GUIDANCE ON THE INVENTORY OF SELECT AGENTS AND TOXINS

7 CFR Part 331, 9 CFR Part 121, 42 CFR Part 73

September 2022

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 welcomed. Submit comments directly to the Federal Select Agent Program at:

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Revision History:
October 2012: Initial posting
March 2013: The revisions are changes to correct editorial errors from previous version and to clarify for toxin material that there is no differentiation between working stock and long-term storage.
June 2014 The document was revised to update toxin language to reflect the technical amendment to the select agent regulations. Specifically, the following language on page 5 was revised: "An entity does not need to apply for an exclusion if the agent is non-viable or the toxin is nonfunctional as these are not regulated. However, it is recommended that an entity maintain information on file in support of the method used for rendering a select agent non-viable or a select toxin nonfunctional so that the entity is able to demonstrate that the agent or toxin is no longer subject to the select agent and toxin regulations."
April 2015: The document was revised to update 1) recombinant and synthetic nucleic acid definitions, 2) language quoted from select agent regulation Section 17(a)(1), (3) include nucleic acids that can produce infectious forms of select agent viruses as regulated material, and 4) Tier 1 Personnel Suitability requirements. The revisions also included external hyperlinks to Security, Personnel Suitability, and Toxin Due Diligence guidance documents and internal hyperlinks to Appendices I and II.
January 2017: The document was revised to update 1) record maintenance and 2) section on material containing select agents or regulated nucleic acids.
March 2017: The document was revised based on changes to the regulations.
December 2020: Minor updates. Fixed broken hyperlinks.
June 2022: Added new appendix section about labeling guidance. Additional minor updates.
September 2022: Added a labeling guidance appendix and other edits to enhance material accountability after soliciting comments from entities.

Introduction

The select agent regulations require an accurate and current inventory for: (1) each select agent (including viral genetic elements, recombinant and/or synthetic nucleic acids, and recombinant and/or synthetic organisms) held in long-term storage; (2) any animals or plants intentionally or accidentally exposed to or infected with a select agent and (3) for each toxin held. 42 CFR § 73.17(a), 7 CFR § 331.17(a), and 9 CFR § 121.17(a).

Contents

Regulated select agents and toxins

The select agents and toxins lists can be found in 42 CFR § 73.3 (Health and Human Services (HHS) only agents), 42 CFR § 73.4 and 9 CFR § 121.4 (Overlap agents), 7 CFR § 331.3 (Plant Protection and Quarantine (PPQ) only agents), and 9 CFR § 121.3 (Veterinary Service only agents).
Accordingly, select agent infected materials, including confirmed clinical specimens, laboratory cultures, animals, animal tissues, plants, and plant tissues, are subject to regulation. As directed by 42 CFR 73.5(a)(3) clinical or diagnostic specimens collected from a patient infected with a select agent must be transferred or destroyed within seven calendar days after delivery of patient care by health care professionals has concluded. Animals inoculated with toxins, however, are not regulated; only toxins or recombinant/synthetic nucleic acids encoding functional forms of the select toxins are regulated.

Inventory records are not required for select agent and toxin strains or constructs that FSAP has excluded from the provisions of the select agent regulations pursuant to 42 CFR § 73.3€ (HHS only agents), 42 CFR § 73.4(e) and 9 CFR § 121.4(e) (Overlap agents), 7 CFR § 331.3(e) (PPQ only agents), and 9 CFR § 121.3(e) (VS only agents). Please see the Exclusion Guidance Document for more information. To apply for a novel exclusion, an entity must provide sufficient documentation that an attenuated select agent or modified toxin no longer poses a severe threat to public health and safety, and/or animal health or animal products, or plant health or plant products, as appropriate. An entity does not need to apply for an exclusion if the agent is non-viable or the toxin is non-toxic as these are not regulated.

However, it is required that an entity maintain information on file in support of the method used for rendering a select agent non-viable or a select toxin non-toxic so that the entity is able to demonstrate that the agent or toxin is no longer subject to the select agent and toxin regulations. *See* 42 CFR § 73.17(a)(8), 7 CFR § 331.17(a)(8), and 9 CFR § 121.17(a)(8).

