



## VS Memorandum (VSM) 800.91

---

### Inspection of U.S. Veterinary Biologics Licensed and Permitted Establishments

#### 1. Purpose and Background

This memorandum provides guidance to licensee/permittees and other regulatory agencies (domestic or international) regarding the Center for Veterinary Biologics' (CVB) onsite inspections and may be used as a guide for self-inspections to determine compliance with the [Virus-Serum-Toxin Act](#) (21 U.S.C. 151-159). The Virus-Serum-Toxin Act requires each manufacturer of a veterinary biological product to be issued a U.S. Veterinary Biologics Establishment License. The premises listed on the Establishment License, the methods of preparation of the veterinary biological product and equipment used, all activities within each establishment, and qualification of personnel are defined in documents filed with CVB. Regulations in title 9, *Code of Federal Regulations* (9 CFR), part [115](#) give authority for any USDA inspector to enter any establishment where any biological product is being prepared, at any hour during the day or night, and inspect without previous notification.

The Virus-Serum-Toxin Act authorizes the Secretary of Agriculture, through the Animal and Plant Health Inspection Service (APHIS), CVB to license and inspect all veterinary biologics. No worthless, dangerous, contaminated, or harmful product may be licensed, produced, or distributed. Facilities, equipment, processes, and personnel associated with the manufacturing, testing, packaging, and distribution of veterinary biological products are subject to regular, unannounced onsite inspections by representatives of CVB-Inspection and Compliance staff. The inspection process, with the CVB controlled testing of serials, rigorously assesses veterinary biological products manufactured, quality control tested, packaged, and distributed under the U.S. Veterinary Biologics Establishment License. The regulations promulgated by the Virus Serum Toxin Act describe the principles and practices of good manufacturing.

Pursuant to the [Congressional Review Act](#) (5 U.S.C. § 801 et seq.), the Office of Information and Regulatory Affairs designated this rule as a non-major rule, as defined by 5 U.S.C. § 804(2).

#### 2. Document Status

- A. Issue Date: 12/08/2020
- B. This document replaces VSM 800.91 dated June 28, 2016.



## VS Memorandum (VSM) 800.91

---

### 3. Reason for Reissuance

- A. This was updated for clarity and consistency with other regulatory documents by adding definitions related to quality management and good manufacturing practices. Issuance of a Certificate of Inspection issued by CVB is also introduced in this guidance document.

### 4. Authority and References

#### A. Authorities

- [Virus-Serum-Toxin Act](#) (37 Stat. 832-833, 21 U.S.C. 151-159)
- [7 CFR 371.4](#)
- [9 CFR 101](#)
- [9 CFR 102](#)
- [9 CFR 103](#)
- [9 CFR 104](#)
- [9 CFR 105](#)
- [9 CFR 108](#)
- [9 CFR 109](#)
- [9 CFR 112](#)
- [9 CFR 113](#)
- [9 CFR 114](#)
- [9 CFR 115](#)
- [9 CFR 116](#)
- [9 CFR 117](#)

#### B. References

- [Animal Welfare Act](#)
- [Global Regulatory Framework Document](#). A guide created by Animal Health Institute (AHI) that compares the USDA methods/regulations to the Rules and Guidance for Pharmaceutical Manufacturers and Distributors (the Orange Book) compiled by the Inspection, Enforcement and Standards Division of Medicines & Health products Regulatory Agency and the Guide to Good Manufacturing Practice for Medicinal Products, prepared by the Pharmaceutical Inspection Convention, Pharmaceutical Inspection Co-operation Scheme (PICs). AHI is responsible for posting and maintaining this document.
- [VSM 800.53](#), Release of Biological Products
- [VSM 800.56](#), Disposal of Unsatisfactory and Undesirable Materials
- [VSM800.57](#), Market Suspensions and Post Marketing Temperature Deviations
- [VSM 800.59](#), Veterinary Biological Product Samples



## VS Memorandum (VSM) 800.91

---

- [VSM 800.60](#), Biological Products Returned to Licensed Establishments
- [VSM 800.63](#), Personnel at Licensed Establishments
- [VSM 800.64](#), Preparation of Experimental Products at Licensed Establishments
- [VSM 800.74](#), Preparation and Distribution of Sterile Diluents
- [VSM 800.78](#), Preparation and Submission of Facilities Documents
- [VSM 800.115](#), Potency and Safety Testing by Unlicensed Facilities
- [VSM 800.116](#), Target Animal Safety Testing Exemption
- [VSM 800.210](#), Manufacturing Deviations Identified Prior to Marketing Release

### C. Definitions

- 1) **Quality Management** is a wide-ranging concept covering all matters that individually or collectively influence the quality of a product. Manufacturers assume the responsibility for the quality of the veterinary biological product and that the product is fit for the intended use, as demonstrated during the licensing process, and comply with all applicable requirements throughout the product's life cycle.
- 2) **Quality Assurance** is the totality of actions within the organization supporting quality management.
- 3) **Good Manufacturing Practice** is a system to ensure products are consistently produced and controlled. CVB oversight regarding periodic review of the licensee/permittee control is twofold. Sample submission and check testing by CVB provides one method of control. The second method is by routine onsite inspections.
- 4) **Quality Control** is the procedures used to ensure starting material, in-process material, and final use product conform to the established specifications required for consistent production.
- 5) **Quality Risk Management** is a systematic process to assess, control, communicate, and review the risks to the quality of the product across the product's life cycle. It is used to develop the control strategy for each stage of manufacturing, from starting material to final distributed product.
- 6) **Validation** is the action of scientifically proving the procedures, processes, equipment, material, activities, and systems lead to the results of delivering a quality product. This includes continual assurance that a process remains in a state of control. Some examples are:
  - Cleaning procedures
  - Testing procedures
  - Production processes



## VS Memorandum (VSM) 800.91

---

- Equipment use
- Computer systems

7) **Calibration** is the demonstration that a particular instrument or device produces results within specified limits by comparison with those produced by a reference or traceable standard over an appropriate range of measurements.

8) **Data Integrity** is the overall accuracy, completeness, and consistency of data.

### 5. Audience

VS employees and members of the biologics industry.

### 6. Guidance

#### A. Process

- 1) The inspection performed by CVB inspectors is in part to determine products were produced and tested by competent people using acceptable facilities, equipment, and validated processes.
- 2) The inspection includes audits of related records, observations to substantiate information on file with CVB, and perambulation of ongoing operations.

#### B. Findings

- 1) Findings are listed under one of the 14 categories of inspection found in subsequent sections of this guidance.
  - a. Violations will be cited as per 9 CFR and may include the applicable section numbers. Additional 9 CFR citations may also apply.
  - b. Violations will be classified as Serious, Less Serious, or Minor.
    - i. Serious – Violations of this degree may affect the quality of the product or products or may be willful.
    - ii. Less Serious – By repetition or situation, may affect quality of a product.
    - iii. Minor – Are not apt to affect quality of product but indicate laxity or error that could become more serious if not corrected. Numerous minor exceptions noted during the inspection indicate poor quality management and should be considered as having cumulative effect.



