SELECT AGENTS AND BIOHAZARDS

BACKGROUND

As part of regulations enacted by the Public Health Security and Bioterrorism Preparedness and Response Act of 2002 (PL 107-188), researchers are now required to register with the federal government and get approval to possess or use any pathogen or toxin that is defined as a “select agent.” By February 7, 2002, most NIAID-supported investigators who own or use a select agent that is listed in 42 CFR 73 should have notified the CDC (published on December 13, 2002, this rule supersedes 42 CFR 72). All researchers who were previously registered must reregister in accordance with the new regulation, and all newcomers must register. Certain specified attenuated strains derived from select agents are excluded from the need to register. The excluded strains are posted and regularly updated at http://www.cdc.gov/od/sap

Additional Requirements for Facilities Transferring or Receiving Select Agents (Title 42 CFR Part 72.6) stems from the Antiterrorism and Effective Death Penalty Act of 1996, which requires the Secretary of Health and Human Services to regulate the transfer of certain biological agents that are harmful to humans. The CDC is responsible for the implementation of this regulation. The CDC’s Select Agent Program (SAP) currently requires the registration of facilities, including government agencies, universities, research institutions, and commercial entities. Helpful information may be found online via the SAP web site at http://www.cdc.gov/od/sap.

These regulations are designed to ensure that these infectious agents and toxins are shipped only to institutions or individuals which are equipped to handle them appropriately and have legitimate reasons to use them; and to implement a system whereby scientists and researchers involved in legitimate research may continue transferring and receiving these agents without undue burden.

The CDC’s Select Agent List and the NIAID list of priority pathogens are included within the following pages. Note that the lists have incomplete overlap. However, reviewers should assess any potential biohazard issues that apply to organisms on either list.

GENOMIC MATERIAL FROM SELECT AGENTS

The following additional guidance regards genomic material from select agents that is subject to 42 CFR 73 is from 42 CFR 73.4(e) and 73.5(e) and specifies genetic elements, recombinant nucleic acids, and recombinant organisms that are subject to the requirements of Possession, Use, and Transfer of Select Agents and Toxins (42 CFR Part 73):

1. Select agent viral nucleic acids (synthetic or naturally derived, contiguous or fragmented, in host chromosomes or in expression vectors) that can encode infectious and/or replication competent forms of any of the select agent viruses.

2. Nucleic acids (synthetic or naturally derived) that encode for the functional form(s) of any of the toxins listed in the Select Agent List if the nucleic acids:
   i. Are in a vector or host chromosome; or
   ii. Can be expressed in vivo or in vitro; or
   iii. Are in a vector or host chromosome and can be expressed in vivo or in vitro.
3. Viruses, bacteria, fungi, and toxins listed in the Select Agent List that have been genetically modified.

Additional clarification

- **Non-viable select agent organisms** (including agents in fixed tissues). Select agent organisms that have been treated in such a manner (e.g. gamma irradiation) that they are no longer able to replicate (i.e. non-viable, inactivated, killed, or dead) are not select agents. See 42 Parts 73.4(f)(2) and 73.5 (f)(2).

- **Purified genomic material or genetic elements from select agent viruses.** Genetic elements (nucleic acids) from select agent viruses are regulated if they are in host chromosomes or expression vectors and if they encode for infectious or replication competent forms of any of the select agent viruses. See 42 Parts 73.4(e)(1) and 73.5 (e)(1).

- **Purified genomic material or genetic elements from select agent bacteria** are select agents if the nucleic acid encodes for a functional form of a listed toxin in a vector or host chromosome and/or can be expressed *in vivo* or *in vitro*. See 42 Parts 73.4(e)(2) and 73.5 (e)(2).

**EVALUATION GUIDANCE FOR SELECT AGENTS AND BIOHAZARDS**

If an application indicates the involvement of select agents or other biohazardous substances, it must specifically address:

- Which select agent(s)/pathogens will be used?
- Is the institution/entity registered (the Program Director/Principal Investigator may state that registration is complete or pending, without providing documentation)?
- Is the entity compliant or exempt from the regulations? If it is exempt, why?
- Are the proposed facilities appropriate for handling, storage, and biocontainment?
- What procedures are in place to monitor biosafety and biocontainment?
- What security precautions (including physical security) are in place? Are security risk assessments complete/pending for all involved personnel?
- How does the entity manage/enforce compliance with the select agent rule? Has a Responsible Official(s) (RO) been designated? How often does the RO conduct inspections? Is there a biosafety committee?

