

Update: Regulation of Select Agents and Toxins in the U.S.



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Centers for Disease Control and Prevention
Office of Public Health Preparedness and Response

Evolution of Select Agent and Toxin Regulations

**Antiterrorism Act
Select Agent
Program
Established
1996**

**Patriot Act
2001**

**Bioterrorism Act
2002**

**Select Agent
Final Rule
March 2005**

**Amerithrax
Attacks
Oct. 2001**

**BSAT
Congressional
Hearing
Oct. 2007**



EO 13486
January 2009

EO 13546
July 2010

Proposed Rule
October 2011

**FBI Amerithrax
Report
August 2008**

**Final Rule
October 2012**



October 2012 HHS Select Agents and Toxins Final Rule

- Tiered/Reduced Select Agent List
- Updated Responsible Official requirements
- Specific physical and cyber security requirements for Tier 1 Biological Select Agents and Toxins (BSAT)
- Personnel Suitability Programs for Tier 1 BSAT
- Occupational Health Programs for Tier 1 BSAT
- Broader Definition of Restricted Experiments
- Updated Transfer Requirements



FEDERAL REGISTER

Vol. 77 Friday,
No. 194 October 5, 2012

Part III

Department of Health and Human Services

42 CFR Part 73
Possession, Use, and Transfer of Select Agents and Toxins; Biennial
Review; Final Rule

Effective Dates

Effective Date	Section
December 4, 2012	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 13, 16, 17, 18, 19, 20, and 21
April 3, 2013	11, 12, 14, and 15

Additions & Removals

HHS Select Agent List

- **Additions**

- SARS-associated coronavirus (SARS-CoV)
- Lujo virus
- Chapare virus

- **Removals**

- *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*

Removals

HHS & Overlap Select Agent List

- **Removals from HHS List**

- Conotoxins, except short, paralytic alpha conotoxins containing the following nucleic acid sequence
- Shigatoxins
- Shiga-like ribosome inactivating proteins
- Staphylococcal Enterotoxins, except A, B, C, D, and E subtypes
- Tick-borne encephalitis complex viruses (Central European subtype)

- **Removals from Overlap List**

- Venezuelan Equine Encephalitis virus (subtypes 1D and 1E). All other subtypes to remain regulated.

Tier 1 Select Agents and Toxins

- Ebola and Marburg viruses
- Variola minor and Variola major viruses
- *Francisella tularensis*
- *Yersinia pestis*
- *Bacillus anthracis***
- *Burkholderia mallei* and *B. pseudomallei*
- Botulinum neurotoxin and neurotoxin-producing strains of *Clostridium botulinum*
- Foot-and-Mouth Disease virus*
- Rinderpest virus*

*USDA-regulated

**Pasteur strain exempt

Specific security requirements for Tier 1 Select Agent Possessors

- **Suitability assessments**
 - Pre-access suitability assessments
 - On-going assessment of the suitability of personnel
- **Physical security standards: access control**
 - Minimum of three security barriers to reach space that contains Tier 1 BSAT
 - Intrusion Detection System

Occupational Health Programs for Tier 1 BSAT

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.

Broader definition of Restricted Experiments

(a) An individual or entity may not conduct or possess products resulting from a restricted experiment with a select agent or toxin unless approved by and conducted in accordance with any conditions prescribed by the HHS Secretary

(b)(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.

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

EXCLUSIONS

Exclusion, Naturally Occurring Select Agents and Toxin

- Select agent or toxin in its naturally occurring environment is excluded provided that it has not been intentionally introduced, cultivated, collected, or otherwise extracted from its natural source.
 - Non-human primates that are naturally infected with Herpes B virus;
 - Castor beans containing ricin.
- If the select agent or toxin has been intentionally introduced, cultivated, collected, or otherwise extracted from its natural source, then it is no longer excluded.
 - Tissues from non-human primates infected with Herpes B;
 - Ricin extracted from the castor bean.

Exclusions

- Non-viable select agents or non-functional toxins.
- Toxins under the control of a principal investigator, treating physician or veterinarian, or commercial manufacturer or distributor are excluded, if
 - Specific quantities of toxins if the aggregate amount under the control of a principal investigator, treating physician or veterinarian, or commercial manufacturer or distributor does not exceed the amount specified.