## VS Memorandum (VSM) 800.91

---

- c. The findings documented as a result of audits and observations for each inspection category should not be considered limiting or all-inclusive.
  - 2) CVB Inspectors provide a summary of finding to the regulated entity after each in-depth inspection.
  - 3) A written response from the licensee/permittee regarding corrective and preventive actions taken for the documented findings are required be submitted to CVB. This may require more than one response from the licensee/permittee.
  - 4) Certificates of Inspection may be issued indicating the manufacturing sites were inspected under the laws of the United States of America and comply with the principles and practices of USDA good manufacturing.
- C. Following is the list of inspection categories, with audits and observations for each. The list also includes information that may be reviewed during the annual Administrative Inspection Reviews. APHIS inspectors may use this list for guidance when conducting inspections. These items may also be beneficial for establishing self-inspections. The overarching regulation regarding inspection of establishments is 9 CFR [115.1](#).

### 1) Licenses and Permits

#### a. Audits

- i. Review the ownership, parent company, and subsidiary and division relationships with the firm's official in charge. If applicable, discuss any future changes or mergers and impacts to production and testing.  
[Reference: 9 CFR [114.1](#)]
- ii. Verify addresses, locations, and other information on the license. Confirm all stages of production are conducted within licensed premises.  
[Reference: 9 CFR [114.1](#)]
- iii. Review U.S. Veterinary Biological Product Permits for Research and Evaluation and any permits for the importation or transportation of organisms or vectors issued to the licensee and compare with information on file at CVB.
  1. Ask for any additional permits the firm may have.
  2. Audit the firm's records for compliance with special requirements listed on the permits and with the regulations covering importation for research and evaluation.



## VS Memorandum (VSM) 800.91

---

3. Determine if any of the permits expired.
- b. Observations
    - i. Note the location of buildings and equipment used to produce, test, and store products to be sure that all premises are properly identified on the establishment license. Note any change in ownership, location, or operation of the establishment. [Reference: 9 CFR [108.1](#)]
    - ii. Verify every product observed in production or testing on the licensed premises has a license or permit. Ensure products prepared under the Food and Drug Export Reform and Enhancement Act do not adversely impact the preparation of licensed/permitted veterinary biological product. [Reference: 9 CFR [114.2\(b\)](#)]
    - iii. If applicable, review non-biological products prepared in the facility and determine if there is any adverse impact to the preparation of licensed/permitted veterinary biological product. [Reference: 9 CFR [103.1](#)]
    - iv. Review permit restrictions and determine if the permittee is in compliance with these restrictions for imported products for distribution and sale.
    - v. Inspect facilities where research material imported under permit is handled, and the conditions for handling this material, to be sure they meet requirements. Check for any other imported biologics on the licensed premises. Biologics exported from the United States may only be returned under a permit for research and evaluation. [Reference: 9 CFR [104.4](#)]
  - c. Administrative Inspection Review
    - i. Licensees/permittees compare information on file regarding the firm's U.S. Veterinary Biologics Establishment License for the establishment, and if applicable, the sites. [Reference: 9 CFR [102.1](#) or [104.1](#)]
    - ii. Activity of each licensed product, including conditional licenses
      1. If a product is not being produced, determine the last date of production. The firm may wish to voluntarily return inactive product licenses for which they no longer have the equipment, facilities, and/or expertise to prepare to APHIS for termination. [Reference: 9 CFR [105.4](#)]



## VS Memorandum (VSM) 800.91

---

2. Review for terminated conditional licenses [Reference: 9 CFR [102.6\(a\)](#)]

### 2) Personnel

#### a. Audit

- i. Request a current copy of the firm's organizational chart or obtain information on official lines of responsibility within the firm.
  1. Review the relationships between production, testing, marketing, and quality assurance. The responsible managers of production and quality control must be independent from each other.
  2. Review spans of responsibility to ensure they are not so extensive as to present a risk to quality.
  3. Review gaps or unexplained overlaps in personnel responsibility. Senior management has the ultimate responsibility to ensure compliance with the regulations.
- ii. Review the firm's process of determining who should have an APHIS Form 2007 on file with CVB and the system used to maintain the listing. Identify the person responsible for periodically reviewing the APHIS Form 2007 file. [Reference: 9 CFR [114.7\(a\)](#)]
- iii. Review training records for essential functions conducted regarding licensed/permitted products. [Reference: 9 CFR [114.7\(b and c\)](#)]
  1. All personnel (including those concerned with cleaning and maintenance) employed in the areas where products are manufactured should be given training in and information on microbiology, hygiene, and biosafety. They should receive additional training specific to the product with which they work. [Reference: 9 CFR [114.7\(c\)](#)]
  2. Personnel working in areas where products are manufactured and tested should receive training and periodic retraining specific to their duties and the products manufactured. [Reference: 9 CFR [114.7\(b and c\)](#)]

#### b. Observations

- i. Determine if personnel designated as the official liaison and alternate liaisons, if applicable, are knowledgeable about the day-to-day activities at



## VS Memorandum (VSM) 800.91

---

the firm and in a position to make agreements with APHIS. [Reference: 9 CFR [114.7\(a\)](#)]

- ii. Observe if employees in key positions have APHIS Form 2007s on file at CVB. Observe if employees follow lines of responsibility as shown on the organizational chart or as explained by management. See Veterinary Services (VS) Memorandum [800.63](#), Personnel at Licensed Establishments, for additional guidance. [Reference: 9 CFR [114.7\(a\)](#)]
  - iii. Observe operations to determine if employees, in general, are adequately trained and supervised so as to be competent in good laboratory techniques and preparation of veterinary biological products. Be aware of personnel health conditions that might affect the product. [Reference: 9 CFR [114.7\(b\)](#)]
  - iv. Observe if there is an adequate number of personnel with necessary qualifications and practical experience available for the functions being performed.
  - v. Determine if adequate measures are taken to prevent breaches in biocontainment or prevention of cross contamination. This may include, but is not limited to, the use of personal protective equipment, change of clothes, and/or showering before leaving the production area. [Reference: 9 CFR [114.7\(c\)\(1\)](#)]
- c. Administrative Inspection Review
- i. Review list of personnel submitted on APHIS Forms 2007s on file with CVB. [Reference: 9 CFR [114.7\(a\)](#)]
    - 1. Review for any key changes in personnel and their responsibilities.
    - 2. Review for deletions, additions, or job changes.
    - 3. Confirm the names of the official liaison, alternates, and site contacts.
  - ii. Personnel responsible for production and quality control should have an adequate background in relevant scientific discipline, together with sufficient practical experience to enable them to perform their duties. [Reference: 9 CFR [114.7\(b\)](#)]