Regulatory definitions that apply to this document

Biological Agent – Any microorganism (including, but not limited to, bacteria, viruses, fungi, rickettsia, or protozoa), or infectious substance, or any naturally occurring, bioengineered, or synthesized component of any such microorganism or infectious substance, capable of causing death, disease, or other biological malfunction in a human, an animal, a plant, or other living organism; deterioration of food, water, equipment, supplies, or material of any kind; or deleterious alteration of the environment.

Toxin – Toxic material or product of plants, animals, microorganisms (including, but not limited to, bacteria, viruses, fungi, or protozoa), or infectious substances, or recombinant or synthesized molecules, whatever their origin and method of production, and includes any poisonous substance or biological product that may be engineered as a result of biotechnology, produced by a living organism; or any poisonous isomer or biological product, homolog, or derivative of such a substance.

Recombinant Nucleic Acids – (1) Molecules that are constructed by joining nucleic acid molecules and that can replicate in a living cell or (2) molecules that result from the replication of those described in (1) above.

Synthetic Nucleic Acids – (1) Molecules that are chemically or by other means synthesized or amplified, including those that are chemically or otherwise modified but can base pair with naturally occurring nucleic acid molecules or (2) molecules that result from the replication of those described in (1) above.

Long-term storage criteria for select agents

Section 17(a)(1) of the select agent regulations explains that long-term storage is the placement of select agents or toxins in a system designed to ensure viability for future use, such as in a freezer or other storage container or lyophilized materials. In addition to freezers and other storage containers and lyophilized materials, the system selected by the entity to preserve specimens for future use can be appropriate to specific select agents, and therefore can include, but is not limited to, refrigerators, liquid nitrogen tanks, and room temperature storage units. As a general rule, long-term storage materials include select agents (including viral genetic elements, recombinant and/or synthetic nucleic acids, and organisms containing recombinant and/or synthetic nucleic acids) and infectious forms of select agent viruses, which are not part of an ongoing experiment or have not been accessed for a significant period of time (e.g., within 30 calendar days).

All select agent materials stored long-term must be kept in a secure location registered with FSAP. Individuals may not access select agents and toxins unless approved by FSAP following a security risk assessment (SRA).

Indicators of long-term storage materials

a) The material is in a highly concentrated state and would not be used in its present state without dilution to a less concentrated state.
    1. Example: A vial containing a high concentration of select agent bacteria is removed from storage and used to inoculate several tubes of broth, and then the vial is returned to storage.
    2. Example: A vial containing a high concentration of select agent bacteria is removed from storage to make additional aliquots (vials) of highly concentrated bacteria from the original stock(s).
    3. Example: Subcultures of highly concentrated select agent bacteria or high titer select agent viruses (plates, broth cultures, cell culture tubes, flasks, etc.) are used to replace the original seed stocks for experiments to be performed within a defined period of time (e.g., within 30 calendar days).

b) The material is not part of an ongoing experiment and will not be used for any work by the entity within a defined period of time (e.g., within 30 calendar days).
    1. Example: A vial of select agent is not planned for use for any entity research project, diagnostic procedure, quality control or other laboratory activity within the defined period of time.

c) The material is not consumed within a defined period of time by the entity (e.g., within 30 calendar days).
    1. Example: A vial of select agent is received by the laboratory but there are no plans to use the contents of the vial for any work within the defined period of time.
    2. Example: A select agent aliquot is collected from an experimental protocol that is preserved for future analysis.

d) The material is placed in an environment where there is infrequent access to the environment.
    1. Example: Viruses are placed in a liquid nitrogen tank that is only accessed infrequently by a member of the laboratory (e.g., within 30 or more calendar days).

Working stock criteria for select agents

Select agents are considered working stock if the materials are part of an ongoing experiment, accessed frequently, or are not stored for an extended period of time. The select agent regulations do not require entities to maintain inventory records in accordance with Section 17(a)(1) for working stock.. Entities should be able to clearly identify how and why material is classified as working stock.

