

CONTROLLED SUBSTANCES

Controlled substances are pharmaceuticals or chemicals strictly regulated under the Controlled Substance Act (CSA). They are placed into schedules based on their medical use, relative abuse potential, dependence liability, and concern for safety. This SOP was created in accordance with CSA regulatory requirements.

The U.S. Drug Enforcement Administration (DEA) recognizes five drug schedules.

Schedule I (C-1)

Principal Investigators (Pis) who wish to possess, receive, or transfer select agents or toxins must gain approval from their department head/chair and notify EHS at least **twelve (12) weeks** prior to such action to allow adequate time to complete the registration process.

Projects involving the use of regulated select agents or toxins are subject to prior **UNK Institutional Biosafety Committee (IBC)** review and approval, regardless of whether such projects involve recombinant or synthetic nucleic acids. Major provisions of the regulations for such projects are described below. Consult the actual regulations or contact EHS for a full description of regulatory requirements.

- The United States Departments of Health and Human Services or Agriculture must approve personnel who work with and/or have access to regulated select agents or toxins. No person should possess or have access to regulated select agents or toxins without first having obtained approval. This process is referred to as Security Risk Assessments. Approvals are valid for a maximum of three years.
- The registration process with CDC/APHIS must be completed prior to possessing or commencing work with regulated select agents or toxins. Registration is valid for a maximum of three years.

- Entities (i.e., UNK) that possess, receive, or transfer regulated agents or toxins must designate a Responsible Official (RO). At UNK, **the Director of EHS serves in this capacity. The EHS Biosafety Officer serves as the Alternate Responsible Official.** The RO is responsible for all official correspondence with federal agencies, including coordination of the registration and security risk assessment processes, oversight and inspection of laboratories, reporting and recordkeeping, and training. PIs also have similar responsibilities with respect to their individual laboratories.
- Work with regulated select agents is subject to the following requirements:
 - Development and implementation of a written safety plan that is consistent with BMBL, NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules, 29 CFR 1910.1450 (OSHA's Lab Standard), 29 CFR 1910.1200 (OSHA's Hazard Communication Standard).
 - Development and implementation of a security plan. Some elements of the plan will be covered by institutional procedures and policies. Work/project specific elements will include IT (information technology) security, barriers (i.e., locks, video surveillance, maintenance and custodial activities, passwords, etc.), etc.
 - Separation of regulated select agent use and storage locations from public areas of the building.
 - Development and implementation of an incident response plan. This plan includes preplanned responses for incidents that may occur within a facility or to the facility. Examples include spills, natural disasters, fire, etc.
 - Initial and annual refresher training for all workers pertinent to the containment level of the work being conducted, the select agent regulations and developed plans.
 - Maintenance of an accurate inventory.
- All regulated select agent transfers (off-site and intra-facility) must be managed through EHS with appropriate documentation/records.
- In some cases, destructions of regulated select agents must be managed through EHS with appropriate documentation/records.
- Immediate notification of theft, loss, or release of regulated select agents must be made to the Responsible Official, who in turn is responsible to notify appropriate federal agencies.

Select Agents and Toxins List

**Denotes Tier 1 Agent*

The following biological agents and toxins have been determined to have the potential to pose a severe threat to both human and animal health, to plant health, or to animal and plant products. An attenuated strain of a select agent or an inactive form of a select toxin may be excluded from the requirements of the Select Agent Regulations. Such exclusions are not completely captured by the footnotes indicated below. Refer to the Select Agent program website for a complete and current list of exclusions.