### 3) Facilities [Premises]

- a. Audit





## VS Memorandum (VSM) 800.91

---

- i. Inspect the premises and compare with the facility documents. See VS Memorandum [800.78](#), Preparation and Submission of Facilities Documents, for additional guidance. [Reference: 9 CFR [108.1](#)]
    1. Dedicated facilities may be required for manufacturing when risks cannot be adequately controlled by operational or technical measures.
    2. Premises should be laid out in such a way as to allow production to take place in areas that are connected in a logical order, corresponding to the sequence of the operations and to the requisite cleanliness levels. [Reference: 9 CFR [108.8\(b\)](#)]
  - ii. When comparing facilities with the filed facility documents, look for evidence of unreported remodeling, new stationary equipment, relocated key items, and other discrepancies. [Reference: 9 CFR [108.6\(a\)](#)]
  - iii. Confirm that legends showing special-use facilities (such as a public diagnostic clinic, diagnostic facilities, separate and apart research areas, export-only products, pharmaceuticals production, and FDA Export Reform and Enhancement Act production) are correct. Determine the location and adequacy of isolation facilities for incoming animals, if required. [Reference: 9 CFR [108.8\(c\)](#), [117.3\(a\)](#), [117.3\(e\)](#)]
  - iv. Evaluate the site's qualification processes for facilities, equipment, and utilities. Determine if the qualification and validation principles incorporate the critical process parameters and critical quality attributes needed for the production of veterinary biological products. [Reference: 9 CFR [102.4\(a\)](#)]
- b. Observations
- i. Verify the premises design, as listed in the blueprint documents, is actually being operated in compliance with the information on file. Processes must have adequate and appropriate isolation for each product to prevent cross-contamination from other products. Evaluate operations for any possible adverse effect on the product. [Reference: 9 CFR [108.8\(b\)](#)]
    1. Ensure other operations where live biological agents are handled, including organisms used in quality control, are appropriate, contained, and separated if production is operated in the same building. The measures used to prevent cross-contamination should be commensurate with the risks. [Reference: 9 CFR [108.8\(c\)](#)]



U.S. DEPARTMENT OF AGRICULTURE

Marketing and Regulatory Programs  
Animal and Plant Health Inspection Service  
Veterinary Services

## VS Memorandum (VSM) 800.91

---

- a) Live biological agents should be handled in rooms or compartments to contain the agent. [Reference: 9 CFR [108.8\(c\)](#)]
- b) Ensure authorized diagnostic facilities at the licensed establishment follow safeguards to mitigate the risks of contamination with pathogenic organisms. [Reference: 9 CFR [117.3\(e\)](#)]
2. Observe traffic patterns through the production area. Prevention of cross-contamination by personnel should be achieved by a set of measures and procedures to eliminate risk. This may include the use of air locks for personnel and equipment. Observe enforcement of movement restrictions. Restricted areas should be posted as such. [Reference: 9 CFR [108.8\(b\)](#)]
3. Animal facilities should be well isolated from other areas, with separate entrances and air handling. [Reference: 9 CFR [117.1\(b\)](#)]
- ii. Observe that premises are carefully maintained; the material, construction, and finish of all areas related to the production of biological products or ingredients of biological products can be thoroughly cleaned. [Reference: 9 CFR [108.8\(a\)](#)]
  1. Walls, floors, and ceilings in areas where product is exposed must be smooth and free of cracks or open joints.
  2. Pipework, light fittings, ventilation points, and other services should be designed to avoid recesses which are difficult to clean.
- iii. Observe the adequacy of the working and in-process storage space to permit the orderly and logical positioning of equipment and materials so as to minimize the risk of errors between different products, antigens, and/or components; to avoid cross contamination; and mitigate the risk of omission or wrong application of any manufacturing or control steps. [Reference: 9 CFR [108.8\(b\)](#)]
- iv. Ensure repairs, maintenance, or remodeling operations do not present a hazard to the quality of products. [Reference: 9 CFR [108.6](#)]
- v. Verify lighting is appropriate and such that it does not adversely affect, either directly or indirectly, the preparation, testing, storage of product, or accurate functioning of equipment. [Reference: 9 CFR [108.4\(g\)](#)]



## VS Memorandum (VSM) 800.91

---

- vi. Verify an adequate supply of hot and cold water and ensure efficient drainage and plumbing systems for production and testing purposes. Ensure drains are properly installed with approved traps and vents and are functioning as expected. Open channels should be avoided where possible, but if needed, they should be shallow to facilitate cleaning and disinfection. [Reference: 9 CFR [108.8\(e\) and \(f\)](#)]
- vii. Verify the heating, ventilation, and air conditioning systems are sufficient to adequately address issues of biocontainment and mitigate cross-contamination for the protection of products and personnel. [Reference: 9 CFR [108.8\(d\)](#)]
- viii. Verify that dressing rooms, toilet facilities, and lavatory accommodations are appropriately placed, sufficient in number, and separated from production. Soap, towels, and hot water should be available. [Reference: 9 CFR [108.9](#)]
- ix. Verify adequate biosafety measures are taken to prevent infection of personnel working with zoonotic agents. [Reference: 9 CFR [108.8\(c\) and \(d\)](#)]
- c. Administrative Inspection Reviews – not applicable to this category unless related to specialized questions during the annual review.

### 4) Equipment

- a. Audits
  - i. Identify equipment and environmental rooms used in production, testing, and storage of product. The equipment should be designed, located, and maintained to suit the intended purpose. [Reference: 9 CFR [108.4\(f\)](#)]
    - 1. Verify that the location of equipment matches the code designated in the blueprint legends.
    - 2. Confirm the unique identity of equipment through production records, maintenance logs, and operation as intended by the manufacturer of the equipment. Repairs and maintenance operations should not present any hazard to the quality of the products.



## VS Memorandum (VSM) 800.91

---

3. Review the records of operation of specialized equipment, determine if the equipment is functioning properly, and ensure recordkeeping is in compliance.
- ii. Verify equipment is cleaned and sterilized according to detailed, written procedures. Determine if sufficient records are maintained. [Reference: 9 CFR [116.4](#)]
  - iii. Review records regarding the calibration of equipment at defined intervals.
    1. Equipment/instrument/device calibrations should be performed using standards traceable to certified standards from organizations such as the National Institute of Standards and Technology if existing.
    2. The results of the calibration must be within the specified limits by comparison to the traceable standard.
    3. The calibrated measurement should be within the defined set of operating parameters, established under specific conditions for use during production and testing.
  - iv. Determine what system is used and what records are kept by the firm to ensure that automatically controlled equipment is operating properly. If the firm has an exemption from having automatic recorders on sterilizers, determine if the records kept meet the provisions of regulations. [Reference: 9 CFR [109.2](#)]
- b. Observations
- i. Look for equipment or compartments not shown on the blueprint and/or the blueprint legend. Determine if they are being used in production, testing, or storage of product and if the equipment or compartment is being used and maintained in compliance with the regulations and manufacturer's recommendations. [Reference: 9 CFR [108.5\(b\)\(2\)](#)]
  - ii. Observe the operation of equipment and compartments and determine if they are being operated properly. Production equipment should not present any hazards to products. If equipment is calibrated, the appropriate range and precision should be available for the operator.



