



Animal and Plant
Health Inspection
Service

Veterinary Services

Center for Veterinary
Biologics

1920 Dayton Avenue
PO Box 844
Ames, IA 50010

(515) 337-6100

Items to Consider for No Tests/Inconclusive/Satisfactory Results Regarding Section V Safety Testing

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Items to Consider for Test Conclusions for Section V Safety Testing

Source Document: title 9, *Code of Federal Regulations*, part 113.39(b), 113.40(b), 113.41, 113.44, 113.45, 113.207(a)

Test summaries with No Test or Inconclusive test conclusions reported for Outline or title 9, *Code of Federal Regulations* (9 CFR), testing should be carefully considered for release. Tests that do not adhere to the stipulations required in the Outline of Production should not be released to the market unless other acceptable documentation is supplied to Inspection and Compliance (IC). An investigation concerning an Out of Specification Test Result may be warranted by the firm.

Definition:

Unfavorable reactions (9 CFR 101.5 (n)): Overt adverse changes which occur in healthy test animals subsequent to initiation of a test and manifested during the observation period prescribed in the test protocol which are attributable either to the biological product being tested or to factors unrelated to such product as determined by the responsible individual conducting the test.

Note: The determination must be scientifically valid and if the conclusion is the reaction was not product related, the ultimate cause of the reaction must be determined.

Out of Specification (OOS): OOS deviations are usually events that result in testing No Test conclusions, failure of validity requirements, Unsatisfactory test results or a contamination event. The most common occurrence is during Outline of Production, Section V testing. OOS results includes *all* test or process results that fall outside the specifications or acceptance criteria established

Test Conclusions (S, NT, I, U): See 9 CFR 101.5(l)

Wet Chick Safety Test

Specific reviews such as 9CFR 113.207(a) should be considered as even a small number of live virus may cause encephalomyelitis in the horse.

All clinical observations and assessments must be documented appropriately by personnel familiar with assessing the health of young birds. Such documents should be supplied to the CVB-Inspection and Compliance (CVB-IC). Below are some items for the Specialist to consider when making a decision on serial release:

1. Were there neurological signs observed? Neurological symptoms may be subtle and exhibited in chicks as dehydration or failure to thrive due to their inability to find or ingest water or food.
2. In the event of a bird death, the following should be done to determine if the death was attributable to the vaccine:
 - a. A full necropsy of the affected bird should be performed with the gross pathological findings documented and supplied with the request for product release.

- b. Tissues for histopathology should be taken and assessed by a person qualified to do so:
 - i. Tissues taken should be properly selected and handled until examined.
 - ii. Tissues to be collected for histopathology **must include the brain**. Other organs to consider sampling for histopathology include, but are not necessarily limited to, heart, liver, thymus, spleen, and bursa of Fabricius.
 - iii. Tissues should not be taken from autolyzed organs. If the frequency of animal observations and animal housing conditions are appropriate, this should not be an issue.
 - iv. Results from all histopathological examinations should be obtained prior to requesting release of product and submitted with such a request.
- c. Review of inactivation steps should be done to confirm there were no deviations from the validated process.

3. Virus isolation and/or virus detection testing should be considered.

Host Animal Safety

- 9 CFR 113.39(b) Cat Safety Testing 2 cats, 10x dose, observe 14 days
- 9 CFR 113.40(b) Dog Safety Test 2 dogs, 10x dose, observe 14 days
- 9 CFR 113.41 Calf Safety Test 2 calves, 10x dose, observe 21 days
- 9 CFR 113.44 Swine Safety Test 2 swine, 2x dose (bacterial) 10x dose (viral)
Observe 21 days
- 9 CFR 113.45 Sheep Safety Test 2 sheep, 2x dose (bacterial) 10x dose (viral)
Observe 21 days

Infrequently, a manufacturer may have test results that indicate a hypersensitivity or other untoward adverse event reaction to a serial of product. This may be an indication the reaction is serial related.

While the manufacturer may have a label claim or information within the Outline Section VI indicating the reaction is expected, market release of a serial is based on the information listed in Section V of the Outline of Production.

- If these reactions are listed in Section V.B. the serial is evaluated based on the information listed in the Outline.
- If the reactions are NOT listed in Section V.B., the manufacturer must request an exception for consideration of market release.

1. Considerations for an exception to Section V.B. of the Outline of Production

- a. The exception request and supporting documentation may be submitted as an attachment to the APHIS Form 2008, or as a stand-alone mail log submission.

- b. All clinical observations and assessments must be documented appropriately by personnel familiar with assessing the health of animals.
2. In the event of a death, the following should be reviewed to determine if the death was attributable to the vaccine
 - a. The manufacturer must provide information demonstrating the death was not attributable to the vaccine.
 - b. The manufacturer must provide evidence what caused the death of the animal.
 - c. Methods that may be used to provide this information include reports from applicable diagnostic laboratories. As an example, the diagnostic report would provide information that the cause of death was not caused an infection caused by the vaccine or a reaction related to the administration of the vaccine
3. If the animal recovers with treatment as prescribed by label indications (Label indications are in fact adverse reactions usually attributable to the product.):
 - a. Documentation regarding the animal health prior to vaccination should be reviewed. The animals should have been examined prior to the start of the test [9 CFR 117.4(a)] and this should be documented [9 CFR 116.6].
 - b. Determine if the animals were animals used in prior safety tests. Animals previously used in other safety tests that may have become sensitized would not be eligible for consideration of a no test as the manufacturer understands the risks associated with this practice.
4. If you have any doubts as to if the firm has adequately confirmed any unfavorable reactions are **not** product related, then discuss this with a CVB-IC Section Leader. It is also appropriate to include the appropriate CVB-Policy, Evaluation, and Licensing Reviewer(s) in such discussions.
5. If these exceptions become frequent the firm may have to provide acceptable data to PEL and request additional information be included in Section V.B. of the Outline. If the supporting data is filed as acceptable, the firm must submit an updated Outline of Production prior to implementing the standard for serial release