Form Approved
OMB Control No. 0920-0576
Expiration: xx/xx/2020

Guidance on the Inventory of Select Agents and Toxins

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

March 2017

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

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:

CDC: LRSAT@cdc.gov
APHIS: AgSAS@aphis.usda.gov

Revision History:
October 12, 2012: Initial posting
March 14, 2013 (Revision 1): The revisions are primarily 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 12, 2014 (Revision 2): 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 16, 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 5, 2017: The document was revised to update 1) record maintenance and 2) Material Containing Select Agents of Regulated Nucleic Acids.
March 2017: The document was revised based on changes to the regulations.

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 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 (placement in a system designed to ensure viability for future use, such as in a freezer or other storage container or lyophilized materials)"; and (2) "any animals or plants intentionally or accidentally exposed to or infected with a select agent (including number and species, location, and appropriate disposition)" and (3) "for each toxin held." The information in this guidance document is meant to provide additional information to regulated entities in meeting the requirements for (1), (2), and (3) above. *See* 42 CFR § 73.17, 7 CFR § 331.17, and 9 CFR § 121.17.

Contents

Public reporting burden: Public reporting burden of this collection of information is estimated to average 30 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. An agency may not conduct or sponsor, and a person is not required to respond to a collection of information unless it displays a currently valid OMB control number. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to CDC/ ATSDR Reports Clearance Officer; 1600 Clifton Road NE, MS D-74, Atlanta, Georgia 30329; ATTN: PRA (0920-0576).

Definitions for regulated select agents and toxins

The select agents and toxins lists can be found in 42 CFR § 73.3 (HHS only agents), 42 CFR § 73.4 and 9 CFR § 121.4 (Overlap agents), 7 CFR § 331.3 (PPQ only agents), and 9 CFR § 121.3 (VS only agents). Accordingly, select agent infected materials, including confirmed clinical specimens, laboratory cultures, animals, animal tissues, plants, and plant tissues, are subject to regulation. 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(e) (HHS only agents), 42 CFR § 73.4(e) and 9 CFR § 121.4(e) (Overlap agents), 7 CFR § 331.3(e) (Plant 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 the 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 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 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.

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, 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) or 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 nucleic acids encoding functional forms of select toxins 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., 30 calendar days).

All select agent materials stored long-term must be kept in a secure location registered with FSAP. All personnel with access to select agent materials must have security risk assessment (SRA) approval and be in compliance with the select agent regulations. In addition, personnel that access Tier 1 select agents must meet additional pre-access suitably and ongoing assessment requirements (Please see the Guidance for Suitability Assessment for more details). Sections 11(f), 14(e) and 15(b) of the select agent regulations outline all of the requirements for possessing Tier 1 agents.

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 specified amount of time (e.g., 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., 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., 30 calendar days).
    1. Example: A vial of select agents is received by the laboratory but there are no plans to use the contents of the vial for any work within the defined time period.
    2. Example: A select agent aliquot is collected from an experimental protocol that is preserved for future analysis within the defined time period.
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., 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. Select agent materials classified as working stock do not require records that contain the information required in section 17(a)(1) of the select agent regulations. 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 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).
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 30 calendar days.
c) The material is consumed within a defined period of time by the entity (e.g., 30 calendar days).
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.

Select agent inventory records

Select agent material includes confirmed clinical specimens, laboratory cultures, animals, animal tissues, plants, and plant tissues 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. 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) of the select agent regulations (*See Appendix I*). Final disposition of the material is required when applicable (e.g., material is no longer in the possession of the entity due to consumption, transfer, destruction, etc.). Documentation of sample volume is not required for select agents (as opposed to select toxins, see below) and does not need to be recorded in the long-term storage inventory record. An entity is responsible for maintaining an accurate and current inventory all toxins possessed and all select agents held in long term storage, which may be verified during an inspection. Please review the Security Guidance document for information regarding inventory reconciliations.

Select toxins and select toxin-exposed animals and animal tissues

Individuals and entities that possess aggregate amounts of select toxins that exceed the amounts listed in 42 CFR § 73.3 (d)(3) of the select agent regulations, must maintain records containing all of the information required in section 17(a)(3) (*See Appendix II*) for all toxin materials. Note that for toxin material, there is no differentiation between working stock and long-term storage, because all regulated toxin material 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.

All personnel with access to select toxin materials must have security risk assessment (SRA) approval and be in compliance with the select agent regulations. In addition, personnel that access Tier 1 select toxins must have additional pre-access suitably and ongoing assessment requirements (Please see the Guidance for Suitability Assessments for more details). Sections 11 (f), 14 (e) and 15 (b) of the select agent regulations outline all of the requirements for possessing Tier 1 agents.

Entities that ship aggregate amounts of select toxin below the amounts listed in 42 CFR 73.3(d)(3) are not required to submit 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 Toxin Due Diligence Provision 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. The number of animals injected with or exposed to a select toxin does not need to be recorded for long-term storage, but may need to be recorded for other purposes.

Until the select toxin is injected into or exposed to the animal, the select toxin is subject 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 the 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 log books, 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., 30 days) 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 must 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. An entity is required to maintain accurate inventory records for each identification number that includes all of the information required in section 17 and an entity is accountable for each vial associated with that number. As vials are removed from inventory for processing, their removal must be noted in the written record to maintain an accurate and current inventory.

