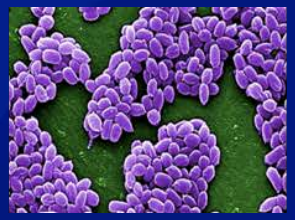


Inactivation Regulatory Requirements

Federal Select Agent Program

Responsible Official (RO) Workshop

July 24, 2019

Exclusion from the Select Agent Regulations

- The select agents regulations list criteria that allow a select agent or a material containing a select agent to be excluded from the requirements of the regulations. See sections 3(d) and 4(d)

- The 4th criteria listed in these sections is the inactivation of the select agent. See sections 3(d)(4) and 4(d)(4)

- The 5th criteria listed in these sections is the removal of the select agent from material. See sections 3(d)(5) and 4(d)(5).

Inactivation regulations

(d) Select agents that meet any of the following criteria are excluded from the requirements of this part:

- Section 3 (d) (4): A select agent or regulated nucleic acids that can produce infectious forms of any select agent virus that has been subjected to a validated inactivation procedure that is confirmed through a viability testing protocol.

  Surrogates

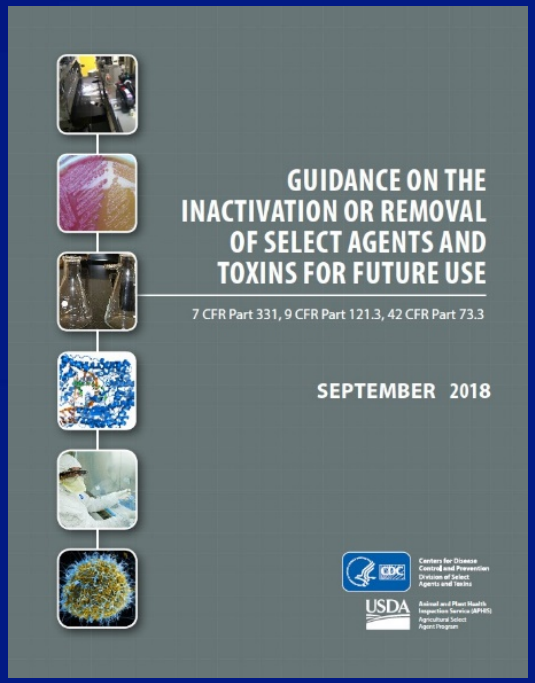
- Section 3 (d) (5): Material containing a select agent that is subjected to a procedure that removes all viable select agent cells, spores, or virus particles if the material is subjected to a viability testing protocol to ensure that the removal method has rendered the material free of all viable select agent.

The inactivation or removal provisions do not apply to:

- Select toxins

Inactivation or removal of a select agent

- An entity must confirm the select agent inactivation or select agent removal procedures in-house via viability testing.
- Guidance on how to develop and validate procedures and protocols, and verify inactivation or select agent removal can be found at https://www.selectagents.gov/irg-intro.html.



Annual Reviews of Inactivation Procedures

- The Responsible Official (RO) must:
  - Review, and revise as necessary, each of an entity's validated inactivation procedures or viable agent removal methods.
- The review must be conducted annually or after any:
  - Change in principal investigator (PI).
  - Change in the validated inactivation procedure or viable agent removal method.
  - Failure of the validated inactivation procedure or viable agent removal method.
- The review must be documented and training must be conducted if there are any changes to the validated inactivation procedure, viable agent removal method, or viability testing protocol.
- The annual review requirement does not necessarily involve revalidating inactivation procedures.

Reporting Requirements for Inactivation Failures

- The RO must investigate to determine the reason for any failure of a validated inactivation procedure or any failure to remove viable agent from material.

- The RO must report immediately by telephone or email failure of the validated inactivation procedure or viable agent removal to FSAP if:

  - The cause of a failure of a validated inactivation procedure or a viable agent removal method cannot be determined, or
  - A report is received of an inactivation failure after the movement of material to another location.

Record Requirements for Inactivation Procedures

- A written description of the validated inactivation procedure or viable select agent removal method used, including in-house validation data.
- A written description of the viability testing protocol used.
- A written description of the investigation conducted by the entity RO involving a procedure failure and the corrective actions taken.
- The name of each individual performing the procedure.
- The date(s) the procedure was completed.
- The location where the procedure was performed.
- A certificate, signed by the PI, that includes the:
  - Date of inactivation or viable select agent removal
  - Validated inactivation or viable select agent removal method used
  - Name of the PI
- A copy of the certificate must accompany any external transfer (entity to entity) of inactivated or select agent removed material.