All working stock select agent materials must be kept and used in a secure location registered with FSAP. All personnel with access to working stock select agent materials must have a current SRA approval and be in compliance with the select agent regulations.

Indicators of working stock materials

a) The material has been diluted from a concentrated state and placed into multiple aliquots in the less concentrated form for immediate use (e.g., within 30 calendar days or as needed by the ongoing experiment).
b) The material is part of an ongoing experiment and will be used for work by the entity within a period of time as defined by experimental protocol.
    1. Example: The material (bacteria, virus) has been propagated for a specific experiment and will be used to infect animals or cells.
    2. Example: A plant infected with a slow growing fungus is maintained at room temperature for a defined period of time (e.g., within 30 calendar days or as dictated by the ongoing experiment).
c) The material is consumed as part of an ongoing experiment within a defined period of time by the entity (e.g., within 30 calendar days or as dictated by the ongoing experiments).
d) The material is placed in an environment where there is frequent access to the material, such as a refrigerator or incubator in an active laboratory to support ongoing experiments.

Select agent inventory records

Select agent material includes confirmed clinical specimens, laboratory cultures containing select agents and recombinant and/or synthetic select agent organisms, as well as genetic elements and recombinant and/or synthetic nucleic acids encoding regulated genetic material. This also includes animals, animal tissues, plants, and plant tissues intentionally or accidentally exposed to or infected with a select agent. Each sample of select agent material stored long-term should correspond to a written record containing all of the information required in Section 17(a)(1-2) of the select agent regulations Final disposition of the material is required to be recorded (e.g., material is no longer in the possession of the entity due to consumption, transfer, destruction).
An entity is responsible for maintaining an accurate and current inventory of all toxins possessed regardless of the amount in their possession as stated in section 7(b) All select agents held in long-term storage, may be subject to verification during the inspection. Please review the Security Guidance document for information regarding inventory reconciliations.

Select toxins and select toxin-exposed animals and animal tissues

Entities must maintain records containing all of the information required in Section 17(a)(3). Note that for toxin, there is no differentiation between working stock and long-term storage, because all regulated toxin material that the entity is registered for must be entered into the inventory records. The current

quantity of each vial must be documented for toxins following each use. The current quantity of each vial that is recorded following the last usage may be examined during an inspection.

Individuals may not access BSAT unless approved by FSAP following a SRA. Entities that ship aggregate amounts of select toxin below the amounts listed in 42 CFR § 73.3(d)(3) are not required to submit an APHIS/CDC Form 2 for approval prior to shipment; however, the entity must use due diligence and maintain documentation of the amount of shipped toxin in order to fulfill their responsibilities under Section 73.16(l). Please see the Select Toxin Guidance for more information.

Once an animal has been injected with or exposed to a select toxin (for example, by inhalation, dermal absorption, or ingestion), the animal is not considered a "select toxin" and does not need to be housed in a registered space (*See* 42 CFR § 73.3(d)(3)). Please note that accurate and current accounting are required for any animals or plants intentionally or accidentally exposed to or infected with a select agent (including number and species, location, and appropriate disposition) (*See* 42 CFR § 73.17(a)(2).

Until the select toxin is injected into or exposed to the animal, the select toxin is subject to the select agent regulations. This includes storage or use of the material (e.g., injection or exposure procedure). If the select toxin is stored or used in the same area as the injected or exposed animal, that area will need to be listed on an entity's approved certificate of registration.

The room where select toxin injection or exposure procedures occur may be assessed using laboratory biosafety level criteria instead of animal laboratory biosafety level criteria. These rooms, however, must be included on an entity's registration and must be managed as regulated space.