Exclusion of an Attenuated Strain

- 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
- To apply, submit a request in writing to the Federal Select Agent Program
 - Must provide documentation establishing that the attenuated strain is eligible for exclusion
- The attenuated strain exclusion is effective upon notification to the applicant
- Listed on the Federal Select Agent Program website at:
<http://www.selectagents.gov/Select%20Agents%20and%20Toxins%20Exclusions.html>
- No longer excluded if subjected to manipulations that restore or enhance virulence

Federal Law Enforcement Exclusion

- Select agent or toxin seized by a Federal law enforcement agency provided that:
 - Report within 24 hours for Tier 1 BSAT
 - Report the seizure of known select agents or toxins (Report of Identification Form) within 7 calendar days
 - Secures and reports theft, loss, or release
 - As soon as practicable transfer to a registered entity (Request to Transfer Form) or destroy and report on the Report of Identification Form

EXEMPTIONS

Exemptions for Diagnostic Laboratories (42 CFR § 73.5)

- **General Diagnostic Exemption (42 CFR 73.5(a))**
- **Proficiency Testing (42 CFR 73.5 (b))**
- **Possession of products licensed or cleared as an investigational drug by the FDA (42 CFR 73.5 (c)(d))**
- **Public health emergency (42 CFR 73.5 (e))**

Exemptions Clinical/Diagnostic

- Clinical or diagnostic laboratories and other entities that possess, use, or transfer a select agent or toxin contained in a specimen presented for diagnosis or verification, or proficiency testing, will be exempt from the requirements, provided that certain conditions are met.

Impact on Laboratory Response Network

QA/QC strains	Tier 1	Select agent status
<i>Bacillus anthracis</i> Pasteur	No	regulated
<i>Bacillus anthracis</i> Sterne	No	excluded
<i>Brucella suis</i> 1330 positive control strain	No	regulated
<i>Brucella melitensis</i> 16 M strain	No	regulated
<i>Francisella tularensis</i> LVS	No	excluded
<i>Yersinia pestis</i> A1122	No	excluded

What must be done to qualify for a clinical/ diagnostic exemption?

A select agent or toxin must be:

- Within 7 calendar days of identification (diagnosis/verification), or within 90 calendar days of receipt (proficiency testing):
 - Transferred (according to the provisions of Section 16)
 - Destroyed on-site by a recognized sterilization inactivation process
 - Retained if the entity is registered for the select agent or toxin

What must be done to qualify for a clinical/ diagnostic exemption?

A select or toxin must also be:

- Secured against theft, loss, or release from the time it is identified to the time it is transferred or destroyed, and reported for any theft, loss, or release
- Identification must be reported to:
 - Federal Select Agent Program within 7 calendar days of identification (diagnosis/verification) or within 90 calendar days of receipt (proficiency testing)
 - Other appropriate authorities as required by Federal, State, or local law
 - Immediate Notification for Tier 1 BSAT
- Less stringent reporting may be allowed during extraordinary circumstances, such as a widespread outbreak.

APHIS/CDC Form 4 Report of Identification

- Clinical or Diagnostic Laboratories
 - Agents used only for diagnosis, verification, or proficiency testing
- Federal law enforcement agency
 - Seizures of known select agent or toxin

