



Animal and Plant
Health Inspection
Service

Veterinary Services

Center for Veterinary
Biologics

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Inspection: Findings related to Title 9 CFR 113.53 - Ingredients of Animal Origin Testing

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Notes:

CVB Inspection and Compliance Policy Concerning Compliance to Title 9 CFR 113.53 – Ingredients of Animal Origin Testing

Background: Title 9 CFR 113.53 requires that each lot of ingredient of animal origin which is not subjected to heat sterilization or other sterilization methods acceptable to the CVB, used to prepare a biological product shall be tested as prescribed in 9 CFR 113.53 by the licensee **or** a laboratory acceptable to the CVB.

- Results of all tests shall be recorded by the testing laboratory **and** made a part of the licensee's records.
- A lot of ingredient found unsatisfactory by any prescribed test shall not be used to prepare a biological product.
- A serial of biological product shall not be released if produced using an ingredient that is found unsatisfactory by any prescribed test.

Title 9 CFR 113.53 is cited in:

- 1) 113.64 (d), *General requirements for live bacterial vaccines*
- 2) 113.100(d), *General requirements for inactivated bacterial products*
- 3) 113.300(d), *General requirements for live virus vaccines*
- 4) 114.9, *Outline Guide for Diagnostic Test Kits*

This document describes policies and practices the IC Section performs when evaluating the acceptability of compliance to 9 CFR 113.53.

Applicability

Testing is required for each lot of ingredients of animal origin (IAO) which is:

- used in the preparation of product
- not heat sterilized prior to use
- not subject to other sterilization methods acceptable to APHIS (viricidal procedure).
Acceptability by APHIS of alternative methods should be noted in the Outline of Production either by a date or Mail Log number.

Inactivated product – IAO must be tested unless exempted in the Outline of Production,

Diagnostic test kits – IAO used in test kits must be tested unless exempted in the Outline of Production

Inspection Findings

1. The licensee/permittee must provide evidence of satisfactory testing as required by 9 CFR 113.53 or have been exempted from the requirement and the respective Outline of Production must contain the exemption.
2. The testing of an IAO may be performed by the licensee/permittee or by an outside laboratory.

CVB Inspection and Compliance Policy Concerning Compliance to Title 9 CFR 113.53 – Ingredients of Animal Origin Testing

3. If exempted from the testing, the acceptable parameters must be detailed in the Outline of Production. Adequate documentation and records must be maintained (if applicable).

Testing Performed by the Licensee/Permittee

1. Records documenting the testing must be in accordance with 9 CFR 116.1, 116.7, and 116.8.
2. See B (below) for violations found.

Testing Performed by an External Laboratory

1. Testing results may be supplied by the testing laboratory in the form of a Certificate of Analysis (C of A).
2. The Biologics Specialist may require the licensee/permittee to provide copies of the bench records documenting the testing.
 - a. If the licensee/permittee cannot provide the Biologics Specialist copies of the bench records during the inspection and it appears that testing was satisfactory, the inspector may allow the firm a limited amount of time (Inspection *Action* item) to provide the bench records for evaluation.
 - b. If the licensee/permittee performs periodic audits of the external laboratory and the audit records are provided to the Biologics Specialist, these records may be used to substantiate that the external laboratory is performing the testing in accordance with the regulations.
3. Records documenting the testing must be in accordance with 9 CFR 116.1, 116.7, and 116.8.

Analysis of Testing

The test records should be sufficient to document that testing was performed in accordance with 9CFR 113.53(c)-(e) as applicable.

Items to consider:

1. Toxicity of test material
2. The minimum amount of IOA (such as FBS) that can be tested is 3.75 mls. But you can prepare the culture media with as much as 15% of the IOA (FBS). Cells may be unable to tolerate a 15% concentration of serum and may exhibit cytotoxicity.
3. The use of positive and negative controls is vital for that reason.
4. The use of “clean” cell lines is vital.
5. The testing can be conducted by another lab and test results can be provided to the manufacturer.

CVB Inspection and Compliance Policy Concerning Compliance to Title 9 CFR 113.53 – Ingredients of Animal Origin Testing

6. There is no requirement to further identify CPE or HA viruses – just make sure they don't use the lot of material.

Other Sterilization Methods

1. Alternative method of sterilization for ingredients of animal origin are reviewed by PEL and if acceptable, documented in the filed OP.
2. The Biologics Specialist reviews documents on file that support the firm is in compliance with the exemption from heat sterilization.

B. Addressing Violations of 9 CFR 113.53

1. If the Biologics Specialist documents that a violation of the regulations has occurred, a risk assessment must be performed regarding product in the marketplace and product not released to the market. Other actions taken besides those listed below will be dependent upon the **documented** (inspection notes) risk assessment.

a. Product released to the market: If the licensee/permittee does not initiate a Voluntary Stop Distribution and Sale action for all affected product, then the inspector must contact the Investigation Manager, an IC Section Leader, or the IC Director to initiate a recommendation for a Mandatory Distribution and Sale.

i. For inactivated product found to have not been tested and there was no exemption in the Outline of Production, a Voluntary Stop Distribution and Sale should be initiated by the firm until they conduct a risk assessment and provide investigations showing evidence the risk is minimal. If the firm does not initiate a Voluntary Stop Distribution and Sale contact as above to recommend a Mandatory Stops Distribution and Sale.

IC should evaluate the firm's assessment of the materials produced to determine impact to animals vaccinated considering:

- Inactivation agent
- Process used for inactivation
- Any adverse events reported possibly related to reactions that could be attributable to live extraneous agents

ii. For diagnostic test kits found to have not been tested without an exemption in the Outline of Production, IC should evaluate the investigation and risk assessment provide by the firm to determine impact to animal population considering:

- Pen-side tests would be a higher risk of introduction of disease to the animals being tested
- Diagnostic test kits used in a laboratory setting would have little to no impact to the health of the US herd
- Extraneous agents may impact the sensitivity and specificity of the diagnostic test result

CVB Inspection and Compliance Policy Concerning Compliance to Title 9 CFR 113.53 – Ingredients of Animal Origin Testing

b. Product not released to the market: The inspector is to contact the IC office and initiate a Hold Release on all future unreleased product (have codes and serials ready to relay) until evidence is provided that a process is in place to test according to the regulations. The Hold Release may be held in place until the Specialist confirms the appropriate testing.

Note: Not having the external laboratory's bench records is not an immediate violation of the regulations. If the licensee/permittee is eventually unable to supply copies of the bench records or has not adequately documented the audit of the external laboratory, then the violation(s) is established.

2. If the licensee/permittee cannot provide the inspector the copies of the testing bench records during the inspection and it appears that the testing results were satisfactory, the inspector may allow the firm a limited amount of time (*Inspection Action* item) to provide the bench records for evaluation prior to initiating actions regarding the violation. The Specialist provides the firm the consequences of not being able to provide copies of the testing to substantiate conformance to the regulations.

3. Also see **ICWI0105**, *Compliance Policy for Issuing Regulatory Actions*.