United States Department of Agriculture

Animal and Plant Health Inspection Service

Regulatory Impact Analysis & Final Regulatory Flexibility Analysis

Final Rule

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Agricultural Bioterrorism Protection Act of 2002; Biennial Review and Republication of the Select Agent and Toxin List; Reorganization of the Select Agent and Toxin List

United States Department of Health and Human Services

Centers of Disease Control and Prevention

[CDC-2011-0012]
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Possession, Use, and Transfer of Select Agents and Toxins; Biennial Review

May 2012

Summary

The *Public Health Security and Bioterrorism Preparedness and Response Act of 2002* (Pub. L. No. 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. APHIS and 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.

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Introduction

This final regulatory impact analysis jointly provides supporting information and analysis for final rules published by the Department of Agriculture's (USDA) Animal and Plant Health Inspection Service (APHIS), amending 7 CFR Part 331 and 9 CFR Part 121, and the Department of Health and Human Services' (HHS) Centers for Disease Control and Prevention (CDC), amending 42 CFR Part 73.

The *Public Health Security and Bioterrorism Preparedness and Response Act of 2002* provides for the regulation of certain biological agents[1] and toxins[2] that have the potential to pose a severe threat to human, animal, or plant health, or to animal or plant products. APHIS and CDC have primary responsibility for implementing the provisions of the Act. Within APHIS, Veterinary Services (VS) select agents and toxins[3] are those that 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[4] 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

[1] Any microorganism (including, but not limited to, bacteria, viruses, fungi, or protozoa), or infectious substance, or any naturally occurring, bioengineered, or synthesized component of any such microorganism or infectious substance, capable of causing: (1) death, disease or other biological malfunction in a human, an animal, a plant, or another living organism; (2) deterioration of food, water, equipment, supplies, or material of any kind; or (3) deleterious alteration of the environment.

[2] The toxic material or product of plants, animals, microorganisms (including, but not limited to, bacteria, viruses, fungi, or protozoa), or infectious substances, or a recombinant or synthesized molecule, whatever their origin and method of production, and includes: (1) any poisonous substance or biological product that may be engineered as a result of biotechnology produced by a living organism; or (2) any poisonous isomer or biological product, homolog, or derivative of such a substance.

[3] The current list of VS select agents and toxins can be found at 9 CFR § 121.3 (VS select agents and toxins) and 9 CFR § 121.4 (overlap select agents and toxins).

[4] The current list of PPQ select agents and toxins can be found at 7 CFR § 331.3 (PPQ select agents and toxins).

severe threat to human health.[5] APHIS and CDC coordinate regulatory activities for overlap select agents and toxins that have been determined to pose a severe threat to human and to 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. The final rules implement the recommendations of the third biennial review. Revision of these regulations is in compliance with the policy outlined in Executive Order 13546, "Optimizing the Security of Biological Select Agents and Toxins in the United States," that requires that the Secretaries of Health and Human Services and Agriculture amend the regulations to establish risk-based tiering of the select agent and toxin lists, and revise the regulations, rules and guidance to accommodate tiered select agent and toxin lists.

This regulatory impact analysis provides a cost-benefit analysis, as required by Executive Orders 12866 and 13563, which 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, and equity).[6] This document also examines the potential economic effects of this rule on small entities as required by the Regulatory Flexibility Act.[7]

[5] The current list of HHS select agents and toxins can be found at 42 CFR § 73.3 (HHS select agents and toxins) and 42 CFR § 73.4 (overlap select agents and toxins).
[6] http://www.whitehouse.gov/omb/inforeg/eo12866.pdf; http://www.reginfo.gov/public/jsp/Utilities/EO_13563.pdf
[7] http://www.sba.gov/advo/laws/regflex.html

Regulatory Revisions of Economic Consequence and Affected Entities

Addition of Select Agents and Toxins to HHS List

CDC will add Chapare to the HHS list of select agents and toxins in 42 CFR § 73.3. The select agents and toxins list currently includes members of the *arenaviridae* family (Junin, Machupo, Sabia, Flexal, Guanarito, and Lassa). Arenaviruses are rodent-borne viruses, some of which have been associated with large hemorrhagic fever outbreaks. Untreated case fatalities can be in excess of 30 percent.

CDC will add Lujo virus, a recently described Old World arenavirus associated with an outbreak of fatal hemorrhagic fever in South Africa, to the HHS list of select agents and toxins. Lujo virus has been phylogenetically identified as an arenavirus and is related to other currently regulated arenaviruses that cause hemorrhagic fever.

CDC will add SARS-associated coronavirus (SARS-CoV), an enveloped virus with a positive-sense RNA genome. RNA viruses that utilize host polymerases contain nucleic acids 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. CDC is adding SARS-CoV to the list of select agents and toxins because of the significant impact a SARS-CoV release would have on the public health system, given its high degree of pathogenicity and, to the best of our knowledge, the lack of vaccines or proven therapeutics to prevent or treat SARS-CoV infections. Furthermore, we note that this 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 should the virus be intentionally or accidentally released.