Select agent-infected animals and animal tissues

Section 17(a)(2) of the select agent regulations requires an accounting of animals intentionally or accidentally exposed to or infected with a select agent (including number and species, location, and appropriate disposition). The intent of this requirement is to ensure that an entity has a system in place to manage and account for the number of research animals used in experimental protocols with select agents. The accounting should include the location of these animals in the facility and their final disposition. This information can be contained in research notes, animal care logbooks, daily check sheets, or other formats. An accidental release of exposed animals or animal exposure to select agents outside of primary containment must be reported using the APHIS/CDC Form 3 (Theft, Loss and Release form), which requires an entity to provide a detailed description and follow-up actions of the incident. An accounting of animals intentionally or accidentally exposed to or infected with a select agent (including number and species, location, and appropriate disposition) will facilitate the investigation of these types of incidents.

Fluid, serum, tissue, or other samples collected from animals infected with or exposed to select agents in the laboratory are considered select agent material, and are subject to the select agent regulations, under Section 17(a)(1). Animals that are infected with select agents for experiments that require longer incubation periods (e.g., within 30 days or as mandated by the experimental protocol) before the agent or disease can be detected are considered to be select agents and must be handled in the same manner as infected animals above. A uniquely identified vial-by-vial inventory record of tissue specimens from a single source or experiment is not required for animals or animal samples, and specimens may be grouped without individual vial identification.

For example, 14 vials of infected mouse lung samples from the same experiment may be grouped under one reference identification number, consistent with the experimental protocol. However, the reference number must be linked to a record that notes 14 vials upon inventory reconciliation. If an entity wishes to group specimen vials in this manner, each primary and secondary container in which the samples are stored should be labeled with the date placed in storage, the agent contained in the sample, and a reference identification that is associated with a written record (inventory record, research notes, etc.) describing those specimens, including the total number of vials. The entity is required to maintain an inventory of all specimens, therefore, an entity using this method would need to have an accurate accounting for each identification number. This should include all of the information required in Section 17 and an entity must be able to account for each vial associated with that number to ensure compliance. As vials are removed from inventory for processing, their removal must be noted in the written record to maintain an accurate and current inventory.

Samples collected from animals that are presumed to have been naturally infected (i.e., not intentionally introduced) would not be considered select agent material and are not required to be handled as regulated material until the samples have been confirmed to contain select agent material. Diagnostic samples from which the presence of a select agent has been detected are subject to the select agent regulations; however, diagnostic samples from which only an antibody response to a select agent is detected are not considered select agent material. In addition, samples taken from animals experimentally infected with select agents are considered select agents and are subject to the select agent regulations, unless the absence of the agent can be demonstrated.

Long-term storage criteria for select agent-infected arthropods

Infected arthropods may be recorded individually or pooled, at the discretion of the entity. The long-term storage inventory of infected arthropod vials may be verified during an inspection. Each vial in long-term storage must have an associated record that contains all of the information required in Section 17(a)(1) (*See Appendix I*).

Long-term storage criteria for select agent-infected plants

The regulations in Section 17(a)(2) require an accurate, current inventory of plants intentionally or accidentally inoculated with a select agent (including number and plant species, location, and appropriate disposition). The intent of this requirement is that an entity has a system in place to manage and account for the number of research plants used in experimental protocols with select agents. The accounting should include the location of these plants in the facility and their final disposition. This information can be contained in research notes, plant logbooks, daily check sheets, or other formats. In the event of a theft, loss, or accidental release outside of primary containment, the incident must be immediately reported to FSAP with a follow-up submission within 7 days on APHIS/CDC Form 3 – Theft, Loss and Release. The submission of the APHIS/CDC Form 3 will provide a detailed description and follow-up actions of the incident.

Plants that are infected with select agents for experimental purposes or as a mechanism to maintain long-term viability and are held for long incubation periods (e.g., within 30 days) are considered long-term storage select agents and require accurate inventory records for each inoculated plant, such as an identification number that includes all of the information required in Section 17(a)(1) and should be handled as select agent material. Plants infected with select agents for experiments that require longer incubation periods (e.g., within 30 calendar days or as mandated by the experimental protocol) before the agent can be detected or disease symptoms detected are considered long-term storage select agents and must be handled in the same manner as infected plants above. These infected plants

can be removed from long-term storage inventory records when they are shown to be uninfected by appropriate testing (documentation must be made available upon request).