## VS Memorandum (VSM) 800.91

---

- iii. Determine if each piece of equipment is uniquely identified so the use of the equipment may be adequately documented and traceable in the manufacturing records when used in production.
- iv. Fixed pipework should be clearly labelled to indicate the contents and, where applicable, the direction of flow.
- v. Assure that all equipment is being sterilized according to applicable requirements. [Reference: 9 CFR [109.1](#)]
  - 1. Exemptions to the regulations must be on file with CVB. Confirm equipment exempted from sterilization requirements listed in the regulations is being treated as allowed for in the exemption on file with CVB. See VS Memorandum [800.78](#), Preparation and Submission of Facilities Documents, for additional guidance on submitting an exemption.
  - 2. Observe equipment design, it should be easily and thoroughly cleaned.
- c. Administrative Inspection Reviews – not applicable to this category unless related to specialized questions during the annual review.

### 5) Sanitation

- a. Audits
  - i. Audit the firm's records to ensure that sanitizing is done at the appropriate time and place, and with the appropriate chemicals, as specified in the facility's blueprint legends.
  - ii. Determine if the chemicals used for sanitation are appropriate for the microorganisms in each room.
  - iii. Ensure adequate biosecurity measures are in place to prevent biological agents being taken outside the manufacturing plant by personnel acting as a carrier. [Reference: 9 CFR [114.7\(c\)\(1\)](#)]
- b. Observations
  - i. The manufacturing environment is operated in such a way as to present minimal risk of causing contamination of materials or product. [Reference: 9 CFR [108.8\(b\)](#)]



## VS Memorandum (VSM) 800.91

---

1. Notice if the outside premises are properly drained, clean, and free of accumulated trash or construction debris. [Reference: 9 CFR [108.10\(a\)](#)]
  2. Note whether an adequate effort is being made to control vermin, especially in animal quarters. [Reference: 9 CFR [108.10\(c\)](#)]
  3. Observe for clutter inside the premises. Determine if the clutter affects product quality. Check for accumulation of unnecessary materials, particularly in halls, production rooms, and coolers.
- ii. Determine if waste disposal methods are in accordance with the applicable regulations. See VS Memorandum [800.56](#), Disposal of Unsatisfactory and Undesirable Materials, for additional guidance. [Reference: 9 CFR [114.15](#)]
  - iii. Every person entering the manufacturing areas should wear protective garments as appropriate to the operations being carried out. Note if special clothing requirement areas are posted and requirements enforced. [Reference: 9 CFR [114.7\(c\)\(1\)](#)]
  - iv. Watch for unsanitary practices by employees, such as eating, drinking, chewing, smoking, or storage of food, drink, smoking materials, or personal medication in the production areas. [Reference: 9 CFR [114.7\(c\)\(2\)](#)]
  - v. Good aseptic techniques should be used to prevent direct contact with the product. Appropriate personal protective equipment must be used to avoid direct contact with the operator's hands and the exposed product, as well as with any part of the equipment that comes into contact with the products.
- c. Administrative Inspection Reviews – not applicable to this category unless related to specialized questions during the annual review.

### 6) Prelicensing - Products Pending Licensure

- a. Audits
  - i. Examine records to confirm that the firm has obtained permission from CVB-Program, Evaluation, and Licensing (PEL) for any research conducted in production facilities with organisms, antigens, or fraction not already approved for a licensed product. Determine impact to licensed/permitted product regarding the preparation of experimental product and review



U.S. DEPARTMENT OF AGRICULTURE

Marketing and Regulatory Programs  
Animal and Plant Health Inspection Service  
Veterinary Services

## VS Memorandum (VSM) 800.91

---

mitigating steps implemented by the firm or required by CVB. Confirm restrictions or conditions required by PEL were met. See VS Memorandum [800.64](#), Preparation of Experimental Products at Licensed Establishments, for additional guidance. [Reference: 9 CFR [103.1](#)]

- ii. Verify that the Seed material is adequately identified and accounted for.
  - iii. Review records for proper disposal of animals used in the preparation or testing of experimental products. [Reference: 9 CFR [117.6](#)]
  - iv. Differentiate between research being conducted using microorganisms related to currently licensed products and work with new microorganisms not related to licensed products. Complete records are required for both, but fewer restrictions may be required for microorganisms related to currently licensed products. [Reference: 9 CFR [116.1\(a\)](#)]
  - v. Review field trial records for compliance with special restrictions and requirements. Account for product prepared and distributed for field trials. Determine if the product was prepared in accordance with the Outline of Production on file. Determine if all responses were reported to PEL. Determine if the detailed records support the summaries sent to PEL. [Reference: 9 CFR [103.3](#)]
  - vi. Review the minutes of Institutional Biosafety Committee meetings. Determine if appropriate members have been appointed. Determine if all biotechnology work and especially recombinant product work are being addressed and if appropriate policy and procedures have been established.
  - vii. Determine if prelicensing serials were prepared in production facilities and tested on licensed premises. [Reference: 9 CFR [102.5\(c\)\(1\)](#)]
  - viii. Determine if the expiration dating on newly licensed products has been confirmed, submitted to PEL for review, and documented in the Outline of Production. [Reference: 9 CFR [114.14](#)]
- b. Observations
- i. Determine if the separation of personnel, supplies, and equipment between research and production is adequate.
  - ii. Observe the in-house controls on movement of personnel, supplies, and equipment and the airflow control between research, production, and testing areas.



## VS Memorandum (VSM) 800.91

---

- iii. Check for production-related testing in research areas.
  - iv. Check methods for disposing of research material. [Reference: 9 CFR [114.15](#)]
  - v. Observe specific research or precicensing activities as requested by PEL. [Reference: 9 CFR [103.1](#)]
  - vi. Observe if employees are following biosafety policies.
  - vii. Determine if biosafety policies are adequate.
- c. Administrative Inspection Review - Licensees/permittees compare information on file regarding the status of precicensing projects related to U.S. Veterinary Biologics Product License applications. [Reference: 9 CFR [102.5](#) or [104.5](#)]

### 7) Seeds and Cells

- a. Audits
  - i. Confirm the Master Seeds and Master Cell Stocks being used in production are the same as those listed in the corresponding Outline of Production. [Reference: 9 CFR [114.5](#)]
  - ii. Confirm the Master Seed and Master Cell Stock were prepared and tested according to the regulations and Outlines of Production. [Reference: 9 CFR [116.1\(a\)\(1\)](#)]
  - iii. The number of passages for seed and cell stocks must be consistent with the information listed in the Outlines of Production. [Reference: 9 CFR [114.5](#)]
    - 1. Review each passage level of seed and cell stock used in the preparation of product.
      - a) Accountability of use (including amount discarded).
      - b) Exact identification of material used.
      - c) Traceability from production lot back to the master stock.
    - 2. Records must be complete and reflect compliance with the regulations and corresponding Outline of Production.