HHS SELECT AGENTS AND TOXINS

Abrin

Bacillus cereus Biovar anthracis*

Botulinum neurotoxins*

Botulinum neurotoxin producing species of Clostridium*

Conotoxins (Short, paralytic alpha conotoxins containing the following amino acid sequence X₁CCX₂PACGX₃X₄X₅X₆CX₇)

Coxiella burnetii

Crimean-Congo haemorrhagic fever virus

Diacetoxyscirpenol

Eastern Equine Encephalitis virus¹

Ebola virus*

Francisella tularensis*

Lassa fever virus

Lujjo virus

Marburg virus*

Monkeypox virus

Reconstructed replication competent forms of the 1918 pandemic influenza virus containing any portion of the coding regions of all eight gene segments (Reconstructed 1918 Influenza virus)

Ricin

Rickettsia prowazekii

SARS-associated coronavirus (SARS-CoV)

Saxitoxin

South American Haemorrhagic Fever viruses:

Chapare, Guanarito, Junin, Machupo, Sabia

Staphylococcal enterotoxins A,B,C,D,E subtypes

T-2 toxin

Tetrodotoxin

Tick-borne encephalitis complex (flavi) viruses:

Far Eastern subtype, Siberian subtype

Kyasanur Forest disease virus

Omsk hemorrhagic fever virus

Variola major virus (Smallpox virus)*

Variola minor virus (Alastrim)*

Yersinia pestis*

OVERLAP SELECT AGENTS AND TOXINS

Bacillus anthracis*

Bacillus anthracis Pasteur strain

Brucella abortus

Brucella melitensis

Brucella suis

Burkholderia mallei*

Burkholderia pseudomallei*

Hendra virus

Nipah virus

Rift Valley fever virus

Venezuelan equine encephalitis virus¹

USDA SELECT AGENTS AND TOXINS

African horse sickness virus

African swine fever virus

Avian influenza virus¹

Classical swine fever virus

Foot-and-mouth disease virus*

Goat pox virus

Lumpy skin disease virus

*Mycoplasma capricolum*¹

*Mycoplasma mycoides*¹

Newcastle disease virus^{1,2}

Peste des petits ruminants virus

Rinderpest virus*

Sheep pox virus

Swine vesicular disease virus

USDA PLANT PROTECTION AND QUARANTINE (PPQ) SELECT AGENTS AND TOXINS

Peronosclerospora philippinensis (*Peronosclerospora sacchari*)

Phoma glycinicola (formerly *Pyrenochaeta glycines*)

Ralstonia solanacearum

Rathayibacter toxicus

Sclerophthora rayssiae

Synchytrium endobioticum

Xanthomonas oryzae

¹ Select agents that meet any of the following criteria are excluded from the requirements of this part: Any low pathogenic strains of avian influenza virus, South American genotype of eastern equine encephalitis virus, west African clade of Monkeypox viruses, any strain of Newcastle disease virus which does not meet the criteria for virulent Newcastle disease virus, all subspecies *Mycoplasma capricolum* except subspecies *capripneumoniae* (contagious caprine pleuropneumonia), all subspecies *Mycoplasma mycoides* except subspecies *mycoides* small colony (*Mmm SC*) (contagious bovine pleuropneumonia), and any subtypes of Venezuelan equine encephalitis virus except for Subtypes IAB or IC, provided that the individual or entity can verify that the agent is within the exclusion category.

² A virulent Newcastle disease virus (avian paramyxovirus serotype 1) has an intracerebral pathogenicity index in day-old chicks (*Gallus gallus*) of 0.7 or greater or has an amino acid sequence at the fusion (F) protein cleavage site that is consistent with virulent strains of Newcastle disease virus. A failure to detect a cleavage site that is consistent with virulent strains does not confirm the absence of a virulent virus.

Key Definitions

Biological Agent: 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

Toxin: 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.

Tier 1 Select Agent or Toxin

A subset of select agents and toxins have been designated as Tier 1 because these biological agents and toxins present the greatest risk of deliberate misuse with significant potential for mass casualties or devastating effect to the economy, critical infrastructure, or public confidence, and pose a severe threat to public health and safety. Entities that possess, use, or transfer Tier 1 select agents and toxins must adhere to the additional requirements detailed within the Select Agent Regulations.