Select agent infected plant tissues (living or dead) that contain infectious select agent propagules are considered long-term storage, as are culture plates and vials containing isolated select agents and are subject to regulation and should correspond to a written record that includes all of the information required in Section 17(a)(1). If several vials or culture plates generated from a single source of material are in long-term storage, they may be grouped under a single reference identification number; the inventory records must indicate how many vials are associated with this reference identification number and a written record must be maintained of the vials and plates removed for accurate inventory reconciliation. The entity must be able to account for each vial or plate associated with the reference identification number. Plants inoculated from a single source and held in long-term storage will be considered individually. Each must be given a unique reference identification number for inventory records and must correspond to a written record that includes all of the information required in Section 17(a)(1) (). As vials or plates are removed from inventory for processing, their removal must be noted in the written record to maintain an accurate and current inventory.

Record Maintenance

Section 17(c) outlines the requirements for the maintenance of complete records involving select agents and toxins. Upon request, the entity must be able to promptly produce those records as well as any information related to the records requirements that is not contained in a record. Such information may be located in:

- Biocontainment certifications
- Laboratory notebooks
- Institutional biosafety and/or animal use committee minutes and approved protocols
- Records associated with occupational health and suitability programs

If any of the above documents contain information related to select agent regulation requirements, FSAP will only review the relevant portions of those documents.

Records required to comply with the select agent regulations must be maintained for 3 years, following final disposition of material.

Record of Final Disposition

Section 17(a)(1)(v) requires an entity to maintain a record of the select agent used, purpose of use, and, when applicable, final disposition for all long-term storage select agent materials that are no longer in their possession. Examples of final disposition may include transfer of material to another registered entity or investigator, consumption of the material during an experiment, or intentional destruction of the material. The disposition can be included with an entity's existing recordkeeping system (e.g., inventory spreadsheet).

Additional Information

If an entity has archived specimens that are accessed infrequently, the container may be sealed with tamper-proof material (e.g., security tape) following inventory verification, and the sealed container can be verified during self-audits. However, any or all archived containers may be required to be opened

during inspection to perform vial-by-vial count verifications.

Each entity should have a written policy to manage its select agent inventory held in long-term storage, including identifying specific individual responsibilities for inventory oversight, an internal audit system to check that appropriate procedures are followed to document changes to the inventory, and training as appropriate for personnel with access to select agent inventory. In addition, the entity should have protocols in place for the transfer (either intra-entity or inter-entity) and accountability of all toxins possessed and all long-term storage inventories of select agents as detailed in Section 11(e).

Appendix I: Labeling Guidance

The guidance below is to enhance material accountability through

- The establishment of standards for labeling samples that are flexible, not overly prescriptive, and assist with prompt identification from the entity's inventory record.

Labels on agent or toxin containers (e.g., tubes) should:

- Be legible
- Be indelible and able to survive surface decontamination with an appropriate disinfectant and the time and temperature extremes expected during storage
- Be permanently affixed to the container
- Contain enough information for a rapid, visual assessment of the contents by a knowledgeable viewer, including (at a minimum):
    - Agent or toxin name
        - Agent strain or toxin isoform (if such information changes the risk, such as an attenuated strain)
    - Date of creation
    - A clear indication of whether the agent is inactivated or not (lack of information will lead to a presumption that the agent is viable, or the toxin is in a toxic form)
    - Name of PI or responsible individual (although this could be included in the inventory records instead, it may be beneficial for laboratories to include this on labels to quickly identify who the responsible PI is or who generated/owns the samples and help resolve any issues with the samples)

If an unlabeled primary container is found while accessing the inventory or during an audit, an entity should try to reconcile with the current inventory in order to identify the select agent or toxin. If unable to reconcile the unlabeled vial and it results in a loss of a select agent or toxin, please refer to TLR guidance).