Removal of Plant, Animal, Human Health (and Overlap) Select Agents and Toxins

APHIS will amend the list of PPQ select agents and toxins in 7 CFR § 331.3 by removing *Xylella fastidiosa*, citrus variegated chlorosis strain, from the list as it no longer meets the criteria for or use as an agroterrorism agent and therefore no longer needs to be designated as a PPQ select agent. APHIS will also remove nine VS select agents and toxins from the list in § 121.3(b): Akabane virus; bluetongue virus (exotic); bovine spongiform encephalopathy agent; camel pox virus; *Ehrlichia ruminantium* (heartwater); Japanese encephalitis virus; malignant catarrhal fever virus (Alcelaphine herpesvirus type 1); Menangle virus; and vesicular stomatitis virus (exotic): Indiana subtypes VSV–IN2, VSV–IN3.

CDC will amend the list of HHS select agents in 42 CFR §73.3 by removing Cercopithecine Herpesvirus 1 (Herpes B virus), *Clostridium perfringens* epsilon toxin, *Coccidioides posadasii/Coccidioides immitis*, Eastern Equine Encephalitis virus (South American type only), Flexal virus, West African clade of Monkeypox viruses, *Rickettsia rickettsii*, the non-short, paralytic alpha conotoxins containing the following nucleic acid sequence X1CCX2PACGX3X4X5X6CX7, 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) from the list as they no longer meet the criteria for use as bioterrorism agents and therefore no longer need to be designated as HHS select agents.

Finally, APHIS and CDC will modify the listing of the overlap select agents by removing certain subtypes of Venezuelan equine encephalitis virus from 9 CFR § 121.4(b) and 42 CFR § 73.4 (b), and clarifying that only Venezuelan equine encephalitis subtypes IAB and IC will remain. While the current regulations have not been shown to impede research concerning select

agents and toxins listed in the Code of Federal Regulations, the removal of certain select agents and toxins may result in marginal savings of both time (registration and documentation processes) and money (cost of compliance) for entities. The overall benefit of this provision is expected to be minimal and impact less than 3 percent of entities affected by the rules.

Tiering of the Lists of Select Agents and Toxins and Revision of Security Requirements

APHIS and CDC will designate as Tier 1 certain agents and toxins on their respective lists of select agents and toxins based on the relative potential of each select agent or toxin to be misused to adversely affect human, plant, or animal health, or plant or animal products, and provide for heightened biosecurity for those select agents and toxins designated as Tier 1.[8]

APHIS will designate foot-and-mouth disease virus and rinderpest virus as Tier 1 VS select agents and toxins. CDC will designate Ebola virus, *Francisella tularensis,* Marburg virus, Variola major virus, Variola minor virus, *Yersinia pestis,* Botulinum neurotoxin, and Botulinum neurotoxin producing species of *Clostridium* as Tier 1 HHS select agents and toxins. In addition, APHIS and CDC will designate *Bacillus anthracis, Burkholderia mallei,* and *Burkholderia pseudomallei* as Tier 1 overlap select agents and toxins. The tiering of the lists of select agents and toxins is designed to emphasize those select agents and toxins with the greatest potential for deliberate misuse that could result in devastating effects to the economy, critical infrastructure, and public confidence.

The rule will require that an entity where a Tier 1 select agent or toxin is held adequately provide for an additional level of physical security of the premises. Entities possessing a Tier 1 select agent or toxin must have a security plan describing procedures for determining the

[8] APHIS is not including PPQ select agents and toxins in this reorganization as none of the plant list agents met the minimum criteria for inclusion on the Tier 1 select agents and toxins list.

suitability of persons who will have access to a Tier 1 select agent or toxin; training on policies and procedures for evaluation and reporting concerning the assessment of personnel suitability to access Tier 1 select agents and toxins; and the ongoing suitability monitoring of individuals with access to Tier 1 select agents and toxins. Furthermore, entities with Tier 1 select agents and toxins must have security enhancements that contain provisions for security barriers, intrusion detection and monitoring, delay/response force, access control, and information security.

Finally, 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.

Miscellaneous Changes that May Pose Economic Impact

APHIS and CDC are revising the regulations to improve the transparency and effectiveness of the select agent regulations as well as provide for enhanced program oversight. These changes include various additions of definitions, as well as the clarification of language concerning security, training, biosafety, biocontainment, and incident response. Miscellaneous changes to the regulations that may result in costs for affected entities are as follows:

- Entities will be required to submit their security plan for initial registration and renewals of registration, as well as at any other time upon request.
- APHIS and CDC approval, based on a security risk assessment, to have access to select agents and toxins will be valid for a maximum of 3 years as opposed to the current standard of 5 years.
- Entities will be required to clearly state the provisions for safeguarding of animals or plants intentionally or accidentally exposed to or infected with a select agent or toxin within their security, biosafety/biocontainment, and incident response plans.