FSAP recommends that an entity document the means of ensuring that select agents are non-viable. 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 collects 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 log books, 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., 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) (*See Appendix I*) and should be handled as select agent material. Plants infected with select agents for experiments that require longer incubation periods (e.g., 30 calendar days) 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) (*See Appendix I*). 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 and 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 is accountable 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 as individuals and 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) (*See Appendix I*). 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) requires the entity to maintain all long term storage records for 3 years. 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 information locations contain information related to select agent regulation requirements, DSAT will only review the relevant portions of those documents.

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, at all times, including when the investigator responsible for the inventory departs the entity as a result of change in employment, retirement, death, sabbatical, or other reasons.

Appendices

The information found in the appendices specifies information that is required by the select agent regulations.

Appendix I. Information required for all select agent materials in long-term storage (Section 17[a][1])

Appendix II. Information required for all select toxin materials in long-term storage (Section 17[a][3])

Appendix III. Material Containing Select Agents of Regulated Nucleic Acids (Section [a][8])

Appendix I. Information required for all select agent materials in long-term storage (Section 17[a][1])

Section 17(a)(1) of the select agent regulations require the entity to maintain an "accurate, current inventory for each select agent (including viral genetic elements, recombinant and/or synthetic nucleic acids, and organisms containing recombinant and/or synthetic nucleic acids) held in long-term storage (placement in a system designed to ensure viability for future use, such as in a freezer or other storage container or lyophilized materials), including:"

i. The name and characteristics (e.g., strain designation, GenBank Accession number, etc.).
ii. The quantity acquired from another individual or entity (e.g., containers, vials, tubes, etc.), date of acquisition, and the source.
iii. Where stored (e.g., building, room, and freezer or other storage container).
iv. When moved from storage and by whom and when returned to storage and by whom.
v. The select agent used and purpose of use, and, when applicable, final disposition.
vi. Records created under section 16 (Transfers).
vii. For intra-entity transfers (sender and the recipient are covered by the same certificate of registration), the select agent, the quantity transferred, the date of transfer, the sender, and the recipient.
viii. Records created under section 19 (Notification of theft, loss, or release).

Appendix II. Information required for all select toxin materials (Section 17[a][3])

Section 17(a)(3) of the select agent regulations require the registered entity to maintain "accurate, current inventory for each toxin held, including:"

i. The name and characteristics.
ii. The quantity acquired from another individual or entity (e.g., containers, vials, tubes, etc.), date of acquisition, and the source.
iii. The initial and current quantity amount (e.g., milligrams, milliliters, grams, etc.).
iv. The toxin used and purpose of use, quantity, date(s) of the use and by whom.
v. Where stored (e.g., building, room, and freezer or other storage container).
vi. When moved from storage and by whom and when returned to storage and by whom, including quantity amount.
vii. Records created under section 16 (Transfers).
viii. For intra-entity transfers (sender and the recipient are covered by the same certificate of registration), the toxin, the quantity transferred, the date of transfer, the sender, and the recipient.
ix. Records created under section 19 (Notification of theft, loss, or release).
x. If destroyed, the quantity of toxin destroyed, the date of such action, and by whom.

Appendix III. Material Containing Select Agents or Regulated Nucleic Acids (Section 17 [a][8])

Section 17(a)(8) of the select agent regulations requires the entity to provide the following if they possess select agents, material containing select agents, or regulated nucleic acids that can produce infectious forms of any select agent virus that have been subjected to a validated inactivation or removal procedure:

i. A written description of the validated inactivation procedure or viable select agent removal method used, including validation data.
ii. A written description of the viability testing protocol used.
iii. A written description of the investigation conducted by the entity Responsible Official involving an inactivation or viable select agent removal failure and the corrective actions taken.
iv. The name of each individual performing the validated inactivation or viable select agent removal method.
v. The date(s) the validated inactivation or viable select agent removal method was completed.
vi. The location where the validated inactivation or viable select agent removal method was performed.
vii. A certificate, signed by the Principal Investigator, that includes the date of inactivation or viable select agent removal, the validated inactivation, or viable select agent removal method used, and the name of the Principal Investigator. A copy of the certificate must accompany any transfer of inactivated or select agent removed material.

The information specified in section 17 (a)(8)(vii) must be retained by the entity that performs the inactivation of viable select agent removal and must accompany the inactivated sample regardless of who it goes to. The certificate needs to be a written certification of the information but doesn't require any specific format. For example, the required information can be added to the inventory log or other documentation. Further, the PI does not have to be present during the performance of the inactivation or select agent removal procedure. This documentation can be batched and recorded outside of containment; however, the information must accompany the samples regardless of who or where they go and the certificate must be signed before samples are removed from registered space. The signature denotes that the PI that is responsible for the specific agent and has reviewed the inactivation procedure used and the validation or verification data. The certificate should be signed as close to the date of inactivation as possible. If the PI is transferring inactivated select agent to their unregistered laboratory, then the signed certificate with the required information must accompany that sample. There is no regulatory requirement for the receiver to keep the certificate, but it is strongly recommended that this information is kept so long as the inactivated sample exists. However, the sender or the PI that performed the inactivation procedure must keep the certificate for 3 years. A PI cannot assign a delegate to sign on their behalf but they can review and sign documents electronically.

Once non-viability, non-infectivity, and/or non-toxicity have been demonstrated, and the record requirements are met, **the material is no longer subject to the regulations.** While it is not a regulatory requirement, it is recommended that entities maintain records that identify the recipients of inactivated materials.