Clarifications

Genetic Elements

The following genetic elements, recombinant and/or synthetic nucleic acids, and recombinant and/or synthetic organisms are regulated as select agents (See sections 3(c) and 4(c) of 42 CFR Part 73, 9 CFR Part 121, and 7 CFR Part 331):

- Nucleic acids that can produce infectious forms of any of the select agent viruses.
- Recombinant and/or synthetic nucleic acids that encode for the functional form(s) of select toxins if the nucleic acids:
 - Can be expressed *in vivo* or *in vitro*, or
 - Are in a vector or recombinant host genome and can be expressed *in vivo* or *in vitro*.
- Select agents and toxins that have been genetically modified.

Additional information is available in the [Guidance on the Regulation of Select Agent and Toxin Nucleic Acids](#).

Select Agent and Toxins Exclusions

Based upon consultations with subject matter experts and a review of relevant published studies and information provided by the entities requesting the exclusions, the Federal Select Agent Program has determined that certain attenuated select agent strains or less toxic select toxins are not subject to the requirements of the select agent regulations. These exclusions are published on the Federal Select Agent Program web site (www.selectagents.gov) and are limited to stated purpose/activities.

An excluded select agent strain or modified toxin will be subject to the regulations if there is a reintroduction of factor(s) associated with virulence, toxic activity, or other manipulations that modify the attenuation such that virulence or toxic activity is restored or enhanced. In addition, excluded select agent strains or modified toxins are not exempt from the requirements of other applicable regulations or guidelines (e.g., NIH guidelines, USDA/APHIS permits, etc.). Any select agent or toxin that is in its naturally occurring environment provided the select agent or toxin has not been intentionally introduced, cultivated, collected, or otherwise extracted from its natural source.

Genetic modifications to excluded attenuated strains may require submission, review, and approval of a separate exclusion request. Consult with EHS to determine applicability of any published exclusion to an attenuated, and/or genetically modified strain. In general, the following types of activities require registration or application for specific exclusion:

- Genetic manipulations of excluded, attenuated strains that enhance or restore virulence are subject to registration. Generally, genetic manipulations that delete or inactivate genes of excluded, attenuated strains would not reasonably be expected to increase virulence and are therefore not subject to registration. However, registration must be sought if the PI later determines that the modification has enhanced virulence.
- Introduction of antibiotic resistance markers **may** require registration or application for a specific exclusion. However, introduction of sequences encoding reporter genes (e.g., GFP or beta-galactosidase) are not subject to registration or separate exclusion. A determination is generally based on whether the antibiotic resistance could compromise the use of the drug to control disease agents used in humans, veterinary medicine, or agriculture.

All provisions of the regulations remain in full-force until the Federal Select Agent Program provides positive, written consideration of an exemption request.

Permissible Toxin Amounts

The following HHS toxins under the control of a principal investigator, treating physician or veterinarian, or commercial manufacturer or distributor, if the aggregate amount does not exceed, at any time, the amounts indicated in the table below:

Toxin	Amount
Abrin	1000 mg
Botulinum toxin	1 mg
Short, paralytic alpha conotoxins	100 mg
Diacetoxyscirpenol (DAS)	10,000 mg
Ricin	1000 mg
Saxitoxin	500 mg
Staphylococcal Enterotoxins (Subtypes A, B, C, D, and E)	100 mg
T-2 toxin	10,000 mg
Tetrodotoxin	500 mg

Possession of the above toxins in amounts less than that indicated in the table does not exempt the possessor from the requirement of UNK IBC review and approval of work with the toxin.

Prohibitions

The following experiments require express prior approval from the Secretary of HHS/USDA:

- Experiments utilizing recombinant DNA that involve the deliberate transfer of a drug resistance trait to select agents that are not known to acquire the trait naturally, if such acquisition could compromise the use of the drug to control disease agents in humans, veterinary medicine, or agriculture.
- Experiments involving the deliberate formation of recombinant DNA containing genes for the biosynthesis of toxins lethal for vertebrates at an LD₅₀ of less than 100 ng/kg body weight.

Generally, HHS and USDA require Agency review and approval of any protocol or project involving the transfer of an antibiotic resistance trait to a listed agent, regardless of whether the antibiotic is used to treat infections in humans or animals.