- Entities will be required to have information security measures, including:
    - Information technology security,
    - Network security,
    - Computer security,
    - Peripheral devices and data storage,
    - Physical security and its application to information security, and
    - Risk management.
- Entities will be required to establish consistent practices for shipping, receiving, and storage of select agents and toxins to ensure that the entity has documented processes for securing and monitoring the shipment, receipt, and storage of these items.
- Entities will be required to supplement current training practices with security awareness and incident response training, as well as provide adequate training to inform individuals of the changes when a registered entity's security, incident response, or biosafety/biocontainment plans have been substantively altered.
- Entities will be required to maintain 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).

Entities Affected by Tiering of Select Agent and Toxin Lists

Entities that possess, use, or transfer certain HHS, VS, or overlap select agents or toxins will be affected by the Tier 1 designation established by this rule. The affected entities will include research and diagnostic facilities, Federal and State governmental entities, academic institutions, and commercial and non-profit institutions. Currently, there are 365 entities registered with APHIS and CDC. Of these entities, there are 292 registered to possess Tier 1

select agents and toxins, including 89 academic, 32 commercial, 106 State government, 47 Federal government, and 18 private (non-profit) institutions.[9]

According to our records, 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.

Moreover, there are 13,488 individuals across all 365 entities registered with APHIS and CDC with an approved security risk assessment (SRA). The Tier 1 select agent and toxin assignment by agency is shown in table 1.

Table 1. Numbers of entities expected to be affected by Tier 1 select agent and toxin classifications

Tier 1 Select Agent and Toxin Assignment					
Agency	**Academic**	**Commercial (Profit)**	**State Government**	**Federal Government**	**Private (non-Profit)**
APHIS	9	4	2	2	2
CDC	80	28	104	45	16
Total	89	32	106	47	18

Expected Benefits and Costs of the Rule

The APHIS and CDC final rules will update the regulations on select agents and toxins as contained in 7 CFR Part 331, 9 CFR Part 121, and 42 CFR Part 73. These regulations require registration, biocontainment/biosafety, incident response, and security measures for the

[9] It should be noted that the areas housing select agents and toxins tend to be small, with an estimated 500 to 2,000 square feet and fewer than 10 individuals with access. Small laboratories within a larger facility are the rule, and dedicated buildings are the exception. As such, the costs of complying with additional security measures are expected to be minimal, given the relatively small physical space housing the select agents and toxins.

possession, use, and transfer of the listed select agents and toxins. The regulations are intended to prevent the misuse of those select agents and toxins, and therefore reduce the potential for those pathogens to harm humans, animals, animal products, plants or plant products. The final rules will improve biosecurity safeguards, and may result in certain costs, depending on an entity's existing security systems. Benefits and costs associated with the final regulations are discussed in this section.

Benefits

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; require the security procedures and assessment checks 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.

Protecting U.S. Agriculture

Should an APHIS select agent be introduced into the United States, the consequences would be significant. Direct losses to agriculture would likely occur as a result of the exposure, such as the death or debility of affected animals or crop losses. Related industries would also be affected by the imposition of domestic and foreign quarantines that result in a loss of markets. Federal and State governments would incur eradication and quarantine enforcement costs in combating spread of the agent and – in the case of intentional introduction – investigative and

law enforcement costs. In addition, there could be disruption of the domestic food supply, due to contamination, consumer risk perceptions, or both. Past food safety incidents have shown that consumers' negative perceptions (both domestic and international) about an implicated food product and the producing country or sector's ability to produce safe food are slow to recede and can have a lasting influence on food demand and global trade.[10] The benefits of the APHIS final rule are the avoided losses of animals or plants that could be attacked by these organisms (because of the reduced risk of release of the select agents and reduced likelihood of exposure for susceptible animals or plants), the avoided public and private costs of eradication, and the avoided negative market effects.

The costs associated with the outbreak of a select agent can be very high, as demonstrated, for example, by the losses to agriculture and the food chain from the foot-and-mouth disease (FMD) outbreak in the United Kingdom in 2001. Those costs amounted to about £3.1 billion ($4.7 billion).[11] In 1999, it was estimated that the potential impacts of an FMD outbreak in California alone would be between $8.5 billion and $13.5 billion.[12] Another study of the expected effects of an FMD outbreak estimated that the value of U.S. exports would decline by as much as 13 percent due to the decline in livestock supply, the anticipated embargo on susceptible U.S. exports, and consumer fears regarding this disease.[13]

Rinderpest is another select agent that could have devastating effects. It is a contagious viral disease of cattle, buffalo, and some wild species of cloven-hoofed animals such as giraffe

