Table 1
Additional significant research accomplishments at NADC.

Disease/disease agent/ research target	Contribution	Researchers	Year(s) reported
Bovine viral diarrhea virus	Isolation of a strain of this virus later recognized as the type strain of BVDV1. Is a component of numerous vaccines.	DE Gutekunst, WA Malmquist	1963
Leptospirosis	Developed culture medium for the isolation and propagation of leptospira bacteria.	HC Ellinghausen Jr, WG McCullough	1965
Pink eye/*Moraxella bovis*	Identification of *Moraxella bovis* as a cause of "pink eye" in cattle.	DE Hughes, GW Pugh Jr, TJ McDonald	1965–1968
Johne's disease/*Mycobacterium avium subsp. paratuberculosis*	Developed fecal culture techniques for early detection of these slow growing mycobacteria.	RS Merkal, AB Larsen	1962–1964
Newcastle disease virus	Development of a killed vaccine against the Newcastle disease virus	HD Stone, AE Richies, WA Boney	1969
Bovine leukemia virus (BLV)	Demonstration that bovine leukemia is caused by a virus.	JM Miller, C Olson	1972
Bovine leukemia virus (BLV)	BLV first cultivated.	MJ Van der Maaten, JM Miller	1974
Fowl cholera/*Pasteurella multocida*	An improved bacterin developed that provided 70% cross protection from other strains of *Pasteurella.*	KA Brogden, KR Rhoades, KL Heddleston	1978
Oxalate metabolism/*Oxalobacter formingenes*	Demonstration of importance of microbial metabolism of oxalate in animal & human health	MJ Allison, KA Dawson, NA Cornick, AL Baetz	1980–1990, 1996
Salmonella typhimurium infection of swine	Identified the prefered colonization sites in swine that are persistently infected with *Salmonella typhimurium.*	RL Wood	1989
Feline calicivirus	First nucleotide sequence of calicivirus 3′-terminal sub genomic RNA.	JD Neill	1991
Brucellosis/*Brucella abortus*	Demonstrated that vaccination of bison with the RB51 strain induced abortion.	SC Olsen, MV Palmer	1996
Swine dysentery/*Brachyspira hyodysenteriae*	Discovery and genetic engineering application of novel gene transfer mechanism (VSH-1)	TB Stanton, SB Humphrey	1997–2008
Bovine viral diarrhea virus and border disease virus	First nucleotide sequence of bovine diarrhea virus 2 strain and border disease virus	JF Ridpath, SR Bolin	1995, 1997
Brucellosis/*Brucella abortus*	Approval of RB51 for use in cattle for prevention of *Brucella abortus* infection	NF Cheville, SC Olsen, MV Palmer	1997
Shipping fever	First genetically engineered live oral vaccine for shipping fever.	RE Briggs, FM Tatum	1999
Bovine tuberculosis/ *Mycobacterium bovis*	Intratonsilar challenge model developed to mimic natural *M. bovis* infection in white-tailed deer.	MV Palmer, DL Whipple, WR Waters	2000
Preharvest food safety	Developed a fecal contamination detector for animal carcasses using light sources of different wavelengths	TA Casey, MA Rasmussen	2003
Bovine tuberculosis/ *Mycobacterium bovis*	A calf aerosol challenge model developed for *M. boivs*	MV Palmer, WR Waters	2003
Johne's disease/*Mycobacterium avium subsp. paratuberculosis*	Demonstrated that milk pasteurization effectively kills *Mycobacterium avium subsp. paratuberculosis*	JR Stabel	2004
Scrapie, Chronic wasting disease (CWD) and transmissible mink encephalopathy	First to complete interspecies transmission studies into cattle. Found that cattle were resistant to scrapie and CWD.	AN Hamir, RA Kunkle, JA Richt, JM Miller, RC Cutlip	2007

Table 1 (*Continued*)

Disease/disease agent/ research target	Contribution	Researchers	Year(s) reported
BSE/Prion	Confirmed that the E211K polymorphism discovered at NADC in 2008 was a germline polymorphism indicating certain rare, atypical BSE cases may be heritable.	EM Nicholson, BW Brunelle, JA Richt, ME Kehrli, JJ Greenlee	2008
Adenovirus	Developed PCR assay to classify ruminant adenovirus to determine serotype/species.	HD Lehmkuhl, LA Hobbs	2008
Bovine tuberculosis/ *Mycobacterium bovis*	Developed a rapid serologic test for cervids that USAHA recommended using in the TB erradication program.	WR Waters, MV Palmer	2011
Johne's disease/*Mycobacterium avium* subsp. *paratuberculosis*	Isolation of the first *M. avium* subspecies *paratuberculosis*-specific monoclonal antibody.	JP Bannantine, JR Stabel	2011

and administrative support staff who have devoted their careers to ARS and the NADC. We also thank Janis K. Hansen for helpful discussions on NADC's early years. Mention of trade names or commercial products in this article is solely for the purpose of completing research objectives and does not imply recommendation or endorsement by the U.S. Department of Agriculture. USDA is an equal opportunity provider and employer.