## VS Memorandum (VSM) 800.91

---

- iv. Each storage container should be adequately sealed, clearly labeled, and kept at an appropriate temperature. Determine if the system of identification is adequate to ensure proper seed/cell stock has been used. [References: 9 CFR [114.4](#) and [114.11](#)]
    - 1. Verify the identity of all working and production seeds and cell stocks and trace their lineage back to the Master Seeds and Master Cell Stocks identified in the Outline of Production. [Reference: 9 CFR [114.5](#)]
    - 2. Verify that the passage levels of the Master Seeds, Working Seeds, Production Seeds, and Master Cell Stocks, including working and production cell stocks, used in producing the product serial are all acceptable based on the corresponding passage levels used in developing the prelicense data and specified in the Outline of Production.
  - v. Determine where Master Seeds and Master Cell Stocks are maintained, handled, and produced. These materials have very specific requirements, which should be consistent with information in the blueprint legends. [Reference: 9 CFR [114.5](#)]
  - vi. Review records of Master Cell Stocks for batches of primary cells to determine their source, if the source animal was free of disease, and if acquisition was according to the regulations. Determine if batches of primary cells have been adequately tested. [Reference: 9 CFR [113.53](#)]
  - vii. Review Master Seed production and testing records. Review immunogenicity test records. Determine if the bench records for each serial of product are complete and clearly trace to the Master Seed. [Reference: 9 CFR [116.1\(a\)](#)]
  - viii. Review records for ingredients of animal origin to determine compliance with the regulations. [Reference: 9 CFR [113.53](#)]
- b. Observations
- i. Observe any production or testing procedures in progress for compliance with the Outline of Production or regulations. Note if the seeds are monitored regularly for virulence, how they are maintained, how frequently they are passed, how they are stored, how much current inventory exists, etc.
  - ii. Determine where Master Seed, Working Seed, and Production Seed are prepared. Only Master Seed may be prepared in separate and apart



## VS Memorandum (VSM) 800.91

---

research facilities; Working Seed and Production Seed must be prepared on licensed premises in acceptable facilities.

- iii. Determine if the methods of maintenance, storage, and inventory of Master Seeds and Master Cell Stocks comply with the regulations and corresponding Outline of Production.
- iv. Check if there are separate storage facilities for virulent or dangerous microorganisms and if there is a possible impact on licensed product quality.

c. Administrative Inspection Reviews

- i. Confirm identity of the Master Cell Stock and/or Master Seed as listed. [Reference: 9 CFR [114.5](#)].
- ii. Confirm inventory status of each cell stock and seed.

### 8) Production (inoculation through batching)

a. Audits

- i. Records must be detailed enough to provide a complete accountability of the production process. [Reference: 9 CFR [116.1\(a\)\(1\)](#)]
  - 1. Review records of production procedures for data integrity, including, but not limited to, accountability and identification of each step.
    - a) Tracing serials and production lots from raw ingredients to filling.
    - b) Checks on yields and reconciliation of quantities should be carried out as needed to ensure there are no discrepancies outside the acceptable limits.
  - 2. Verify that records are complete, and that each critical procedure is listed in the Outline of Production.
  - 3. Review records for data integrity. If recordkeeping deficiencies are found, determine if they apply only to that serial or lot, or if they are consistent deficiencies for that product, group of products, or all products.
- ii. Determine if the serial or production lot has been prepared according to the version of the Outline of Production in effect when the lot was presented to CVB for market release (this includes sample submission);



## VS Memorandum (VSM) 800.91

---

compare the date of production with the date on the outline used for reference. [Reference: 9 CFR [114.2\(a\)](#)]

1. Check to see that each step listed in the outline is documented in the records.
  2. Review the records to determine if all critical steps are described in the Outline of Production.
  3. If deviations from the outline are noted, determine if they apply only to that serial or lot, that product, a group of products, or all products.
- iii. Determine if the manufacturer's recordkeeping system provides for the unique identification, tracking, and recording of each ingredient and if safeguards are in place to prevent errors in the preparation of the product. [Reference: 9 CFR [114.4](#)]
- iv. Determine how serial numbers are assigned and what system is used.
- v. Production operations must follow clearly defined steps as listed in the Outline of Production. The Outline of Production must contain all critical procedures in production to be considered accurate and sufficient. [Reference: 9 CFR [114.8\(d\)](#)]
1. Determine how annual outline reviews are done and by whom. The process should be documented.
  2. Determine frequency of reviews and if the reviews are sufficient.
- b. Observations
- i. Evaluate any production procedure in progress for compliance with the most recent Outline of Production and facility documents. [Reference: 9 CFR [102.5\(c\)\(1\)](#)]
  - ii. Determine if the identity of in-process material is maintained. Ensure suitable tags or labels are used to adequately identify all ingredients used in the preparation of biological products. Note the manner of identification used and the consistency of its use (e.g., color coding, lot numbers, product name). [Reference: 9 CFR [114.4](#)]
  - iii. Observe whether proper laboratory techniques and sterile practices are followed by laboratory personnel where required. [Reference: 9 CFR [114.7\(c\)](#)]



## VS Memorandum (VSM) 800.91

---

1. Operations on different products should not be carried out simultaneously or consecutively in the same room unless there is no risk of mix-up or cross contamination.
  - iv. Check that the equipment and workstations/rooms are cleared of previous products, documents, and materials prior to use for current production step.
  - v. Observe the preparation of equipment, media, and other ancillary procedures in the service area for compliance with the regulations and applicable special outlines. [Reference: 9 CFR [113.50](#)]
  - vi. Note any production procedures that differ from the Outline of Production and evaluate the effect on the product. Even though the procedures may be within limits of acceptable laboratory practice or are intended to improve the product, variations are not allowed unless the outline is changed to reflect the variations. Determine if approved outlines are available to be used, and are used by, line supervisors. [Reference: 9 CFR [114.2\(a\)](#)]
  - vii. Look for any procedures that may adversely affect the product.
  - viii. Verify open circuit operations involving products or components not subsequently sterilized are carried out within a laminar air workstation within the production room or by another acceptable method, such as the use of quick-connect devices. [Reference: [108.8\(d\)](#)]
  - c. Administrative Inspection Reviews – note that Special Outlines may be applicable to other categories of inspection, such as testing.
    - i. Confirm the file date of the most current Outline of Production/Special Outline [Reference: 9 CFR [114.8\(e\)\(1\)](#)].
    - ii. Review the date of the last annual review. [Reference: [114.8\(d\)](#)]
- 9) Final Production (filling to labeling and packaging)**
- a. Audits
    - i. Review filling records for recorded losses or gains, fill checks, and filling problems. Determine compliance with the fill ranges as filed in the Outline of Production. Determine how overfilled or underfilled vials are handled and if the firm has a written policy covering this. [Reference: 9 CFR [116.1\(a\)\(1\)](#)]