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[10] Buzby, J.C. *Effects of food-safety perceptions on food demand and global trade.* Changing Structure of Global Food Consumption and Trade /WRS-01-1. Economic Research Service/USDA.
[11] Thompson, D., P. Muriel, D. Russell, P. Osborne, A. Bromley, M. Rowland, S. Creigh-Tyte, and C. Brown. *Economic costs of the foot and mouth disease outbreak in the United Kingdom in 2001.* Rev. Sci. Tech. 21,675–687, 2002.
[12] Ekboir, J.M. *Potential impact of foot-and-mouth disease in California: the role and contribution of animal health surveillance and monitoring services*. Davis, CA: Agricultural Issues Center, Division of Agriculture and Natural Resources, University of California, Davis, 1999.
[13] Paarlberg, P.L., J.G. Lee, A.H. Seitzinger. *Potential revenue impact of an outbreak of foot-and-mouth disease in the United States.* Vet Med Today: Food Animal Economics, JAVMA, Vol 220, No. 7, 2002.

and wildebeest that can cause illness in all susceptible animals that come in contact with infected animals or contaminated surfaces. A recent estimate of the cost of this disease to animal health and its control in Asia and Africa since 1986 was $610 million.[14] As the result of an extensive international campaign, rinderpest was eradicated globally last year. Should the rinderpest virus be released into the environment once again, a serious outbreak would endanger livestock and susceptible wildlife.

Protecting Public Health and Safety

The agents and toxins placed on the HHS select list have the potential to pose severe threats to public health and safety. The benefits of the CDC final rule derive from the strengthened prevention against their accidental or intentional release. The cost of such an event in human life could be high. An outbreak of one of the select agents also would require a complex and expensive emergency response effort. This effort would include extensive public health measures, such as quarantine, isolation, preventative treatment and health testing for large numbers of potentially exposed persons, and extensive decontamination. Substantial costs would likely be incurred by hospitals and other medical facilities and institutions of government at all levels.

An outbreak, or widespread fear of one, also would likely create significant secondary effects to society including a potentially rapid increase in health anxiety among healthy individuals. This could result in overcrowded healthcare facilities and emergency rooms, and the disruption of everyday business operations, transportation, and other normal behavior.

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[14] Normile, D. *Rinderpest. Driven to extinction.* Science, Vol 319, No. 5870, 2008.

Impacts from the October 2001 anthrax attacks exemplify the costs that the regulatory revisions will help to prevent. The anthrax attacks caused 5 fatalities and 17 illnesses, disrupted business and government activities, closed substantial parts of the Postal Service, and caused widespread apprehension and changes in behavior. Costs included more than $23 million to decontaminate one Senate office building, approximately $2 billion in revenues lost to the postal service, and as much as $3 billion in additional costs to the Postal Service for cleanup of contamination and procurement of mail-sanitizing equipment.[15] There were substantial costs due to lost productivity throughout the economy and investigations into the incident.

An outbreak of smallpox, which was eradicated globally in 1979, would have a huge negative impact on human health and economic stability. Based on an analysis performed by the Department of Homeland Security, it is estimated that the U.S. economic losses associated with an intentional smallpox virus release could easily exceed $70 billion, including costs associated with public avoidance and tourism losses. Human health consequences (fatalities and illnesses) would be significant. Even if limited to a single (target) city, direct costs of the release would include decontamination and site remediation costs, medical treatment costs, business disruption, and lost economic productivity due to illness and fatalities. Additionally, costs associated with decreases in international tourism and public avoidance due to fear of exposure could affect the entire economy. These direct impacts would cause a ripple effect throughout the national economy as changes in demand and consumption affect related industries and households that may not experience any of the initial consequences.

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[15] "Regulatory Impact Analysis for 42 CFR Part 73: Possession, Use, and Transfer of Select Biological Agents and Toxins Final Rule. Centers for Disease Control and Prevention, Department of Health and Human Services. February 3, 2005."
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"The US Postal Service Response to the Threat of Bioterrorism through the Mail, " Congressional Research Service Report for Congress, February 2002. <http://www.au.af.mil/au/awc/awcgate/crs/rl31280.pdf.> Date Accessed: May 18, 2010.

These are examples of the exceedingly costly impacts of a major disease outbreak. Deliberate introduction greatly increases the probability of a select agent becoming established and causing wide-ranging and devastating impacts to the economy, potential loss of market access for consumer goods and services, other disruptions to society, and diminished confidence in public and private institutions.

Costs

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 ensure prevention 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. APHIS and 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. We have updated these general cost observations, as summarized in table 2 at the end of this section.[16]

New Requirements for Conducting a Security Risk Assessment

Under the final regulations, individuals will be required to undergo a security risk assessment every 3 years as opposed to the current standard of every 5 years. This change will allow for the more timely identification of individuals whose status has fallen into one of the prohibited or restricted categories. With an estimated cost of $240 per person for providing background checks, incurred by the Federal Bureau of Investigation's Criminal Justice Information Services (FBI/CJIS), the regulations will increase the frequency of FBI/CJIS security risk assessments by approximately 67 percent. However, the benefit in terms of being able to identify individuals whose status has fallen into one of the prohibited or restricted categories within 3 rather than 5 years will outweigh the increase in cost. Assuming a uniform distribution in the number of background investigations conducted each year, given the current 13,488 individuals having approved SRAs, the present value of these government-borne costs over five years will increase by $1.96 million across all registered entities.[17] The annual increase in costs will total about $432,000.

