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Exclusion Guidance Document

(42 CFR §§ 73.3, 73.4; 9 CFR §§ 121.3, 121.4; 7 CFR § 331.3)

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Centers for Disease Control and Prevention (CDC)
Division of Select Agents and Toxins
Animal and Plant Health Inspection Service (APHIS)
Agriculture Select Agent Services

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Change/Highlight Section

Revisions: This is a living document subject to ongoing improvement. Feedback or suggestions for improvement from registered select agent entities or the public are welcome. Submit comments directly to the Federal Select Agent Program at:

CDC: LRSAT@cdc.gov

APHIS: AgSAS@aphis.usda.gov

Revision History:

March 27, 2013: Initial Posting

March 2017: Updates include new regulatory requirements, improved language and corrected errors, and changes to Regulatory Exclusions list.

Introduction

The Federal Select Agent Program (FSAP) oversees the use, possession, and transfer of select agents and toxins at registered entities throughout the United States. The select agent regulations provide criteria for the exclusion of select agents and toxins (See [42 CFR §§ 73.3, 73.4](#); [9 CFR §§ 121.3, 121.4](#); [7 CFR § 331.3](#)). This guidance document provides additional information to entities or individuals who request to exclude attenuated strains of select agents or select toxins modified to be less potent or toxic from the requirements of the select agent regulations.

Regulatory Exclusions

In accord with [42 CFR §§ 73.3, 73.4](#); [9 CFR §§ 121.3, 121.4](#); [7 CFR § 331.3](#), select agents or toxins that meet any of the following criteria are excluded from the select agent regulations:

- 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 is excluded.
- Non-viable select agents or nontoxic select toxins are excluded.
- A select agent or toxin that has been subjected to decontamination or a destruction procedure when intended for waste disposal is excluded.
- If a select agent or regulated nucleic acid that can produce infectious forms has been subjected to a validated inactivation procedure and confirmed through a viability testing protocol, it is excluded:
 - Surrogate strains known to possess the same inactivation properties can be used to validate an inactivation procedure.
 - In case of strain-to-strain variations of inactivation resistance, the inactivation procedure validated on a less resistant strain must also be validated on the more resistant strain.
- Material containing a select agent is excluded when subjected to a procedure that removes all viable select agent cells, spores, or virus particles and the material is subjected to a viability testing protocol to ensure that the removal method has rendered the material free of all viable select agent.
- Select agents or regulated nucleic acids that can produce infectious forms of any select agent virus not subjected to a validated inactivation procedure or material containing a select agent not subjected to a procedure that removes all viable select agent cells, spores, or virus particles may be excluded if:
 - After requesting a determination by the FSAP, the material is determined by FSAP to be effectively inactivated or effectively removed. To apply for such a determination, an individual or entity must submit a written request and supporting scientific information to FSAP (see below). FSAP will issue a written decision granting or denying the request. The purpose of this provision in the regulations is to allow FSAP to address those rare situations where there may be a need to take material out of containment without following the exact requirements for viability testing. For example, consider a situation where an entity filters serum that contains a select agent but the recovered volume is so low that the requirement to perform a viability test on every sample would further deplete the sample volume and not leave enough for experiments. In these situations, an entity may submit a request to FSAP to apply an alternative select agent removal or inactivation procedure and/or an alternative means of validation. To apply for this determination, a registered individual or entity must submit a written request including:
 - A justification regarding the alternative procedure including a description of what material is to be waived.

- The inactivation protocol and viability test to be used.
 - Validation data.
 - Any other supporting information/references, such as scientific references.
 - FSAP will issue a written decision granting or denying the request.
- Except as required in § 73.16(l), the aggregate amount of the toxin under the control of a principal investigator, treating physician or veterinarian, or commercial manufacturer or distributor is excluded as long as it does not, at any time, exceed the following amounts: 1000 mg of Abrin; 1 mg of Botulinum neurotoxins; 100 mg of short, paralytic alpha conotoxins containing the following amino acid sequence X1CCX2PACGX3X4X5X6CX7¹ 10,000 mg of Diacetoxyscirpenol; 1000 mg of Ricin; 500 mg of Saxitoxin; 100 mg of Staphylococcal enterotoxins (subtypes A-E); 10,000 mg of T-2 toxin; or 500 mg of Tetrodotoxin. Provided that,
 - (i) The toxin is transferred only after the transferor uses due diligence and documents the identification of the recipient and the legitimate need (e.g., prophylactic, protective, bona fide research, or other peaceful purpose) claimed by the recipient to use such toxin. Documentation should include, but is not limited to, the recipient identity information (name, institution, address, telephone number and email address); name of the toxin and the total amount transferred; and the legitimate need claimed by the recipient. Notwithstanding the provisions of paragraph (d) of this section, the HHS Secretary retains the authority to, without prior notification, inspect, and copy or request the submission of the due diligence documentation to CDC.
- An animal inoculated with or exposed to an HHS select toxin is excluded.
- HHS select toxins identified in an original food sample or clinical sample are excluded.
- For those laboratories that are not exempt under § 73.5 (a) and § 73.6 (a), Botulinum neurotoxin that is produced as a byproduct in the study of Botulinum neurotoxin producing species of *Clostridium* is excluded so long as the toxin has not been intentionally cultivated, collected, purified, or otherwise extracted, and the material containing the toxin is rendered non-toxic and disposed of within 30 days of the initiation of the culture.
- Waste generated during the delivery of patient care by health care professionals from a patient diagnosed with an illness or condition associated with a select agent is excluded as long as the waste is decontaminated or transferred for destruction by complying with state and federal regulations within seven calendar days of the conclusion of patient care.
 - Waste including specimens associated with patient care must be secured against theft, loss, or release during the period between identification and transfer or

