

**SELECT AGENTS AND TOXINS –
CLINICAL AND/OR DIAGNOSTIC LABORATORY ACTIVITIES**

(For assistance, please contact EHS at (402) 472-4925, or visit our web site at <http://ehs.unl.edu/>)

Introduction

Clinical and/or diagnostic laboratories and other entities that possess, use, or transfer select agents and toxins may be exempt from United States Departments of Agriculture (USDA) and Health and Human Services (HHS) Select Agent and Toxins regulations (42 CFR 73, 9 CFR 121, and 7 CFR 331) if certain conditions are met. The exemption is contingent upon complete and total adherence to all requirements of the exemption. A listing of select agent organisms (including genetic elements) and toxins is provided in Appendix I of this SOP.

Scope

This SOP describes the exemption conditions applicable to clinical and/or diagnostic laboratories and other entities that possess, use, or transfer human, animal, overlap, or plant select agents contained in specimens presented for diagnosis or verification. An exemption also exists for entities that possess, use, or transfer select human, animal, and/or overlap select agents/toxins contained in a specimen presented for proficiency testing. Possession, use, or transfer of select agents for other purposes, including but not limited to research and medical uses, are beyond the scope of this SOP. See Appendix II for definitions.

Diagnosis/Verification

Following confirmatory identification, clinical and/or diagnostic laboratories possessing a select agent in or from a specimen (plant, animal, environmental) are subject to certain regulatory requirements established by the United States Departments of Agriculture (USDA) and/or Health and Human Services (HSS). In summary:

- The reference laboratory (the laboratory providing the confirmatory/definitive identification) must file a formal report with the **appropriate agency** based on the classification (human, animal, overlap, or plant) of the select agent or toxin. Reports are filed with the USDA Animal and Plant Health Inspection Services (APHIS) for select agents and toxins affecting plants and animals. Reports are filed with the HHS Centers for Disease Control and Prevention (CDC) for select agents and toxins affecting humans. Reports for overlap (affecting humans and animals) agents can be filed with CDC or APHIS. The Responsible Official (RO) or Facility Director (FD) is responsible to file the official report with the appropriate agency.
- The notification to CDC or APHIS must be made within the specified **time frame** for the specific select agent/toxin. With the exceptions noted below, written

reports, using the most current CDC/APHIS Form 4, must be filed by the RO or FD within seven (7) calendar days of confirmed identification.

- All select agents/toxins affecting plants require immediate notification to APHIS via email, telephone, or facsimile, followed by submission of Form 4 within 7 calendar days.
- Select agents/toxins affecting animals that require immediate notification to APHIS (followed by submission of Form 4 within 7 calendar days) include: African horse sickness virus, African swine fever virus, Avian influenza virus, Bovine spongiform encephalopathy agent, Classical swine fever virus, Foot and mouth disease virus, Rinderpest virus, and Swine vesicular disease virus.
- Select agents/toxins affecting humans that require immediate notification to CDC include: Botulinum neurotoxins, Ebola virus, Lassa fever virus, Francisella tularensis, Marburg virus, South American haemorrhagic fever viruses (Junin, Machupo, Sabia, Flexal, Guanarito), Variola major virus (Smallpox), Variola minor virus (Alastrim), and Yersinia pestis.
- Select agents/toxins affecting humans and animals (overlap agents) that require immediate notification to CDC or APHIS (followed by submission of Form 4 within 7 calendar days) include: Hendra virus, Nipah virus, Rift Valley fever virus, Venezuelan Equine Encephalitis virus, Bacillus anthracis, and Brucella melitensis.
- The select agent or toxin and associated specimens must be **transferred** to a registered facility or **destroyed** within seven (7) calendar days of definitive identification. Transfer prior to definitive identification is not subject to any special requirements, other than compliance with transport rules (e.g., DOT or IATA). Transfer after definitive identification requires prior approval from CDC or APHIS, as appropriate.
- The select agent or toxin and associated specimens must be **secured** against theft, loss, or release during the period between positive identification and transfer or destruction.
- In accordance with CDC regulations (but the same provision is lacking from the USDA regulations), select agents affecting humans and overlap agents must be **reported to other federal, state, and local authorities** as required by other laws. This generally pertains to disease surveillance reporting.