Revisions to Security, Biocontainment/Biosafety, and Incident Response Plans

Entities will be required to revise and implement security, biocontainment/biosafety, and incident response plans to enhance the safeguarding of animals or plants intentionally or

[16] Except where otherwise noted, updated data on the costs of implementation of the final rules were compiled from experts at the Centers for Disease Control and Prevention and the Animal and Plant Health Inspection Service.

[17] We calculate the additional cost associated with the change in the frequency of background investigations by assuming a uniform distribution of background checks: 2,698 per year when the background checks are valid for 5 years, compared to 4,496 per year when the background checks are valid for 3 years. With $240 the cost of one background check, annual costs total about $648,000 (when valid for 5 years) compared to about $1.08 million (when valid for 3 years), yielding an annual additional cost of about $432,000, Comparing the present values of the costs over five years, $2.94 million vs. $4.90 million, yields an additional present value cost over five years of $1.96 million, when using a discount rate of 3.25 percent (bank prime loan interest rate reported by the Board of Governors of the Federal Reserve System, March 13, 2012).

accidentally exposed to or infected with a select agent or toxin. These revisions to each plan are intended to be a comprehensive reflection of the regulations and provide necessary guidance regarding the handling of animals and plants inoculated with select agents.

Security Plan

The security plan will be submitted for initial registration and renewals of registration, in addition to the current standard of submission upon request. The affected entities will incur an additional cost related to shipment of the security plan to the agency, unless submitted via electronic mail or fax. A Postal Service Mail Flat Rate envelope will cost $4.95 to mail. We estimate an average of 130 entities will be renewing their registration with the Select Agent Program per year. If all of the entities were to choose to submit their security plans via the Postal Service, the total cost would be $643.50.

The final rules add provisions for information security to security plan requirements. These measures include network connectivity monitoring, restriction of user permissions to only mission-specific files and applications, measures to prevent network infiltration by malicious code, and configuration management including regular patching and system software updates. These measures are consistent with industry recommendations on information security policy. Inappropriate access by unauthorized personnel, internal and external misuse of resources, and the threat of malicious code can impact the integrity of the research conducted at facilities, as well as threaten the containment of select agents and toxins. According to a recent study, malicious attacks alone are on the rise with an increase in such attacks from 12 percent of breaches in 2008 to 24 percent of breaches in 2009.[18] The cost of implementing these measures

[18] "2009 Annual Study: US Cost of Data Breach," Ponemon Institute Research Report, January, 2010. <http://www.ponemon.org/local/upload/fckjail/generalcontent/18/file/US_Ponemon_CODB_09_012209_sec.pdf> Date Accessed: May 18, 2010.

will vary among the affected entities based upon their current levels of information security. Based on site-specific inspections, we believe many of the entities already employ one or more of the measures. The specific changes to information security that must be included in an entity's security plan are:

- Means to ensure that all external connections to the systems which manage security for the registered space are isolated or have controls that permit and monitor only authorized and authenticated users. The estimated cost of firewall software ranges between $24 and $37 per license or between $8,760 and $13,505 for all 365 registered entities. Encryption software is estimated to cost between $79 and $199 per system or between $28,835 and $72,635 for all 365 registered entities.
- Means to 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. Site-specific inspections indicate that the affected entities already employ this measure.
- Means to 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. The cost for antivirus software is estimated at $80 per user per year or up to $1,079,040 per year for all 13,488

individuals with approved SRAs. Computer intrusion detection software is estimated at $15 per computer or approximately $5,475 for each computer across all 365 registered entities.[19]

- Means for a robust configuration management practice for information systems to include regular patching and updates made to operating systems and individual applications. Such activity will require the time of the computer system administrator. It is estimated this could take up to 8 hours per month at $25 per hour for a total of $200 per month per entity or up to $876,000 per year for all 365 registered entities; and
- Establish procedures that provide backup security measures in the event that access control systems, surveillance devices, and/or systems that manage the requirements of the final rules are rendered inoperable. The use of security guards, for example, to ensure safekeeping of select agents and toxins under such circumstances is estimated at approximately $8 to $25 per hour or $2,920 to $9,125 per hour across all 365 registered entities, depending on location.[20]

The security plan will also require entities to establish consistent practices for shipping, receiving, and storage of select agents and toxins to ensure that the entity has documented processes for securing and monitoring the shipment, receipt, and storage of these items. This requirement is designed to clarify current language in the regulations, and will cost little more than the time it takes to revise the security plan.

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[19] 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

[20] This revision will affect those entities relying solely on information systems for security. We do not anticipate a significant increase in costs to registered entities as a result of this provision as most entities already employ security measures beyond information security.