¹ C = Cysteine residues (indicated in bold) are all present as disulfides, with the 1st and 3rd Cysteine, and the 2nd and 4th Cysteine forming specific disulfide bridges; The consensus sequence includes known toxins α -MI and α -GI (shown above) as well as α -GIA, Ac1.1a, α -CnIA, α -CnIB; X1 = any amino acid(s) or Des-X; X2 = Asparagine or Histidine; P = Proline; A = Alanine; G = Glycine; X3 = Arginine or Lysine; X4 = Asparagine, Histidine, Lysine, Arginine, Tyrosine, Phenylalanine or Tryptophan; X5 = Tyrosine, Phenylalanine, or Tryptophan; X6 = Serine, Threonine, Glutamate, Aspartate, Glutamine, or Asparagine; X7 = Any amino acid(s) or Des X; and “Des X” = “an amino acid does not have to be present at this position.” For example if a peptide sequence were XCCHPA then the related peptide CCHPA would be designated as Des-X.

destruction, and any theft, loss, or release of the waste including specimens must be reported to FSAP. All patient-generated waste including specimens kept more than seven days after the conclusion of acute patient care are subject to the select agent regulations. There is no requirement to document the transfer or destruction of waste, including specimens generated from the patient, provided that the waste is decontaminated or transferred for destruction by complying with state and federal regulations within seven calendar days of the conclusion of patient care.

- Any South American genotypes of Eastern Equine Encephalitis Virus and any West African Clade of Monkeypox virus is excluded provided that the individual or entity can identify that the agent is within the exclusion category.
- Any subtypes of Venezuelan equine encephalitis virus except for Subtypes IAB or IC are excluded, provided that the individual or entity can identify that the agent is within the exclusion category.
- Low pathogenic strains of avian influenza virus are excluded, provided that the individual or entity can identify that the agent is within the exclusion category.
- Any strain of Newcastle disease virus which does not meet the criteria for virulent Newcastle disease virus are excluded, provided that the individual or entity can identify that the agent is within the exclusion category.
- All subspecies of *Mycoplasma capricolum* except subspecies capripneumoniae (contagious caprine pleuropneumonia) and all subspecies *Mycoplasma mycoides* except subspecies *mycoides* small colony (*Mmm* SC) (contagious bovine pleuropneumonia).

Requests for Exclusion of Attenuated Strains or Toxins Modified to be Less Potent or Toxic

The HHS Secretary or APHIS Administrator will grant or deny the request for reconsideration as promptly as circumstances allow and will state, in writing, the reasons for the decision.

If an excluded attenuated strain or modified toxin is subjected to any manipulation that restores or enhances its virulence or toxic activity, the resulting select agent or toxin will be subject to the select agent regulations.

Review of Exclusion Requests

FSAP reviews requests for exclusions and may seek input from CDC'S Intragovernmental Select Agents and Toxins Technical Advisory Committee (ISATTAC), which is comprised of employees from CDC, NIH, FDA, USDA/Animal and Plant Health Inspection Service (APHIS), USDA/Agricultural Research Service (ARS), USDA/Center for Veterinary Biologics (CVB) and the Department of Defense (DOD). The ISATTAC reviews requests for the exclusion of attenuated strains and modified toxins of HHS only or overlap select agents and toxins. For VS only agents, federal subject matter experts from APHIS, ARS, and CVB will review the request.

Some of the criteria used to determine if a strain or toxin should be excluded are given below. The entities request should contain the following:

- a) Documented history of not causing disease in humans, or relevant animal or plant models.
- b) Defined genetic mutations or alterations known to attenuate virulence in humans or relevant animal or plant models.
- c) Data showing the mutations have a low frequency of reversion to wild-type virulence.
- d) Level of difficulty in engineering the attenuated strain to restore wild-type virulence. For each pathogen, the sample size and type of animal or plant model used to test virulence is important.
- e) Quantitative measures demonstrating a change in virulence in an appropriate animal or plant model.
- f) Information regarding tests that may be conducted to differentiate animals or plants exposed to the attenuated strain from those infected with the wild-type organism.
- g) Related published scientific papers supporting the methods and data provided for the exclusion.

See the data requirements necessary for consideration of an exclusion request for [highly pathogenic Avian influenza \(HPAI\) virus](#) on the FSAP website.

Request to Appeal a Decision Denying an Exclusion Request

An individual or entity may make a written request to the HHS Secretary or APHIS Administrator for reconsideration of a decision denying an exclusion application. The written request for reconsideration must state the facts and reasoning upon which the individual or entity

believes the decision was incorrect. FSAP will grant or deny the request for reconsideration as promptly as circumstances allow and will state, in writing, the reasons for the decision. You may submit the written request to your FSAP file manager.

Exclusion of Select Agents or Toxins Seized by a Federal Law Enforcement Agency

Under sections 3(f) and 4(f) of the select agent regulations, certain federal law enforcement activities are excluded from the select agent regulations (e.g., collecting evidence from a laboratory crime scene) as long as the law enforcement agency meets the requirements of the exclusion:

1. As soon as practicable, the federal law enforcement agency transfers the seized agent or toxin to an entity eligible to receive such agent or toxin or destroys the agent or toxin by a recognized sterilization or inactivation process.
2. The federal law enforcement agency safeguards and secures the seized agent or toxin against theft, loss, or release and reports any theft, loss, or release of such agent or toxin.
3. The federal law enforcement agency reports the seizure of the select agent or toxin by submitting the [APHIS/CDC Form 4](#). For more information please contact FSAP.