Exclusion Guidance Document

Prepared by

Federal Select Agent Program

U.S. Department of Agriculture (USDA)/Animal and Plant Health Inspection Service (APHIS)

U.S. Department of Health and Human Services (HHS)/Centers for Disease Control and Prevention (CDC)

Preface

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:

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Introduction

The Federal Select Agent Program 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 and 73.4, 9 CFR § 121.3 and 121.4, 7 CFR 331.3). This guidance document is meant to provide additional information to entities or individuals who request to exclude attenuated strains of select agents or inactivated select toxins from the requirements of the select agent regulations.

Regulatory Exclusions

Based on input from public comment and federal subject matter experts, the HHS Secretary and APHIS Administrator have determined that these agents do not pose a significant risk to public, animal, or plant health. Select agents or toxins that meet any of the following criteria are excluded from the select agent regulations [*See* Sections 3 and 4 of 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.
- Non-viable select agents or nonfunctional select toxins.
- Low pathogenic strains of avian influenza virus.
- Any strain of Newcastle disease virus which does not meet the criteria for virulent Newcastle disease virus.
- 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).
- South America genotypes of Eastern Equine Encephalitis virus (EEEV).
- Any subtypes of Venezuelan Equine Encephalitis virus (VEEV) except for subtypes IAB or IC.
- The West African clade of Monkeypox virus.
- HHS toxins under the control of a principal investigator, treating physician or veterinarian, or commercial manufacturer or distributor, if the aggregate amount does not, at any time, exceed the following amounts: 100 mg of Abrin; 0.5 mg of Botulinum neurotoxins; 100 mg of short, paralytic alpha conotoxins containing the following amino acid sequence $X_1CCX_2PACGX_3X_4X_5X_6CX_7$[1]; 1,000 mg of Diacetoxyscirpenol; 100 mg of Ricin; 100 mg of Saxitoxin; 5 mg of Staphylococcal enterotoxins (subtypes A, B, C, D, E); 1,000 mg of T-2 toxin; or 100 mg of Tetrodotoxin.

[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.

Requests for Exclusion of Attenuated Strains or Inactive Toxins

An entity or individual may request to exclude an attenuated strain of a select agent or an inactive form of a select toxin from the select agent regulations. To apply for exclusion, an individual or entity must submit a written request (on official entity letterhead) requesting the exclusion of an attenuated strain or inactive toxin. The request must contain the rational for the exclusion of the strain or toxin and scientific references or supporting documentation that demonstrates the attenuated strain or inactive toxin does not pose a severe threat to public health and safety, animal health or animal products, and plant health or plant products.

A written decision granting or denying the request will be issued. The exclusion will be effective upon notification to the applicant. Exclusions will be listed on the Federal Select Agent Program website at http://www.selectagents.gov/.

If an excluded attenuated strain or inactivated 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 [*See* Section 3 and Section 4 (e)(2)].

Review of Exclusion Requests

The Federal Select Agent Program reviews requests for exclusions and may seek input from the Intragovernmental Select Agents and Toxins Technical Advisory Committee (ISATTAC), which is comprised of Federal government employees from the CDC, the National Institutes of Health (NIH), the Food and Drug Administration (FDA), the 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 inactive toxins of HHS only or overlap select agents and toxins. For Veterinary Services (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 information that is responsive to these criteria:

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 which support the methods and data provided for the exclusion.

The data requirements necessary for consideration of an exclusion request for highly pathogenic Avian influenza (HPAI) virus are listed on the Federal Select Agent Program website http://www.selectagents.gov/resources/usdatemplate-for-ai.pdf.

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. The HHS Secretary 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 file manager or to the Federal Select Agent Program.

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

This provision allows Federal law enforcement agencies to conduct certain law enforcement activities (e.g., collecting evidence from a laboratory crime scene) without being in violation of the regulations. The provision does not authorize the seizure of a select agent or toxin by a Federal law enforcement agency; rather, it establishes the conditions under which a Federal law enforcement agency may seize a known select agent or toxin without violating the regulations. Any seizure of a known select agent or toxin by a Federal law enforcement agency must be conducted in accordance with all applicable laws and regulations. Any known select agent or toxin seized by a Federal law enforcement agency will be excluded from the requirements of the regulations during the period between seizure of the agent or toxin and the transfer or destruction of such agent or toxin provided that (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; and (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 the Federal Select Agent Program.

Useful links and Resources

For more information concerning the exclusion of attenuated strains or inactive toxins and other select agent and toxins facts please visit the following websites:

List of excluded attenuated strains and inactivated toxins:
http://www.selectagents.gov/Select%20Agents%20and%20Toxins%20Exclusions.html

National Select Agent Registry (NSAR): http://www.selectagents.gov/index.html

NIH OBA guidelines: http://oba.od.nih.gov/oba/rac/Guidelines/NIH_Guidelines.htm.

BMBL 5th edition: http://www.cdc.gov/biosafety/publications/bmbl5/BMBL.pdf.