In addition to the preceding description of changes to security plans for all affected entities, entities possessing a Tier 1 select agent or toxin must include the following additional security measures that may result in additional costs of operation.

The security plan must describe procedures for individuals who will have access to a Tier 1 select agent or toxin. These procedures must include reporting of incidents or conditions that could affect an individual's ability to safely work with select agents and toxins or to safeguard them from theft, loss or release. These procedures must also include the training of all entity employees on entity policies and procedures for reporting, evaluation, and corrective actions concerning the assessment of personnel suitability to access Tier 1 select agents and toxins. Finally, the security plan must 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.

In addition to the time cost associated with revising the security plan to include these Tier 1 modifications, it is estimated that the cost for conducting a pre-access suitability assessment of personnel might include identity verification, credential/education verification, and a police background check. The cost of performing these tasks could range between $100 and $120 per SRA-approved individual working with Tier 1 select agents and toxins, and could reach approximately $1.3 million to $1.6 million, if all 13,488 individuals with approved SRAs were to have access to Tier 1 select agents and toxins. However, only a fraction of SRA-approved individuals are expected to work with Tier 1 select agents and toxins.

Entities with Tier 1 select agents and toxins will be required to have a minimum of three barriers where each subsequent barrier adds to the delay in reaching secured areas where select agents and toxins are used or stored. Based on information received through site-specific

inspections, most of these entities currently employ a minimum of three barriers.[21] All registered space or areas that reasonably afford access to the registered space with Tier 1 select agents and toxins must be protected by an intrusion detection system (IDS) unless physically occupied, and must be staffed with personnel monitoring the IDS who are capable of evaluating and interpreting the alarm and alerting the designated security response force or law enforcement. Entities possessing Tier 1 select agents and toxins must also provide back up security measures for information security networks and integrated access controls and related systems for the registered space during emergencies. Again, based on information received through site-specific inspections, it is believed that the affected entities already generally employ backup security measures as an industry standard.

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. There is an associated time cost to conduct an audit, especially when there must be a procedure in place to protect the integrity of the research associated with the inventory.

Entities that possess foot-and-mouth disease virus or rinderpest virus will be required to have a minimum of four barriers, one of which must be a perimeter security fence or equivalent which is monitored 24 hours a day and 7 days a week to detect the presence of unauthorized persons, vehicles, materials, or unauthorized activities. These facilities must further provide an on-site armed security response force with a roving patrol 24 hours a day and 7 days a week. Response time must not exceed 5 minutes from the time of an intrusion alarm or report of a

[21] This requirement is also designed to clarify current language in the regulations, and will cost the time it takes to revise the security plan.

security incident. Additionally, facilities possessing foot-and-mouth disease virus or rinderpest virus must provide closed circuit television surveillance with monitoring and recording 24 hours a day and 7 days a week, and a transport vehicle with GPS tracking designed to serve as a containment vehicle.

Entities that possess Variola major or Variola minor virus must require that personnel with access to either of these viruses have Top Secret security clearance and that Variola major or Variola minor virus storage locations be under the surveillance of monitored closed circuit television. After-hours access to Variola major or Variola minor virus must be restricted to individuals with specific permission from the principal investigator. After-hours access procedures must require notification of the entity's security staff prior to entry into the Variola laboratory and upon exit. These facilities must further 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; 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; 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; 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; identify security force personnel designated to strengthen onsite response capabilities, and who will be onsite and available at all times to carry out their assigned response duties; provide for security patrols to periodically check external areas of the registered areas to include physical barriers and building entrances; require that all on-duty security force personnel shall be capable of maintaining continuous communication with support and response assets by way of a security

operations center; require that Variola major and Variola minor material in long-term storage be stored in tamper-indicating containers; require that all spaces containing working or permanent Variola major or Variola minor stocks be locked and protected by an intrusion alarm system that is activated upon the unauthorized entry of a person anywhere into the area; require that alarms required pursuant to this section annunciate in a continuously manned security operations center located within the facility; and 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.

APHIS and CDC believe affected entities are largely in compliance with these added measures based on information obtained through site-specific inspections.

Biocontainment/Biosafety and Incident Response Plans

The biocontainment/biosafety and incident response plans will require enhanced detail of operational procedures. Specifically, the biocontainment/biosafety plan will describe biosafety and containment procedures for animals or plants intentionally or accidentally exposed to or infected with a select agent or toxin. The incident response plan will be based on a site-specific risk assessment. The response procedures in the incident response plan must account for hazards associated with the select agent or toxin and appropriate actions to contain such select agent or toxin, including any animals or plants intentionally or accidentally exposed to or infected with a select agent. The incident response plan will also include policies or procedures for entities with Tier 1 select agents or toxins. These include the entity's response procedures for the failure of an intrusion detection or alarm system, and law enforcement notification procedures in the event of a theft or suspicious activity that may be criminal in nature involving a Tier 1 select agent or toxin.