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May 13, 1999

VETERINARY SERVICES MEMORANDUM NO. 800.91

Subject: Categories of Inspection for Licensed Veterinary Biologics Establishments

To: Biologics Licensees, Permittees, and Applicants
Directors, Center for Veterinary Biologics

I. PURPOSE

The purpose of this memorandum is to provide a list of the categories which are used for in-depth inspections of licensed veterinary biologics establishments by inspectors of the Animal and Plant Health Inspection Service (APHIS) under the provisions of 9 CFR Part 115. Licensees should use this list of categories of inspection as an aid in understanding APHIS inspections and as a guide for self-inspections to determine their compliance with the Virus-Serum-Toxin Act (VSTA).

II. GENERAL

Regulations in 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. APHIS does these unannounced inspections of licensed veterinary biologics establishments to determine whether products are being prepared in compliance with the VSTA and regulations. Internal guidelines have been developed for APHIS inspectors that list 14 categories of inspection for in-depth inspections, and what audits and observations may be made in each category. This list of categories is not necessarily all-inclusive, but may help the veterinary biologics industry to maintain compliance with the VSTA and regulations.

III. GUIDELINES

When inspecting licensed veterinary biologics establishments, APHIS inspectors should use the 14 categories of inspection described in this section to define inspection responsibilities and serve as a format for the inspection report. The checklist of audits and observations given for each inspection category should not be considered limiting or all-inclusive. Inspectors can inspect the entire premises of the establishment, including the following: all buildings, compartments, and other places; all biological products, and organisms and vectors in the establishment; all materials and equipment, such as chemicals, instruments, apparatus, and the like; and the methods used in the manufacture of, and any record pertaining to, the production, testing, disposition, sale, or distribution of veterinary biological products produced at each establishment.

Following is the list of inspection categories, with audits and observations for each, that APHIS inspectors may use for guidance when conducting inspections:

A. Licenses and Permits

1. *Audits* :

a. Compare the firm's U.S. Veterinary Biologics Establishment License with information on file at the Center for Veterinary Biologics (CVB). Review the ownership, parent company, and subsidiary and division relationships with the firm's official in charge. Verify addresses, locations, and other information on the license.

b. Discuss the activity of each licensed product with the official in charge. Be sure that conditional licenses have not expired. Confirm that the firm's file of U.S. Veterinary Biological Product Licenses matches information from CVB files.

c. If a product is not being produced, determine the last date of production (batching or similar date). The firm may wish to voluntarily return inactive product licenses to APHIS for termination. If the firm wishes to voluntarily return an inactive license or if a product has not been produced in over 5 years, report the situation to Licensing and Policy Development (LPD) for action.

d. For product licenses with restrictions, determine if the firm is following the restrictions.

e. Determine if the facility is approved for storing veterinary biological products imported under a U.S. Veterinary Biological Permit for Distribution and Sale. Determine if the firm is in compliance with 9 CFR 104.

f. Check 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 under 9 CFR 122, and compare with information on file at CVB. Ask for any additional permits the firm may have. Audit the firm's records for compliance with special requirements listed on the permits and with the regulations covering importation for research and evaluation. Check to determine if any of the permits have expired.

2. *Observations*:

a. 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.

b. Verify that every product observed in production or testing on the licensed premises has a license or permit.

c. Check for compliance with special requirements of permits to import product for distribution and sale.

d. 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.

B. Personnel

1. *Audits*:

a. Compare the firm's APHIS Form 2007 file with information on file at CVB for changes in key personnel. Check for deletions, additions, or job changes. Ask the official in charge to certify that the information on file at CVB is correct. Confirm the names of the official liaison and alternates.

b. Review the firm's system for keeping the APHIS Form 2007 file up to date. Identify the person responsible for making periodic reviews of the 2007 file.

c. Request a current copy of the firm's organization chart or obtain the information necessary to allow you to establish official lines of responsibility within the firm. Check the relationships between production, testing, and marketing.

d. Determine if job titles accurately reflect job responsibilities.

e. Determine who supervises the care and welfare of animals, and which veterinarian determines the health of admitted animals.

2. *Observations:*

a. Observe if employees in key positions have APHIS Form 2007's on file at CVB. Observe if employees follow lines of responsibility as shown on the organizational chart or as explained by management.

b. Observe operations to determine if employees, in general, are adequately trained and supervised so as to be competent in good laboratory techniques. Be aware of personnel health conditions that might affect the product.

c. Notice if the number of employees is adequate, if they are observing in-house rules, and their general attitude toward their work.