Proficiency Testing

Laboratories in possession of select agents affecting humans and/or animals that are contained in specimens presented for diagnosis or verification are also exempt and must follow the same general rules for reporting, transfer/destruction, and security. However, in the case of proficiency testing, the time frame for transfer or destruction and reporting is established at 90-days from the time of receipt. There are no exemption provisions for proficiency testing for select agents affecting plants.

Identification

“Identification” occurs at that point and time that a definitive test confirms the presence of a select agent in or from a specimen. Presumptive or suspect identification based on clinical signs or symptoms and non-confirmatory tests does not trigger regulatory

requirements, including exemption conditions, for select agents. All associated specimens, samples, and isolates (including regulated genetic elements, nucleic acids, and recombinant organisms – See EHS SOP, **Select Agents**) are subject to the requirements established for the diagnostic/clinical lab exemption once the identification of a select agent is confirmed, regardless of whether the confirmation is made by the same or another laboratory. The clock and regulatory obligations begin on the day of confirmatory identification.

Reporting

For internal tracking purposes only, UNL laboratories are required to notify EHS of suspect specimens and/or presumptive identification of select agents and toxins. Notification should be made before confirmation testing is initiated and include laboratory contact name, phone number, and e-mail address; suspect agent identification; and a description of all associated specimens, samples, and isolates retained on-site pending confirmatory analysis. Initial reporting to EHS can be accomplished by e-mail (bosthus1@unl.edu), fax (402-472-9650), or telephone (472-4927).

Upon confirmatory identification of a select agent or toxin, UNL laboratories must notify EHS immediately of the results. If any associated specimens, samples, and isolates were retained on-site pending confirmatory analysis they must be destroyed or transferred to a registered facility within 7 days of confirmed identification of a select agent. Transfer must be preceded by transfer approval from CDC or APHIS (CDC/APHIS Form 2), as arranged by the RO or FD.

The RO or FD of the reference laboratory (laboratory providing confirmatory/definitive identification) must complete and submit CDC/APHIS Form 4 to the appropriate agency within seven (7) calendar days of confirmatory identification, even when an immediate report was filed by telephone, fax, or e-mail. Form 4 is available on the CDC and APHIS web sites.

Reporting of select agents affecting humans (including overlap agents) to other federal, state, or local authorities for purposes other than compliance with the select agent regulations (i.e., disease surveillance reporting) is the responsibility of the laboratory, and is a condition of the exemption. The RO does not conduct this type of reporting.

Copies of forms and documented reports must be maintained for a minimum of three years. Both the RO and FD are responsible to maintain documentation/ records as discussed above.

Transfer or Destruction

As a condition of the clinical/diagnostic laboratory exemption, all specimens, samples, and isolates (including regulated genetic elements, recombinant organisms, etc.) must be destroyed, inactivated/rendered incapable of replication, or transferred to a **registered** facility within seven (7) calendar days following confirmatory identification. If a secondary laboratory is utilized for confirmatory testing, EHS recommends complete and total transfer of all associated specimens, samples, and isolates at the time that confirmatory testing is requested; or destruction of unneeded specimens, samples, and

isolates at the same time. This eliminates the need for later transfer permission from the CDC or APHIS or destruction, as well as adherence to specific timeframes and security measures.

The RO or FD must secure approval from CDC or APHIS prior to transferring any specimen, sample, or isolate after confirmatory identification of a select agent. With the exceptions noted below, transfers must be conducted as follows:

- Must be authorized by CDC or APHIS. The RO or FD must apply for approval by filing APHIS/CDC form 2.
- Receiver must be registered.
- Sender must be adhering to the exemption conditions or be registered.
- Exceptions: (1) A select agent or toxin that is contained in a specimen for proficiency testing may be transferred without prior authorization from CDC or APHIS provided that, within seven (7) calendar days prior to the transfer the sender reports to CDC or APHIS the select agents or toxin to be transferred and the name and address of the recipient for the tracking of select agents or toxins including those contained in a specimen presented for proficiency testing; (2) special circumstance by HHS.
- In accordance with all applicable packaging/shipping/transport laws (e.g., IATA or DOT, as applicable).
- In some cases, additional CDC or APHIS import/export/interstate permits may be required.