These revisions to the regulations will enhance the effectiveness of these plans. To the extent that the new requirements are already being performed by the entities, the only additional costs incurred will be the time expended in revising entities' biocontainment/biosafety and incidence response plans.

Additionally, the biocontainment/biosafety plan will include an occupational health program, along with required enrollment for individuals with access to Tier 1 select agents and toxins. Occupational health programs may include baseline assessments (e.g., physical exam, vaccinations, diagnostic laboratory testing, blood tests, and general healthcare screening) and periodic physical examinations. The cost of an appropriate occupational health program will be dependent on various factors including location, number of SRA-approved individuals working with Tier 1 select agents, and the bundle of services offered. We estimate the cost of a comprehensive occupational health care program to establish baseline assessments will range between $107 and $204 per SRA-approved individual working with Tier 1 select agents and toxins.[22] We further estimate that the implementation of a comprehensive occupational health care program could cost between $1.4 million and $2.8 million, should all 13,488 individuals with approved SRAs participate. However, only a fraction of SRA-approved individuals are expected to work with Tier 1 select agents and toxins.

[22] Based on an evaluation of the standard cost of a physical exam, tetanus vaccination, respiratory test, and a diagnostic laboratory test. Data compiled and updated from experts at Centers for Disease Control and Prevention and Animal and Plant Health Inspection service (2012).

Training

The final regulations will require entities to supplement current training practices with security awareness and incident response training. Furthermore, entities will be required to provide training if a registered entity's security, incident response, or biosafety or biocontainment plan is substantively altered. Entities with Tier 1 select agents and toxins must conduct annual insider threat awareness briefings on how to identify and report suspicious behavior. The cost of supplemental training will be a time cost added to the training programs currently required. The additional time devoted to the training programs will enhance the effectiveness of the security, incident response, and biosafety or biocontainment plans.

Table 2. 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
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] See footnote 17 of this document. 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.

Recordkeeping

Entities will be required to maintain an accurate, current inventory of any animals or plants intentionally or accidentally exposed to or infected with a select agent (including number and species, location, and appropriate disposition). The incremental costs of the changes associated with the requirements of the responsible official, as well as any alternate(s), will be those costs incurred to fill any knowledge gaps regarding the oversight of select agents and toxins, which could involve coursework/training/travel costs.

Final Regulatory Flexibility Analysis

The Regulatory Flexibility Act requires agencies to evaluate the potential effects of their proposed and final rules on small businesses, small organizations and small governmental jurisdictions. This final regulatory flexibility analysis describes expected impacts of this rule on small entities, as required by section 604 of the Act.

Need for and Objectives of the Rule

Section 201 of Subtitle A and Section 212(a) of Subtitle B[23] of the *Public Health Security and Bioterrorism Preparedness and Response Act of 2002* (Pub. L. 107-188), requires the HHS and USDA Secretaries to establish and maintain lists of select agents and toxins that they have determined to have the potential to pose a severe threat to human, animal or plant health, or to animal or plant products. Each respective Secretary is further required to review and republish the select agent and toxin list biennially or more often as needed and revise the list as necessary.

[23] Title II (Enhancing Controls on Dangerous Biological Agents and Toxins)—Subtitle B (Department of Agriculture) of Public Law 107-188 may be cited as the "Agricultural Bioterrorism Protection Act of 2002."

Each respective Secretary implements regulations that provide the requirements for possession, use and transfer of select agents and toxins.

These revisions of the regulations are in compliance with the policy outlined in Executive Order 13546, "Optimizing the Security of Biological Select Agents and Toxins in the United States." The Executive Order requires that the Secretaries of Health and Human Services and Agriculture amend the regulations to establish risk-based tiering of the select agent and toxin list, and revise the regulations, rules, and guidance to accommodate a tiered select agent and toxin list. The final rules implement revision and republication of the list following the recommendations of the third biennial review.

Significant Issues raised by Public Comment in response to the Initial Regulatory Flexibility Analysis

One public commenter expressed concerns that the additional security requirements would lead to an increase in "the regulatory burden and costs across all [select agents and toxins]." The commenter charged that the "regulatory changes fail to achieve the goal of minimizing the impact of the regulations on the legitimate uses of [select agents and toxins] in research; research that the EO notes is essential to national security."

Several public commenters expressed concerns over the opportunity cost of the associated time needed for compliance with the revised regulations, specifically the opportunity cost associated with time that would otherwise be devoted to research.

APHIS and CDC did not find sufficient evidence to indicate that actual costs of compliance and the opportunity costs of administrative duties associated with implementation of the final regulations would place an undue burden on a substantial number of small entities. The revised regulations will improve the transparency and effectiveness of the select agent

regulations, as well as provide for enhanced program oversight, which will, in turn, provide improved security for research efforts in the long term.

Comments filed by the Small Business Administration in response to the Proposed Rule

There were no significant issues raised by the Small Business Administration in response to the initial regulatory flexibility analysis.