USDA		REPORTING THE IDENTIFICATION OF A SELECT AGENT OR TOXIN FROM A CLINICAL/DIAGNOSTIC SPECIMEN (APHIS/CDC FORM 4A)		FORM APPROVED OMB NO. 0578-0213 OMB NO. 0928-0076 EXP. DATE 10/31/2014	
INSTRUCTIONS					
Detailed instructions are available at http://www.selectagents.gov/CDForm.html . Answer all items completely and type or print in ink. This report must be signed and submitted to either APHIS or CDC:					
Animal and Plant Health Inspection Service Agricultural Select Agent Program 4700 River Road Unit 2, Mailstop 22, Cubicle 1A07 Riversdale, MD 20737 FAX: (301) 734-3652 Email: AgriculturalSelectAgentProgram@aphis.usda.gov			Centers for Disease Control and Prevention Division of Select Agents and Toxins 1600 Clifton Road NE, Mailstop A-46 Atlanta, GA 30333 FAX: (404) 718-2066 Email: CDCForm4@cdc.gov		Accession Number: (For Program Use Only)
Submit completed form only once by either email, fax, or mail					
SECTION A – REFERENCE LABORATORY INFORMATION					
1. Name of individual completing Sections A and B: First: _____ MI: _____ Last: _____		2. Email address: _____		3. Telephone #: _____	
4. <input type="checkbox"/> Registered Entity (APHIS or CDC Registration #: _____) <input type="checkbox"/> Clinical or Diagnostic Laboratory (non-registered entity (NRE)) (NRE #: (provided by APHIS or CDC): _____)			9. Entity name: _____		
5. Responsible Official or Laboratory Supervisor name: First: _____ MI: _____ Last: _____			10. Address (NOT a post office address): _____		
6. Telephone #: _____ 7. Fax #: _____		8. Email address: _____		13. Zip Code: _____	
SECTION B – SELECT AGENT OR TOXIN IDENTIFIED FROM CLINICAL/DIAGNOSTIC SPECIMEN(S)					
1. Select Agent or Toxin Identified: _____			2. Date identified: _____		
3. Case/patient/sample ID #(s): _____		4. # of samples received: _____		6. Case/patient origin (zip code): _____	
5. Sample type(s) received: _____					
7. Dispositions of select agent or toxin (complete all that apply): <input type="checkbox"/> Transferred (Provide entity name and date of transfer. Entity: _____ Date: _____) <input type="checkbox"/> Destroyed (Provide destruction method and date. Method: _____ Date: _____) <input type="checkbox"/> Retained (Provide name of person retaining sample. Name: _____)					
8. Were any of the samples containing a select agent or toxin handled outside of primary containment which may have led to an unintentional release and/or exposure to the select agent or toxin? <input type="checkbox"/> No <input type="checkbox"/> Yes (If Yes, you are required under 7 CFR Part 331.19, 9 CFR Part 121.19, and 42 CFR Part 73.19 to complete and submit an APHIS/CDC Form 3)					
9. Do you anticipate receiving additional samples/specimens for this case/patient that originate from the initial case (e.g. patient, environmental sample)? <input type="checkbox"/> No <input type="checkbox"/> Yes (If Yes, please refer to the guidance instructions at www.selectagents.gov for further directions.)					
10. Has the sender(s) (i.e. sample provider(s)) of the specimen(s) been notified of the identification of the select agent or toxin? <input type="checkbox"/> No <input type="checkbox"/> Yes <input type="checkbox"/> N/A NOTE: Please request completed and signed Sections C & D from each laboratory that was in possession of the specimen(s).					
11. Comments / Notes: 					
I hereby certify that the information contained in Sections A and B of this form is true and correct to the best of my knowledge. I understand that if I knowingly provide a false statement on any part of this form, or its attachments, I may be subject to criminal fines and/or imprisonment. I further understand that violations of 7 CFR 331, 9 CFR 121, or 42 CFR 73 may result in civil or criminal penalties, including imprisonment.					
Signature of Responsible Official/Laboratory Supervisor: _____					Date Signed: _____

What are the requirements for a provider of proficiency samples?

- At least seven calendar days prior to the transfer, the sender of the proficiency samples must report to APHIS or CDC:
 - Select agent or toxin to be transferred
 - Name and address of the recipient

Shipping and Receiving (Section 16)

- 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.

GUIDANCE

Guidance (www.selectagents.gov)

- Frequently Asked Questions
- Incident Response
- Information Systems Security Control
- Inventory Requirements
- Long Term Storage
- Occupational Health Program
- Physical Security Control
- Responsible Official
- SA Grams
- Security Risk Assessment Tool
- Shipment and Receipt of Packages
- Suitability Assessment
- Toxin Due Diligence
- Training

Tour of www.selectagents.gov

The screenshot shows a Windows Internet Explorer browser window displaying the National Select Agent Registry website. The address bar shows the URL <http://www.selectagents.gov/index.html>. The website header includes the APHIS logo (301-851-3300) and the CDC logo (404-216-2100). The main title is "National Select Agent Registry". A navigation menu includes "Home", "Resources", "About Us", "Forms", "Helpful Information", "Select Agents & Toxins", and "FAQ's". The page is dated "Last Updated: Tuesday, February 26, 2013".