Security

Immediately following confirmatory identification, specimens, isolates, and all regulated genetic materials associated with the select agent must be secured against theft, loss, or release until the materials have been transferred to a registered facility, inactivated/rendered incapable of replication, or destroyed. Suspected or known theft, loss, or release (including known or suspected exposures) of a specimen or associated materials must be reported immediately to the RO and UNL Police Department.

Secured means that individuals not associated with the laboratory diagnostic process do not have access (able to carry, use, or manipulate) at any point in time to specimens, isolates, or other regulated materials. The standard of security is generally met if all of the following are met:

- All select agents and toxins have been secured in locked cabinets, rooms, or other containers;
- The containers cannot be forced open without tools and without visible signs of damage;
- Rooms are secure against entry by unauthorized personnel;
- Keys, combinations, etc. are controlled; and
- Access to the area is limited to employees of the entity.

Suspected or Know Exposures

Suspected or known exposures to a select agent, even in the context of a diagnostic/clinical laboratory, may be considered a “release” and therefore reportable to APHIS/CDC. All such situations must be reported to EHS immediately.

(Created 12/07; Reviewed 5/08; Revised 11/08)

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Appendix 1

Regulated Agents and Toxins

Agent	Type	Agency	Time Limit	Notification Type *
Viruses				
African horse sickness virus	Animal	APHIS	Immediate	P, F, E + 4
African swine fever virus	Animal	APHIS	Immediate	P, F, E + 4
Akabane virus	Animal	APHIS	7- days	4
Avian influenza virus (highly pathogenic)	Animal	APHIS	Immediate	P, F, E + 4
Bluetongue virus (exotic)	Animal	APHIS	7- days	4
Bovine spongiform encephalopathy agent	Animal	APHIS	Immediate	P, F, E + 4
Camel pox virus	Animal	APHIS	7- days	4
Cercopithecine herpesvirus 1 (Herpes B virus)	Human	CDC	7- days	4
Classical swine fever virus	Animal	APHIS	Immediate	P, F, E + 4
Crimean-Congo haemorrhagic fever virus	Human	CDC	7- days	4
Eastern Equine Encephalitis virus	Human	CDC	7- days	4
Ebola virus	Human	CDC	Immediate	P, F, E + 4
Foot and Mouth disease virus	Animal	APHIS	Immediate	P, F, E + 4
Goat pox virus	Animal	APHIS	7- days	4
Hendra virus	Overlap	CDC or APHIS	Immediate	P, F, E + 4
Japanese encephalitis virus	Animal	APHIS	7- days	4
Lassa fever virus	Human	CDC	Immediate	P, F, E + 4
Lumpy skin disease virus	Animal	APHIS	7- days	4
Malignant catarrhal fever virus (Alcelaphine herpesvirus type 1)	Animal	APHIS	7- days	4
Marburg virus	Human	CDC	Immediate	P, F, E + 4
Menangle virus	Animal	APHIS	7- days	4
Monkey pox virus	Human	CDC	7- days	4
Newcastle disease virus (virulent)**	Animal	APHIS	7- days	4
Nipah virus	Overlap	CDC or APHIS	Immediate	P, F, E + 4
Peste des petits ruminants virus	Animal	APHIS	7- days	4
Reconstructed 1918 influenza virus (Reconstructed replication competent forms of the 1918 pandemic influenza virus containing any portion of the coding regions of all eight genes segments)	Human	CDC	7- days	4
Rift Valley fever virus	Overlap	CDC or APHIS	Immediate	P, F, E + 4
Rinderpest virus	Animal	APHIS	Immediate	P, F, E + 4
Sheep pox virus	Animal	APHIS	7- days	4
South American haemorrhagic fever viruses (Junin, Machupo, Sabia, Flexal, Guanarito)	Human	CDC	Immediate	P, F, E + 4
Swine vesicular disease virus	Animal	APHIS	Immediate	P, F, E + 4
Tick-borne encephalitis complex (flavi) viruses (Central European tick-borne encephalitis, Far Eastern tick-borne encephalitis, Russian spring and summer encephalitis, Kyasanur forest disease, Omsk hemorrhagic fever)	Human	CDC	7- days	4
Variola major virus (Smallpox virus)	Human	CDC	Immediate	P, F, E + 4
Variola minor virus (Alastrim)	Human	CDC	Immediate	P, F, E + 4
Venezuelan Equine Encephalitis virus	Overlap	CDC or APHIS	Immediate	P, F, E + 4
Vesicular stomatitis virus (exotic): Indiana subtypes VSV-IN2, VSV-IN3	Animal	APHIS	7- days	4
Bacteria				