## VS Memorandum (VSM) 800.91

---

- ii. Determine the lyophilization requirements for each product. Review lyophilization records of selected serials for compliance and recordkeeping practices. Determine if temperature probe readings are identified on the recording charts.
  - iii. Determine if all reprocessing was authorized. Changes to composition of completed liquid product, prior to filling and/or labeling, can only be done when provided for in the Outline of Production or when authorized by CVB. [Reference: 9 CFR [114.18](#)]
  - iv. Review records of controlled freezing to determine if procedures follow the Outline of Production for products where this is critical, such as Marek's Disease Vaccine.
  - v. Determine if losses incurred through breakage, loss of vacuum, etc., are recorded in the serial records. [Reference: 9 CFR [116.1\(a\)\(1\)](#)]
  - vi. Determine if the firm can substantiate the container label, the carton label, and the enclosure used were appropriate for the final use product. [Reference: 9 CFR [116.3\(b\)](#)]
  - vii. Determine if subserials are being appropriately identified when further processed at different times or under different conditions, such as lyophilization in different dryers or at different times. [Reference: 9 CFR [101.3\(i\)](#)]
  - viii. Review the records to determine if all critical processes are described in the Outline of Production. [Reference: 9 CFR [114.8\(d\)](#)]
  - ix. Review records for data integrity. [Reference: 9 CFR [116.1\(a\)](#)]
- b. Observations
- i. Observe and evaluate actual filling procedures, including aseptic technique, fill checks, proper mixing during fill, appropriate temperature control, and maintenance of concurrent records. Determine if employees adhere to the specifications listed in the Outline of Production and how to handle unacceptably filled vials.
  - ii. Confirm lyophilization procedures. Determine if placement of probes is adequate. Note stoppering devices.
  - iii. Note in-house procedures for vial and label inspection, sampling, identification of unlabeled vials, and how product is controlled until released. Ensure suitable tags or labels are used to adequately identify all



## VS Memorandum (VSM) 800.91

---

ingredients used in the preparation of biological products. [Reference: 9 CFR [114.4](#)]

- iv. Review handling of diluent, how and where it is stored, and how it is accounted for. See VS Memorandum [800.74](#), Preparation and Distribution of Sterile Diluents, for additional guidance. [Reference: 9 CFR [113.54](#)]
- v. Examine freezing procedures. Determine the time interval from filling to start of freezing and the rate at which product temperature is lowered is in accordance with the Outline of Production.
- vi. Observe several selected serials for product uniformity, color, volume, texture, opacity, labeling, packaging, serial number readability, and expiration date. Check labels to ensure they have not rubbed off and are legible. [Reference: 9 CFR [112.1\(d\)](#)]
- vii. Determine if products other than biologics are filled, packaged, or labeled on the licensed premises. Determine if adequate separation of licensed serials of product and unlicensed product is maintained during filling, packaging, and labeling.
- viii. Review records for any process deviations, including detailed summary of deviation, root cause analysis, investigation report, corrective and preventative actions (CAPA), and the review process to determine CAPA effectiveness. See VS Memoranda [800.210](#), Manufacturing Deviations Identified prior to Marketing Release, and VS Memoranda [800.57](#), Market Suspensions and Post Marketing Temperature Deviations, for additional guidance. [Reference: 9 CFR [114.2\(a\)](#)]
- c. Administrative Inspection Reviews – not applicable to this category unless related to specialized questions during the annual review.

### 10) Labels and Packaging

- a. Audits
  - i. Review the files of the firm's label inventories for inactive, expired, superseded, or obsolete labels. Obsolete material should be destroyed, and the disposal recorded. [Reference: 9 CFR [116.3\(a\)](#)]
  - ii. Review the process regarding expiration date determinations. Ensure the process accounts for compliance with the regulations and the applicable Outline of Production. Include the process used for relabeling, for



## VS Memorandum (VSM) 800.91

---

example, when an extension of dating is approved by CVB. [Reference: 9 CFR [114.13](#)]

- iii. Review the label control process for new and revised labels. Determine if the process is in control and can ensure compliance with the regulations. [Reference: 9 CFR [112.1\(a\)](#)]
  - iv. Compare the label stock against the CVB filed label for accuracy. [Reference: 9 CFR [112.1\(b\)](#)]
    1. Printed labeling materials are considered critical to the conformity of the product. Pay special attention to the safe and secured storage of these materials.
    2. Ensure that the firm maintains accountability for all labels printed for use on licensed products. Review inventory records and compare with actual inventories. Determine accountability of damaged and destroyed labels. [Reference: 9 CFR [116.3\(b\)](#)]
  - v. Review the method used to ensure the correct label, with the correct serial number and expiration date, were used for each labeling and packaging event. [Reference: 9 CFR [112.1\(b\)](#)]
  - vi. If product is moved from the required storage temperature and allowed to acclimate to room temperature prior to labeling, evaluate the process used and if the impact to the final product has been determined. [Reference: 9 CFR [114.11](#)]
- b. Observations
- i. Review the process used to ensure all labels and labeling material printed is accounted for and the inventory is accurate. This should include the amount used, destroyed, and returned to stock to provide for adequate reconciliation. [Reference: 9 CFR [116.3\(b\)](#)]
  - ii. Determine serial numbers and expiration dates printed on labeling material are legible and remain legible throughout the dating period. [Reference: 9 CFR [112.1\(d\)](#)]
  - iii. Observe the process in which serial numbers and expiration dates are inspected and verified for accuracy. [Reference: 9 CFR [101.3\(h\)](#) and [101.4\(f\)](#)]
  - iv. If multiple labeling or packaging events occur at the same time, pay attention to the controls in place to mitigate the risk of mix-ups or



## VS Memorandum (VSM) 800.91

---

substitutions. Different products should not be labeled or packaged in close proximity unless there is a physical segregation of processes and materials.