What's New?

Website is being revamped based on Revised Select Agent regulations.

Influenza viruses containing the Hemagglutinin from the Goose/Guangdong/1/96 lineage, Request for Information and Comments

On October 17, 2012, the U.S. Department of Health and Human Services (HHS) posted in the Federal Register a notice seeking public comment regarding the classification of highly pathogenic avian influenza (HPAI) variants – specifically, influenza viruses that contain an HA from the A/goose/Guangdong/1/96 lineage. These variants have been shown to be transmissible in the ferret model and have been associated with infections in humans.

[October 2012 Federal Register Notice](#) (PDF 203K) and [February 2013 Federal Register Notice](#) (PDF 220K) seeks the public's opinion as to whether CDC should regulate such research to ensure labs follow appropriate biosafety controls.

PLEASE NOTE: We are reopening the comment period on February 8, 2013, to allow interested persons additional time to prepare and submit comments. Written or electronic comments must be received on or before March 11, 2013.

Those interested parties wishing to make a comment during the extended public comment period should visit <http://www.regulations.gov/#/docketDetail;D=CDC-2012-0010>.

APHIS/CDC Select Agent Regulations

The U.S. Departments of Health and Human Services (HHS) and Agriculture (USDA) published final rules (42 C.F.R. Part 73.7 C.F.R. Part 331. and 9 C.F.R. Part 121) in the

<http://www.selectagents.gov/index.html>

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Change Text Size: [A](#) [A](#) [A](#)

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If you have questions or comments about this website, contact lrsat@cdc.gov.

To report the identification of select agent or toxin, <http://www.selectagents.gov/CDForm.html>.

Anonymous Reporting

To provide a mechanism for you to report safety, security, or other concerns associated with select agents and toxins, Department of Health & Human Services, Office of Inspector General (OIG) maintains a hotline which offers a confidential means for reporting this vital information. When reporting these issues to OIG, please ensure that you indicate it is a "Select Agent Program" issue.

OIG Hotline contact information:

Voice: 1-800-HHS-TIPS (800-447-8477)
Fax: 1-800-223-8164
Web: <https://oig.hhs.gov/fraud/report-fraud/index.asp>
Mail: Office of Inspector General
Department of Health & Human Services
Attn: Hotline
P.O. Box 23489

Resources

Resources - Windows Internet Explorer

http://www.selectagents.gov/Resources.html

File Edit View Favorites Tools Help

Resources

agent and toxin laboratories. The videos describe how to prepare for an inspection and what transpires during and after an inspection.

[Click here to view the videos online & download](#)

Compliance Assistance

Please select from the below list of documents to assist in complying with the requirements of the Select Agents regulations:

- [Checklists](#)
- [Comparative Analysis of the Fourth and Fifth Editions of BMBL](#)
- [Containment Facility Design and Construction \(Secondary Barriers\)](#)
- [Containment for Work with Eastern Equine Encephalitis virus](#)
- [Guidance for Completing the Shipper's Declaration for Dangerous Goods](#)
- [Guidance for Meeting Training Requirements of the Select Agent Regulations](#)
- [Guidance for Suitability Assessments](#)
- [Guidance for the Inactivation of Select Agents and Toxins](#)
- [Guidance on the Shipment and Receipt of Packages with Select Agents and Toxins](#)
- [Guidance on the Use of Infectious Waste Treatment and Radiation Facilities Outside of Registered Space](#)
- [Guidelines for Avian Influenza Viruses](#)
- [Incident Response Plan](#)
- [Information Systems Security Control Guidance Document](#)
- [Long Term Storage](#)
- [NIH Guidelines](#)
- [Occupational Health Program Guidance Document for Working with Tier 1 Select Agents and Toxins](#)