WHAT'S NEW WITH INACTIVATION OF SELECT AGENTS?

POLICIES

Deviation from a Validated Inactivation Procedure or Removal Method

(May 12, 2017)

- (8) Investigate to determine the reason for any failure of a validated inactivation procedure or any failure to remove viable select agent from material. If the Responsible Official is unable to determine the cause of a deviation from a validated inactivation procedure or a viable select agent removal method; or receives a report of any inactivation failure after the movement of material to another location, the Responsible Official must report immediately by telephone or email the inactivation or viable agent removal method failure to CDC or APHIS.

- It was and is the intent of the FSAP that the use of the phrase “a deviation from a validated inactivation procedure or a viable select agent removal method” means “a failure of a validated inactivation procedure or a viable select agent removal method.”

Chemical Inactivation of Whole Tissue or Homogenized Tissue

(February 13, 2018)

- In meeting the in-house validation/verification of inactivation by chemical inactivation of whole tissue or homogenized tissue, it is FSAP policy to allow entities to select one tissue type, either:
  1. The tissue that is expected to have the highest concentration of the specific agent to be inactivated.
  2. Determine agent concentration for the agent to be inactivated in a tissue before performing inactivation (to use as the maximum limit for that agent) to serve as a surrogate for other tissues, including those in other animal models, so long as all standardized conditions are held constant such as the agent used, tissue size, and ratio of tissue to volume of inactivating chemical.

- A **safety margin** must be incorporated into the final chemical inactivation procedure to ensure the effective inactivation of the agent.

Certificate Meaning and PI Signature (August 3, 2018)

- The purpose of the certificate is for the PI, or designee, to certify that the information contained on the certificate is correct.
- The signature of the PI, or designee, on the certificate will certify that the information listed is true, complete, and accurate.
- The certificate must be signed by the appropriate PI, or designee, when an agent is inactivated and before the “inactivated material” is removed from registered space or the biocontainment level required for that material.

Select Agent Inactivation In-House Validation

(August 10, 2018)

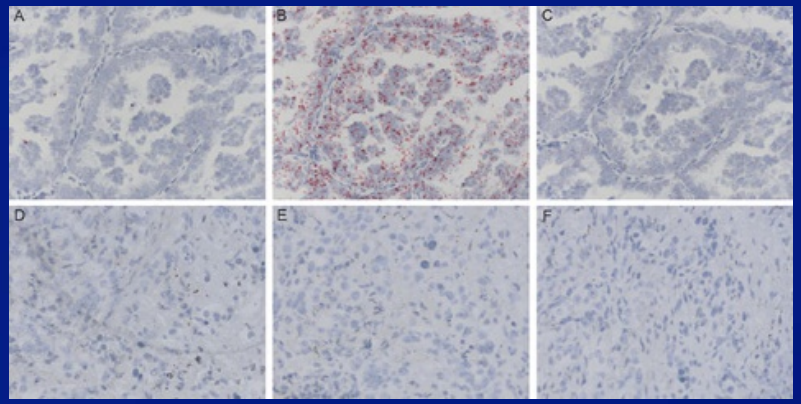
- For the regulatory exclusion to be valid, **in-house validation** must be completed prior to the use of the procedure to render a select agent non-viable for future use or to render any nucleic acids that can produce infectious forms of any select agent virus non-infectious for future use.
- An entity can:
  - Use exact conditions of a commonly accepted procedure (such as autoclaving) whose efficacy is confirmed with data generated from a viability testing protocol (validated) in-house by the entity.
  - Use a published procedure with adherence to the exact published conditions whose efficacy is confirmed with data generated from a viability testing protocol (validated) in-house by the entity.
  - Use an entity-derived procedure with specific conditions whose efficacy is confirmed with data generated from a viability testing protocol (validated) in-house by the entity.

Exclusion of Formalin-Fixed, Paraffin-Embedded Tissues

(October 9, 2018)

- A select agent or regulated nucleic acids that can produce infectious forms of any select agent virus contained in a formalin-fixed, paraffin-embedded (FFPE) tissue has been effectively inactivated if the FFPE process used is a recognized method (e.g. a previously published method shown to be effective such that validation does not have to occur in house for FFPE tissues) for that particular agent or regulated nucleic acids.

- It is therefore the policy of the FSAP that such material is not subject to the select agent regulations.



REGULATORY INTERPRETATIONS

Surrogates
(April 21, 2017)

- The select agent regulations provide that surrogate strains that are known to possess equivalent properties with respect to inactivation can be used to validate an inactivation procedure. However, the select agent regulations also provide that if there are known strain-to-strain variations in the resistance of a select agent to an inactivation procedure, then an inactivation procedure validated on a lesser resistant strain must also be validated on the more resistant strains.

