentionally or accidentally exposed to or infected with a select agent (including number and species, location, and appropriate disposition);

* * * * *

■ 17. Section 73.20 is revised to read as set forth below.

§ 73.20 Administrative review.

(a) An individual or entity may appeal a denial, revocation, or suspension of registration under this part. The appeal must be in writing, state the factual basis for the appeal, and be submitted to the HHS Secretary within 30 calendar days of the decision.

(b) An individual may appeal a denial, limitation, or revocation of access approval under this part. The appeal must be in writing, state the factual basis for the appeal, and be submitted to the HHS Secretary within 180 calendar days of the decision.

(c) The HHS Secretary's decision constitutes final agency action.

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