Potentially Affected Small Entities

Potentially affected entities include laboratories, other research institutions, and related entities in possession of Tier 1 select agents or toxins, and, to a somewhat lesser extent, those entities possessing the newly added select agents and toxins. Affected entities (other than Federal and State governmental entities) are likely found within the following North American Industry Classification System (NAICS) categories:

- 541711, Research and Development in Biotechnology;
- 541712, Research and Development in the Physical, Engineering, and Life Sciences (except Biotechnology);
- 325412, Pharmaceutical Preparation Manufacturing;
- 325413, In-Vitro Diagnostic Substance Manufacturing;
- 325414, Biological Product (except Diagnostic) Manufacturing;
- 541940, Veterinary Services;
- 611310, Colleges, Universities and Professional Schools;
- 621511, Medical Laboratories;
- 622110, General Medical and Surgical Hospitals.

The Small Business Administration (SBA) has established small-entity size standards based on the NAICS categories. An entity classified within NAICS 541711, 541712, 325413 or 325414

is considered small with 500 or fewer employees, and one within NAICS 325412 is considered small with 750 or fewer employees. An entity in NAICS 541940 or 611310 is considered small with annual receipts of $7 million or less. Entities classified within NAICS 621511 are considered to be small if they have annual receipts of not more than $13.5 million. An entity classified within NAICS 622110 is considered to be small with annual receipts of not more than $34.5 million

While the breakdown of the size of the establishments, as reported by the 2007 Economic Census, does not precisely fit the SBA guidelines, the data indicate that the vast majority of the entities in industries potentially affected by this rule, other than post-secondary institutions, can be considered small, as shown in table 3. According to the 2007 Economic Census, the most recent available, 98 percent of entities in NAICS 541711 and 541712, 92 percent of entities in NAICS 325412, 95 percent of entities in NAICS 325413, 96 percent of entities in NAICS 325414, 99 percent of entities in NAICS 541940, 89 percent of entities in NAICS 621511, and 35 percent of entities in NAICS 622110 can be classified as small.[24] According to data from the U.S. Department of Education's Integrated Postsecondary Education Data System (IPEDS), 14 percent of reporting post-secondary institutions had revenue of less than $7 million in fiscal year 2008-09, and could therefore be considered small.[25]

Any entity that possesses, uses or transfers listed select agents or toxins is required to comply with the select agent regulations, and may incur costs associated with the provisions of the final rules. The additional costs that may be incurred are small in comparison to the long-

[24] Based on the small business size standards matched to industries described in the North American Industry Classification System (NAICS), as modified by the Office of Management and Budget in 2007, and reported in the Small Business Administration's (SBA) Small Business Size regulations contained in 13 CFR 121.
[25] Source: United States Department of Education, Institute of Education Sciences, National Center for Education Statistics Integrated Postsecondary Education Data System (IPEDS).

term benefits of additional protection against the release of select agents and toxins that would result in devastating effects to the economy.

Table 3. Prevalence of small entities within industries expected to be directly affected by the rule.

NAICS Code	Number of Firms		Annual Revenue, Receipts, or Value of Shipments	
SBA Small-entity Standard based on Employment	< 500 Employees	500 + Employees	< 500 Employees	500 + Employees
541711 R&D in Biotechnology (commercial and non-profit)	1,954	35	$8.8b	$8.4b
541712 R&D in the Life Sciences (commercial and non-profit)	7,696	135	$27.2b	$43.9b
325412 Pharmaceutical Preparation mfg [a/]	916	75	$55.8b	$87.0b
325413 In-vitro Diagnostic Substance Mfg[a/]	245	14	$6.3b	$4.1b[b/]
325414 Biological Product (except Diagnostic) Mfg [a/]	335	15	$6.9b[b/]	$9.5b[b/]
SBA Small-entity Standard based on Annual Receipts	< $10 million in Receipts	$10 million + in Receipts	< $10 million in Receipts	$10 million + in Receipts
541940 Veterinary Services	24,422	53	$21.4b	$587m
621511 Medical Laboratories	2,186	258	$3.7b	$19.0b
622110 General Medical and Surgical Hospitals	1,067	1,984	$12.7b[b/]	$644.4[b]
611310 Colleges, Universities, and Professional Schools	Employment breakdown Undetermined		Receipts Undetermined	

[a] The size standard is measured by the number of establishments for this NAICS series rather than by the number of firms since the Economic Census does not provide statistics on the breakdown on size by the number of firms. As a result, the proportion of small entities may be inflated.
[b] Figure excludes proprietary data.
Source: The 2007 Economic Census. Department of Commerce, Census Bureau.

Projected Reporting, Recordkeeping, and Other Compliance Requirements

Reporting and recordkeeping requirements associated with the final regulations are discussed in the Benefits and Costs section of this document and in the final rules, APHIS-2009-0070 and CDC-2011-0012, under the heading "Paperwork Reduction Act."

Steps taken by APHIS and CDC to minimize Significant Economic Impacts on Small Entities

Based on our review of available information, APHIS and CDC 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.