(Created 12/07; Reviewed 5/08; Revised 11/08)

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Bacillus anthracis	Overlap	CDC or APHIS	Immediate	P, F, E + 4
Brucella abortus	Overlap	CDC or APHIS	7- days	4
Brucella melitensis	Overlap	CDC or APHIS	Immediate	P, F, E + 4
Brucella suis	Overlap	CDC or APHIS	7- days	4
Burkholderia mallei (formerly Pseudomonas mallei)	Overlap	CDC or APHIS	7- days	4
Burkholderia pseudomallei (formerly Pseudomonas pseudomallei)	Overlap	CDC or APHIS	7- days	4
Botulinum neurotoxin producing species of Clostridium	Human	CDC	7- days	4
Ehrlichia ruminantium (Heartwater)	Animal	APHIS	7- days	4
Francisella tularensis	Human	CDC	Immediate	P, F, E + 4
Mycoplasma capricolum subspecies capripneumoniae (contagious caprine pleuropneumonia)	Animal	APHIS	7- days	4
Mycoplasma mycoides subspecies mycoides small colony (MmmSC) (contagious bovine pleuropneumonia)	Animal	APHIS	7- days	4
Ralstonia solanacearum, race 3, biovar 2	Plant	APHIS	Immediate	P, F, E + 4
Rathayibacter toxicus	Plant	APHIS	Immediate	P, F, E + 4
Xanthomonas oryzae pv. oryzae	Plant	APHIS	Immediate	P, F, E + 4
Xylella fastidiosa (citrus variegated chlorosis strain)	Plant	APHIS	Immediate	P, F, E + 4
Yersinia pestis	Human	CDC	Immediate	P, F, E + 4
Rickettsial				
Coxiella burnetii	Human	CDC	7- days	4
Rickettsia prowazekii	Human	CDC	7- days	4
Rickettsia rickettsii	Human	CDC	7- days	4
Fungi				
Coccidioides immitis	Human	CDC	7- days	4
Coccidioides posadasii	Human	CDC	7- days	4
Peronosclerospora philippinensis (Peronosclerospora sacchari)	Plant	APHIS	Immediate	P, F, E + 4
Phoma glycinicola (formerly Pyrenochaeta glycinis)	Plant	APHIS	Immediate	P, F, E + 4
Sclerophthora rayssiae, var. zeae	Plant	APHIS	Immediate	P, F, E + 4
Synchytrium endobioticum	Plant	APHIS	Immediate	P, F, E + 4
Toxins				
Abrin	Human	CDC	7- days	4
Botulinum neurotoxins	Human	CDC	Immediate	P, F, E + 4
Clostridium perfringens epsilon toxin	Human	CDC	7- days	4
Conotoxins	Human	CDC	7- days	4
Diacetoxyscirpenol	Human	CDC	7- days	4
Ricin	Human	CDC	7- days	4
Saxitoxin	Human	CDC	7- days	4
Shigatoxin	Human	CDC	7- days	4
Shiga-like ribosome inactivating proteins	Human	CDC	7- days	4
Staphylococcal enterotoxins	Human	CDC	7- days	4
T-2 toxin	Human	CDC	7- days	4
Tetrodotoxin	Human	CDC	7- days	4

* P = telephone; F= facsimile; E= email; 4= CDC/APHIS Form 4

**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.

(Created 12/07; Reviewed 5/08; Revised 11/08)

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Appendix II Definitions

Diagnosis means the analysis of specimens for the purpose of identifying or confirming the presence or characteristics of a select agent or toxin provided that such analysis is directly related to protecting the public health or safety, animal health or animal products, or plant health or plant products.

Proficiency testing means the process of determining the competency of an individual or laboratory to perform a specified test or procedure.

Specimen means samples of material from humans, animals, plants, or the environment or isolates or cultures from such samples for the diagnosis, verification, or proficiency testing.

Verification means the demonstration of obtaining established performance (e.g., accuracy, precision, and the analytical sensitivity and specificity) specifications for any procedure used for diagnosis.