- v. Observe steps taken prior to and during labeling or packaging events
  - 1. Operations should ensure the work area, line, printing machine, and other equipment are clean and free of previously used material. A line-clearance should be performed in accordance with a written procedure (e.g. a check list).
  - 2. Labeling and/or packaging lines should be identified by product and lot numbers.
  - 3. Materials should be checked upon delivery to the labeling/packaging department for quantity and identity.
- vi. Observe how long serials are out of the cooler during finishing procedures. Determine if the firm has established maximum time product can be out of the cooler and can substantiate effects to quality of the product. Determine if this time may be detrimental to the product, including the lifetime of the product. Establish how they record/monitor out of cooler time. [Reference: 9 CFR [114.11](#)]
- c. Administrative Inspection Reviews
  - i. Confirm listing of active filed labels is complete. [Reference: 9 CFR [116.3\(a\)](#)].
  - ii. Review use of temporary or extended use labels for compliance requirements applied. [Reference: 9 CFR [112.1\(b\)](#)]

### 11) Testing (Quality Control)

- a. Audits
  - i. Review laboratory records for all testing performed, especially testing required by the Outline of Production or regulations. This includes selected tests for ingredients/raw materials, bulk lots, serials, Seeds, Cell Stocks, and diluents. [Reference: 9 CFR [113.5\(a\)](#)]
    - 1. Determine if all critical steps of the test were documented. The records should include the following:
      - a) Test material and dosage (as applicable).





## VS Memorandum (VSM) 800.91

---

- b) Testing dates; initiation, observations, conclusion.
  - c) Test results including calculations. Observations of results must be clearly described and documented.
  - d) Each step is authenticated by the individual performing that step.
  - e) Reference to the equipment used.
2. Results of quality parameters, including but not limited to references and controls, should be trended and checked for consistency with the expected results.
3. Review test records for data integrity.
- ii. Note if tests contain the proper controls and if critical components, reagents, and equipment are monitored for quality before and/or during the test. [Reference: 9 CFR [113.2\(b\)\(c\)\(d\)](#)]
  - iii. Make sure all tests summarized on APHIS Form 2008 reports are supported by review of the testing bench records. See VS Memorandum [800.53](#), Release of Biological Products, for additional guidance. [Reference: 9 CFR [116.7](#)]
  - iv. Review any tests conducted by the firm that are not reported on the APHIS Form 2008. Determine if the results of such tests may indicate an issue with the purity, safety, or potency of the product and require special attention. Note: The firm may test product in accordance with requirements from an importing country. Test results that raise questions regarding the purity, safety, potency, or efficacy of a serial should be reported to CVB in accordance with VS Memorandum [800.57](#), Market Suspensions and Post Marketing Temperature Deviations. [Reference: 9 CFR [116.5\(b\)](#)]
  - v. Evaluate whether retests are conducted according to regulations and/or the Outline of Production. [Reference: 9 CFR [113.5\(d\)](#)]
  - vi. Check to see that the blueprint legend lists those microorganisms that are not named in the Outline of Production but that are necessary for testing purposes, such as organisms used for growth promotion testing or controls. [Reference: 9 CFR [108.5\(b\)\(1\)](#)]
  - vii. If the firm is authorized to use unlicensed facilities for potency testing in the Outline of Production, review testing records from the contract testing



## VS Memorandum (VSM) 800.91

---

facility. Also review licensee's audit plan of the contract testing facility to ensure ongoing quality control. See VS Memorandum [800.115](#), Potency and Safety Testing by Unlicensed Facilities, for additional guidance.

- viii. If the firm was given an animal safety exemption, review the product file for nonconformance to the Outline of Production and impacts to product. See VS Memorandum [800.116](#), Target Animal Safety Testing Exemption, for additional guidance.

### b. Observations

- i. Observe testing procedures to determine if they are being performed in compliance with the Outline of Production and the regulations. [Reference: 9 CFR [113.5\(a\)](#)]
- ii. Observe testing procedures to determine if the firm is using proper laboratory technique along with proper recordkeeping. [Reference: 9 CFR [113.5\(c\)](#)]
- iii. Observe if proper testing controls are used and recorded. [Reference: 9 CFR [113.5\(c\)](#)]

### c. Administrative Inspection Reviews

- i. Confirm identity of the listed references used for potency testing of final product. [Reference: 9 CFR [113.8\(c\)](#)].
- ii. Review expiration dating of each reference to confirm reference was within dating when used for release testing. [Reference: 9 CFR [113.8\(d\)](#)]
- iii. Review lists of incomplete APHIS Form 2008 submissions (2008 Forms submitted without samples or samples submitted without 2008 Forms). [Reference: 9 CFR [116.7](#)]

## 12) Animals

### a. Audits

- i. Determine if the firm is a registered research facility or a licensed animal dealer under the [Animal Welfare Act](#). Record the registration or license numbers for reference. Review the last APHIS Animal Care inspection report to see if there were any deficiencies. Determine if they have been corrected.



U.S. DEPARTMENT OF AGRICULTURE

Marketing and Regulatory Programs  
Animal and Plant Health Inspection Service  
Veterinary Services

## VS Memorandum (VSM) 800.91

---

- ii. For animals used in production and testing, review procurement and test records for completeness, accuracy, and compliance with requirements in the Outline of Production and Animal Welfare regulations. Where required, ensure that proper health certificates have been issued and filed (e.g., equine infectious anemia testing records for horses used in production or testing). [Reference: 9 CFR [116.6](#), [117.3](#), [117.4](#), and [117.6](#)]
  - iii. Review records for data integrity. Determine the completeness of records for animals used in production or testing and examine these records when inspecting according to the production and testing categories listed in this memorandum. [Reference: 9 CFR [116.6](#)]
  - iv. Determine if the firm keeps accurate records to identify animals and trace their final disposition. Certain animals must be quarantined before being removed from the premises and when moved must be accompanied by the appropriate forms. [Reference: 9 CFR [117.5](#) and [117.6](#)]
- b. Observations
- i. Check for compliance with requirements of the Animal Welfare Act. Animals not subject to the Act should also be cared for in the spirit of the Act. Report items needing immediate attention to the Animal Care Sector Supervisor at once.
  - ii. Note whether animals are adequately identified. [Reference: 9 CFR [117.3\(c\)](#)]
  - iii. Determine if a firm has necropsy facilities for animals used for production and test purposes.
  - iv. Determine if the admitting veterinarian examines the animals before admittance or in a separate quarantine area on premises. Note if another employee examines the animals for the veterinarian. [Reference: 9 CFR [117.3\(a\)](#)]
  - v. Determine whether there is any preconditioning or treatment of animals that might adversely affect testing or production. [Reference: 9 CFR [117.4\(c\)](#)]
- c. Administrative Inspection Reviews – not applicable to this category unless related to specialized questions during the annual review.