  - **Viruses** from the **same family** can be suitable surrogates for select agent viruses,
  - **Bacteria** from the **same genus** can be suitable surrogates for select agent bacteria, and
  - **Any positive single stranded RNA** can be suitable surrogates for regulated positive single stranded RNA.

PI Signature on Inactivation Certificate

(April 11, 2017)

- The PI is the one individual who is designated by the entity to direct a project or program and who is responsible to the entity for the scientific and technical direction of that project or program (including all inactivation procedures or removal procedures associated with that project).

- In the absence of that PI, an individual designated by that PI and approved by the entity RO may sign the certificate.

- In order for an individual to be the PI's designee to sign the certificate, a person must be listed on the entity's registration and have the knowledge and expertise to provide scientific and technical direction regarding the validated inactivation procedure or the procedure for removal of viable select agent to which the certificate refers.

Inactivation Certificates

(May 16, 2019)

Does a copy of the PI-signed inactivation certificate need to accompany any transfer outside of containment?

- A copy of an inactivation certificate must accompany the inactivated material when the inactivated material is transferred externally (from your entity to another entity). It is recommended that an inactivation certificate also accompany the transfer of inactivated material internally (from one PI to another PI at the same registered entity). Additionally, regardless of whether a transfer is made, an entity remains responsible for the record keeping requirements found in Section 17(a)(8) of the select agents and toxins regulations. An original certificate must be generated for every sample inactivated regardless of any future transfer.

- FSAP recommends that entities maintain the certification of inactivation as long as the material is in their possession.

Inactivation Certificates

Does a certificate have to be generated if the inactivated select agent or regulated nucleic acids or select agent removed material stays within registered space?

- Yes. For each select agent that has been subjected to a validated inactivation procedure or a procedure for removal of viable select agent, a registered entity must generate 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.

The location of the inactivated or select agent removed material does not change the requirement to generate a certificate.

INACTIVATION COMPLIANCE ISSUES

Inactivation Compliance Issues

- Surrogates: Entity validated the inactivation procedure with one family of viruses and then used the same parameters to inactivate other viral families.
  - Corrective action: Required entity to follow policy for surrogates. Viruses from the same family can be suitable surrogates for select agent viruses.

- Certificates: PI signing certificates before the inactivation procedure is performed. PI has approved of the experiment and outside of initial validation, there is no requirement for verification viability testing, therefore the entity determined that the certificate can be signed before inactivation is performed.
  - Corrective action: Required entity to review method used and sign certificates after inactivation has occurred.

Inactivation Compliance Issues

Inactivation validation:

- Inactivation of viruses whose genomes are infectious (+ strand RNA) and only testing for inactivation of virus.
  - Corrective action: Required the entity to not only confirm no viable virus, but also no nucleic acids that can produce infectious forms of any of the select agent viruses.

- Volumes of inactivated material tested during viability testing are insufficient in our view, but we do not have a requirement for volumes that must be tested.
  - Corrective action: Requested the entity justify their volumes to show they would be able to detect an inactivation failure.

- Verification viability testing only without initial validation
  - Corrective action: Resulted in DSAT issuing a policy (8/10/18) clarifying that **in-house validation** must be completed prior to the use of the procedure.

Inactivation Compliance Issues

Inactivation validation:

- Use of published formalin penetration rates in an inactivation procedure without validating the rates/procedure in house.
  - Corrective action: Required entity to validate rates/procedure up-front, in-house.
- Use a published gamma irradiation inactivation curve as basis for the irradiation times in an inactivation procedure without validating the procedure in house.
  - Corrective action: Required entity to validate rates/procedure up-front, in-house.
- Use of an inactivation procedure on a higher titer virus than what was used when validating the procedure.
  - Corrective action: Required entity to validate the inactivation procedure in-house with the higher titer or only use the validated procedure on titers equal to or less than what was used during validation.

OTHER RELEVANT DECISIONS

Electronic Signature-Certificates

(SA Gram 9/7/18)

- For electronic signature, the method used should:
  - Identify and authenticate a person using at least two factors of authentication, including something the person knows (i.e., email password) and something the person has (e.g., a mobile phone with SMS text message access);
  - Provide a means to preserve the integrity of the signed record that is (a) portable, (b) independently verifiable, (c) tamper-evident, (d) granular, and (e) verifiable in the long-term.
- The electronic signature should also:
  - Capture the intent such as indicate a person's approval of the document
  - Be backed by an audit trail

INACTIVATION QUESTIONS?

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