Issues relating to select agents and biohazards are not scored, but they can affect a reviewer’s assessment under the following review criteria.

- **Investigator:** The investigator/collaborator appears to lack knowledge about appropriate methods for working with select agents and biohazardous agents.
- **Environment:** Appropriate containment is not proposed.
- **Approach:** Inappropriate plans are provided.

If the application poses serious hazards, these hazards should be identified by the Scientific Review Group, and any concerns about the adequacy of safety procedures will be highlighted
as a special note (BIOHAZARD) on the summary statement. \textbf{If the proposed project is egregiously hazardous, then reviewers should consider rating the application \textquotedblleft NRFC\textquotedblright \ (Not Recommended for Further Consideration).}

\textbf{NOTE:} Applicants from foreign countries are required to follow the same select agent and biohazard regulations that apply to domestic applicants.
**CDC LIST OF SELECT AGENTS AND TOXINS**


### HHS AND USDA SELECT AGENTS AND TOXINS

- **7 CFR Part 331, 9 CFR Part 121, and 42 CFR Part 73**

<table>
<thead>
<tr>
<th>HHS SELECT AGENTS AND TOXINS</th>
<th>OVERLAP SELECT AGENTS AND TOXINS</th>
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<tbody>
<tr>
<td>Abrin</td>
<td><em>Bacillus anthracis</em></td>
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<tr>
<td>Botulinum neurotoxins</td>
<td><em>Brucella abortus</em></td>
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<tr>
<td>Botulinum neurotoxin producing species of <em>Clostridium</em></td>
<td><em>Brucella melitensis</em></td>
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<tr>
<td>Cercopithecin herpesvirus 1 (Herpes B virus)</td>
<td><em>Brucella suis</em></td>
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<tr>
<td><em>Clostridium perfringens</em> epsilon toxin</td>
<td><em>Burkholderia mallei</em> (formerly <em>Pseudomonas mallei</em>)</td>
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<tr>
<td><em>Coccioides posadasii/Coccioides immittis</em></td>
<td><em>Burkholderia pseudomallei</em> (formerly <em>Pseudomonas pseudomallei</em>)</td>
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<td>Conotoxins</td>
<td><em>Hendra virus</em></td>
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<td><em>Coxella burnetii</em></td>
<td><em>Nipah virus</em></td>
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<td>Crimean-Congo haemorrhagic fever virus</td>
<td><em>Rift Valley fever virus</em></td>
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<tr>
<td>Diacetoxycirpenol</td>
<td><em>Venezuelan Equine Encephalitis virus</em></td>
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<td>Eastern Equine Encephalitis virus</td>
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<td>Ebola virus</td>
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<td><em>Francisella tularensis</em></td>
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<td>Lassa fever virus</td>
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<td>Marburg virus</td>
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<tr>
<td>Monkeypox virus</td>
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<tr>
<td>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)</td>
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<tr>
<td><em>Ricin</em></td>
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<td><em>Rickettsia prowazekii</em></td>
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<td><em>Rickettsia rickettsii</em></td>
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<td>Saxtoxin</td>
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<td>Shiga-like ribosome inactivating proteins</td>
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<td>Shigatoxin</td>
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<td>South American Haemorrhagic Fever viruses</td>
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<td>Flexible</td>
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<td>Guaranito</td>
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<td>Junin</td>
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<td>Machupo</td>
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<td>Sabia</td>
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<td><em>Staphylococcal enterotoxins</em></td>
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<td><em>T-2</em> toxin</td>
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<td>Tetradotoxin</td>
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<td>Tick-borne encephalitis complex (flav) viruses</td>
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<td>Central European Tick-borne encephalitis</td>
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<td>Far Eastern Tick-borne encephalitis</td>
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<tr>
<td>Kyasanur Forest disease</td>
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<td><em>Omsk Hemorrhagic Fever</em></td>
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<tr>
<td>Russian Spring and Summer encephalitis</td>
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<tr>
<td>Variola major virus (Smallpox virus)</td>
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<tr>
<td>Variola minor virus (Alastrim)</td>
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<tr>
<td><em>Yersinia pestis</em></td>
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### Note: The select agent list is distinct from:

* NIAID's Emerging and Re-emerging Infectious Diseases (next pages), and

List of NIAID Emerging and Re-emerging Diseases
http://www3.niaid.nih.gov/topics/emerging/list.htm

Group I—Pathogens Newly Recognized in the Past Two Decades
Acanthamebiasis
Australian bat lyssavirus
Babesia, atypical
Bartonella henselae
Ehrlichiosis
Encephalitozoon cuniculi
Encephalitozoon hellem
Enterocytozoon bieneusi
Helicobacter pylori
Hendra or equine morbilli virus
Hepatitis C
Hepatitis E
Human herpesvirus 8
Human herpesvirus 6
Lyme borreliosis
Parvovirus B19

Group II—Re-emerging Pathogens
Enterovirus 71
Clostridium difficile
Mumps virus
Streptococcus, Group A
Staphylococcus aureus

Group III—Agents with Bioterrorism Potential
NIAID—Category A
- *Bacillus anthracis* (anthrax)
- *Clostridium botulinum* toxin (botulism)
- *Yersinia pestis* (plague)
- *Variola major* (smallpox) and other related pox viruses
- *Francisella tularensis* (tularemia)
- Viral hemorrhagic fevers
  - Arenaviruses
    - LCM, Junin virus, Machupo virus, Guanarito virus
  - Lassa Fever
  - Bunyaviruses
    - Hantaviruses
    - Rift Valley Fever
  - Flaviruses
    - Dengue
  - Filoviruses
    - Ebola
    - Marburg

NIAID—Category B
- *Burkholderia pseudomallei*
- *Coxiella burnetii* (Q fever)
- Brucella species (brucellosis)
- *Burkholderia mallei* (glanders)
- *Chlamydia psittaci* (Psittacosis)
- Ricin toxin (from Ricinus communis)
- Epsilon toxin of *Clostridium perfringens*
- Staphylococcus enterotoxin B
- Typhus fever (Rickettsia prowazekii)
- Food- and waterborne pathogens
  - Bacteria
Diarrheagenic *E. coli*
- Pathogenic *Vibrios*
- Shigella species
- Salmonella
- *Listeria monocytogenes*
- *Campylobacter jejuni*
- *Yersinia enterocolitica*
  - Viruses (Caliciviruses, Hepatitis A)
  - Protozoa
    - *Cryptosporidium parvum*
    - *Cyclospora cayatanensis*
    - *Giardia lamblia*
    - *Entamoeba histolytica*
    - Toxoplasma
  - Fungi
    - Microsporidia
- Additional viral encephalitides
  - West Nile virus
  - LaCrosse
  - California encephalitis
  - VEE
  - EEE
  - WEE
  - Japanese Encephalitis virus
  - Kyasanur Forest virus

**NIAID—Category C**
Emerging infectious disease threats such as Nipah virus and additional hantaviruses.

**NIAID priority areas:**
- Tick-borne hemorrhagic fever viruses
  - Crimean-Congo Hemorrhagic Fever virus
- Tick-borne encephalitis viruses
- Yellow fever
- Multidrug-resistant TB
- Influenza
- Other Rickettsias
- Rabies
- Prions
- Chikungunya virus
- Severe acute respiratory syndrome-associated coronavirus (SARS-CoV)
- Antimicrobial resistance, excluding research on sexually transmitted organisms*
  - Research on mechanisms of antimicrobial resistance
  - Studies of the emergence and/or spread of antimicrobial resistance genes within pathogen populations
  - Studies of the emergence and/or spread of antimicrobial-resistant pathogens in human populations
  - Research on therapeutic approaches that target resistance mechanisms
  - Modification of existing antimicrobials to overcome emergent resistance
- Antimicrobial research, as related to engineered threats and naturally occurring drug-resistant pathogens, focused on development of broad-spectrum antimicrobials
- Innate immunity, defined as the study of non-adaptive immune mechanisms that recognize, and respond to, microorganisms, microbial products, and antigens
- *Coccidioides immitis* (added February 2008)
- *Coccidioides posadasii* (added February 2008)

* NIAID Category C Antimicrobial Resistance—Sexually Transmitted Excluded Organisms