### 13) Distribution



## VS Memorandum (VSM) 800.91

---

- a. Audits
  - i. Evaluate the method used by the licensee/permittee to reconcile estimated and actual inventories prior to marketing release. [Reference: 9 CFR [116.2](#)]
  - ii. Determine whether distribution records are adequate for inventory control.
  - iii. Determine if the firm's records are such that the firm could carry out a total stop sale or recall down to user level should it become necessary. [Reference: 9 CFR [116.5\(a\)](#)]
  - iv. Review the written procedure for product recalls or stop sale events. Ensure it covers all levels and includes communication plan with CVB. [Reference: 9 CFR [105.3](#)]
    - 1. The process should be regularly reviewed and updated as needed. The effectiveness of the process should be evaluated periodically to confirm it is robust and fit for use.
    - 2. Review documentation of any recent product recall or stop sale. Determine if the actions taken were appropriate and in accord with the regulations. See VS Memo [800.57](#), Market Suspensions and Post Marketing Temperature Deviations, for additional guidance.
  - v. Determine control processes for distribution of restricted products. [Reference: 9 CFR [102.5\(d\)](#)]
  - vi. Review distribution records for data integrity. [Reference: 9 CFR [116.2](#)]
- b. Observations
  - i. Evaluate the system(s) of control and identification on pre- and post-release serials used to prevent inadvertent distribution of unreleased serials. [Reference: 9 CFR [113.6](#)]
    - 1. Storage areas should be adequately designed and operated to allow orderly storage of pre- and post-release serials.
    - 2. Segregated areas should be provided for material and products that are in a quarantine, rejected, returned, or recalled status.



## VS Memorandum (VSM) 800.91

---

3. If quarantine status is ensured by storage in separate areas, these areas must be clearly marked, and access restricted to authorized personnel.
- ii. Determine if cooler space is adequate for licensed products at the normal level of production. The storage area should be clean and dry. Confirm the storage temperature is maintained within acceptable temperature limits. [Reference: 9 CFR [114.11](#)]
- iii. Review the release system with the firm to ensure adequate documentation and control. Verify who is designated to receive marketing release authorizations from Inspection and Compliance. [Reference: 9 CFR [113.6](#)]
- iv. Compare the marketable inventory as reported on APHIS Form 2008 with the actual inventory. Determine if the firm uses a standard inventory variance and if this variance is reasonable. Any changes in inventory beyond the firm's variance standard or in the absence of a firm standard should be reviewed further. [Reference: 9 CFR [116.2](#)]
- v. Observe coolers and warehouses for expired product, product deemed unacceptable for marketing, or product returned from the marketplace. [Reference: 9 CFR [114.15](#)]
  1. Determine how these goods are handled and final disposition.
  2. Review recordkeeping for returned goods. Determine if the firm re-distributes products and if the methods are acceptable. See VS Memorandum [800.60](#), Biological Products Returned to Licensed Establishments, for additional guidance. [Reference: 9 CFR [114.11](#)]
- vi. Evaluate shipping methods to determine if product is always protected against improper storage and handling. [Reference: 9 CFR [114.11](#)]
- c. Administrative Inspection Reviews – not applicable to this category unless related to specialized questions during the annual review.

### 14) Miscellaneous

- a. Audits
  - i. Discuss the establishment's pharmacovigilance program with the responsible official and/or Consumer Compliant Contact (CCC). Evaluate the pharmacovigilance system used to maintain detailed records for every



## VS Memorandum (VSM) 800.91

---

adverse event report (AER) received for biological product it produces or distributes. [Reference: 9 CFR [116.9](#)]

1. Review the establishment's written procedures describing the actions to be taken upon receipt of an AER for any licensed or permitted biological product. Ensure it includes a records retention policy of 3 years after the date the adverse event report is received.
  2. Ensure appropriately trained and experienced personnel are responsible for managing adverse event issues, including investigating these complaints. A CCC should be identified for each licensee or permittee and have an APHIS Form 2007 on file.
  3. Following receipt of an AER, ensure timely and proper action was taken if the product was found to be worthless, contaminated, dangerous, or harmful. [Reference: 9 CFR [116.5\(b\)](#)]
- ii. Review the written procedure for process deviations and/or quality defects, including the procedure for the root cause analysis. See VS Memoranda [800.210](#), Manufacturing Deviations Identified prior to Marketing Release. [Reference: 9 CFR [114.2\(a\)](#) and [116.5\(a\)](#)]
1. Sufficiently trained personnel and resources should be available for handling, assessing, investigating, and reporting out the results.
    - a) The processes in place should facilitate the investigation into the quality of the product/process in question.
    - b) Documentation should include the description of the reported deviation.
    - c) An appropriate level of root cause analysis work should be applied during the investigation. In cases where the true root cause cannot be determined, consider identifying the most likely root cause(s) and address those issues.
    - d) Where human error is suspected or identified as the root cause, this should formally be justified. Consideration should be given to ensure the processes and procedural or system-based errors or problems are not overlooked.
  2. The manufacturer should have the ability to determine and implement risk-reducing action to mitigate the severity and probability of harm to the end user. Implementation of risk reducing actions should be



## VS Memorandum (VSM) 800.91

---

monitored, as new risks could be inadvertently introduced through the corrective and/or preventative actions.

3. When a process deviation or quality defect is discovered or suspected in a lot/batch, consider checking other batches or related products to determine if they are also affected. The scope of the issue must be determined.
  4. Previous process deviations should be reviewed to determine if this is a recurring problem that requires attention and possibly further regulatory action.
  5. Implement corrective and preventative actions. Monitor and assess the effectiveness of such actions.
- iii. Ensure that only authorized samplers sign the APHIS Form 2020. Arrange to train new and current samplers as necessary. Verify the list of authorized samplers. See VS Memorandum [800.59](#), Veterinary Biological Product Samples, for additional guidance. [Reference: 9 CFR [113.3\(a\)](#)]
  - iv. Verify that products found unsatisfactory by the firm were destroyed and reported destroyed on an APHIS Form 2008. Ensure the reason for destruction listed on the APHIS Form 2008 matches the production/testing records reviewed. Determine if the licensee/permittee investigated why the product was found unsatisfactory for marketing.
  - v. Check the blueprint legends for notation of storage location of APHIS reserve samples.
- b. Observations
- i. Inspect storage areas to verify that products reported destroyed by the firm are not still being retained by the firm.
  - ii. Inspect the quarantine area for separation and security.
  - iii. Observe that only authorized samplers are selecting samples for APHIS testing. [Reference: 9 CFR [113.3\(a\)](#)]
  - iv. Review sampling techniques. Be sure samples collected are representative of the entire serial. Review the methods of authentication and verify compliance with the regulations. Check the method of packing samples for shipment. [Reference: 9 CFR [113.3\(a\)\(1\)\(iv\)](#)]
  - v. Review APHIS Form 2020 preparation with the sampler.



## VS Memorandum (VSM) 800.91

---

- vi. Observe reserve samples for proper authentication, ensure they are made tamper evident, and document the chain of custody. See VS Memorandum [800.59](#), Veterinary Biological Product Samples, for additional guidance. [Reference: 9 CFR [113.3\(e\)](#)]
- vii. Determine that products "to be destroyed under APHIS supervision" have been properly quarantined. Observe the destruction of these products and report it on APHIS Form 2045. Review the inventory and accounting of any samples retained from unsatisfactory serials.
- c. Administrative Inspection Reviews – not applicable to this category unless related to specialized questions during the annual review.

### 7. Implementation/Applicability

Updated policy in this memorandum is effective immediately.