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Select Agents and Toxins

The screenshot shows a Windows Internet Explorer browser window displaying the National Select Agent Registry website. The address bar shows the URL: <http://www.selectagents.gov>Select%20Agents%20and%20Toxins.html>. The browser's menu bar includes File, Edit, View, Favorites, Tools, and Help. The Favorites bar shows 'Select Agents and Toxins'. The website header features the APHIS logo (101-851-3200) and the CDC logo (404-210-2100). The main title is 'National Select Agent Registry'. A navigation menu includes Home, Resources, About Us, Forms, Helpful Information, Select Agents & Toxins, and FAQ's. The page is dated 'Last Updated: Monday, May 17, 2010'. The main content area is titled 'Select Agents and Toxins' and contains the following text:

The *Public Health Security and Bioterrorism Preparedness and Response Act of 2002, Subtitle A of Public Law 107-188* requires the Department of Health and Human Services (HHS) to establish and regulate a list of biological agents and toxins that have the potential to pose a severe threat to public health and safety. The *Agricultural Bioterrorism Protection Act of 2002* requires the United States Department of Agriculture (USDA) to establish and regulate a list of biological agents that have the potential to pose a severe threat to animal health and safety, plant health and safety, or to the safety of animal or plant products (Select Agents). CDC and APHIS share responsibility for some agents because they potentially threaten both humans and animals (overlap agents). The laws require HHS and USDA to review and republish the lists of Select Agents and toxins on at least a biennial basis.

This page includes links to the list of Select Agents and toxins and information about additions or deletions that have been made to the list based on recommendations made from the biennial review or advances in research.

[Select Agents and Toxins List](#)
[Select Agents and Toxins Exclusions](#)
[Select Agents and Toxins Restricted Experiments](#)
[Permissible Toxin Amounts](#)

Addition of Reconstructed 1918 Influenza virus to the list of HHS Select Agents and Toxins
(October 20, 2005)

HHS published an [interim final rule](#) (PDF 56KB) in the *Federal Register* on October 20, 2005 to add "Reconstructed replication competent forms of the 1918 pandemic influenza virus containing any portion of the coding regions of all eight gene segments" to the list of HHS Select Agents and toxins. The addition of the reconstructed 1918 pandemic influenza virus to the HHS Select Agents and toxins became effective on October 20, 2005.

The [CDC/NIH Biosafety in Microbiological and Biomedical Laboratories, 5th edition](#) includes information on the minimum containment for experiments involving this agent.

For more information on the biennial review of the lists of Select Agents and toxins, go to:

- [CDC Federal Register Notice](#) (PDF 59KB)

The browser's status bar shows 'Internet | Protected Mode: Off' and the system tray displays the time as 1:54 PM on 3/1/2013.

Frequently Asked Questions

The screenshot shows a Windows Internet Explorer browser window displaying the National Select Agent Registry website. The address bar shows the URL <http://www.selectagents.gov/FAQ.html>. The website header includes the APHIS logo with the phone number 301-851-3500 and the CDC logo with the phone number 404-216-2100. The main title is "National Select Agent Registry". A navigation menu contains links for Home, Resources, About Us, Forms, Helpful Information, Select Agents & Toxins, and FAQ's. The page is dated "Last Updated: Tuesday, February 19, 2013". The main content area is titled "Frequently Asked Questions" and lists several categories of FAQs: General FAQ's about Select Agents and Toxins, Legislature, Regulation, and Guidelines FAQ's, Registration FAQ's, Report of the Identification of a Select Agent or Toxin FAQ's, Biosafety FAQ's, Security FAQ's, Security Risk Assessments FAQ's, Training FAQ's, Transfers FAQ's, Due Diligence FAQ's, SARS FAQ's, and Responsible Official FAQ's. On the right side, there are options to "Change Text Size" and "Share This Page" (with a sub-link for "Print This Page"). The Windows taskbar at the bottom shows the system tray with the date and time as 1:56 PM on 3/1/2013.

www.selectagents.gov



For more information please contact Centers for Disease Control and Prevention

**1600 Clifton Road NE, Atlanta, GA 30333
Telephone, 1-800-CDC-INFO (232-4636)/TTY: 1-888-232-6348
E-mail: cdcinfo@cdc.gov Web: www.cdc.gov**

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.



**Centers for Disease Control and Prevention
Office of Public Health Preparedness and Response**