C. Facilities

1. *Audits:*

a. Inspect all the premises and compare with the facility documents.

b. When comparing facilities with the filed drawings, look for evidence of unreported remodeling, new major equipment, relocated key items, and other discrepancies.

c. Check that legends showing special-use facilities (such as a public diagnostic clinic, separate and apart research areas, export-only products, pharmaceutics production, and FDA Export Reform and Enhancement Act production) are correct. Determine the location and adequacy of isolation facilities for incoming animals, if required.

2. *Observations:*

a. Verify that the actual use of production and testing rooms is as reported in the legends. Evaluate this use for any possible adverse effect on the product.

b. Observe the material, construction, and finish of all areas related to the production of biological products or ingredients of biological products. Verify that these areas may be readily and thoroughly cleaned.

c. Verify that the lights, ventilation systems, heating and cooling systems, hot and cold water supplies, and drainage systems are adequate and functioning.

d. Observe the arrangement and construction of the facilities. Determine if this arrangement and construction provide adequate and appropriate isolation for each product to prevent cross-contamination from other products.

e. Observe traffic patterns through the production area. Check enforcement of movement restrictions. A restricted area should be posted.

f. Evaluate the adequacy of the available space.

g. Verify that dressing rooms, toilets, and lavatories are appropriately placed, sufficient in number, and separated from production. Soap, towels, and hot water should be available.

D. Equipment

1. *Audits:*

a. Identify the automatically controlled equipment, environmental rooms, and other specialized equipment used in production, testing, and storage of product. Check that the location of this equipment matches the blueprint legends.

b. Review the records of operation of major specialized equipment, and determine if the equipment is functioning properly and recordkeeping is in compliance.

c. Determine what validation system is used and what records are kept by the firm to ensure that automatically controlled equipment is operating properly (see 9 CFR 109.1 and 109.2). If the firm has an exemption from having automatic recorders on sterilizers, determine if the records kept meet the provisions of 9 CFR 109.2.

2. *Observations:*

a. Check for major specialized equipment or environmental rooms not listed on the blueprint legend, and determine if they are being used in production, testing, or storage of product. Determine compliance.

b. Observe the operation of automatically controlled equipment and environmental rooms, and determine if they are being operated properly by the firm.

c. Note if each item of major equipment is uniquely marked so it may be identified in the records.

d. Check that all equipment is being sterilized according to 9 CFR 109.1 or has the appropriate exemption. Determine if equipment exempted under 9 CFR 109.2 is being adequately sterilized.

E. Sanitation

1. *Audits:*

a. 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.

b. Determine if the chemicals used for sanitation are appropriate for the microorganisms in each room.

2. *Observations:*

a. Notice if the outside premises are properly drained, are clean and orderly, and are free from accumulated trash or construction debris. No nuisance is allowed.

b. Note whether a conscientious effort is being made to control vermin, especially in animal quarters.

c. Check waste disposal methods to see if they are in accordance with VS Memorandum 800.56.

d. Check the inside premises for clutter. Check for accumulation of unnecessary materials, particularly in halls, production rooms, and coolers.

e. Notice whether all personnel, including maintenance people who enter production areas, are wearing appropriate clothing. Note if special clothing requirement areas are posted and requirements enforced.

f. Check for unsanitary practices by employees.

F. Establishments and/or Products Pending Licensure

1. *Audits:*

a. Examine records to confirm that the firm has obtained permission from LPD for any research that is conducted in production facilities, and that the firm has complied with any special requirements that were established.

b. Verify that the Master Seed is adequately identified and accounted for.

c. Check records for proper disposal of animals used in the preparation or testing of experimental products.

d. Differentiate between research being conducted using micoorganisms 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.

e. Review field trial records for compliance with special restrictions and requirements. Determine the response rate of all participants. Were all the responses reported to LPD? Do the detailed records support the summaries sent to LPD?

f. For microorganisms related to licensed product but not approved for use in the production of licensed product: Check the firm's records for permission to maintain these microorganisms in the licensed establishment, for methods of maintenance, and for security procedures.

g. 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.

h. Determine if prelicensing serials were prepared in production facilities and tested on licensed premises.

2. *Observations:*

a. Determine if the separation of personnel, supplies, and equipment between research and production is adequate.

b. Observe the in-house controls on movement of personnel, supplies, and equipment and the airflow control between research, production, and testing areas.

c. Check for production-related testing in research areas.

d. Check methods for disposing of research material.

e. Observe specific research or prelicensing activities as requested by LPD.

f. Observe if employees are following biosafety policies.

g. Determine if biosafety policies are adequate.

G. Seeds and Cells

1. *Audits:*

a. List the bacterial and viral Master Seeds and Master Cell Stocks that are examined during the inspection, noting which were checked by observation, audit of records, or both. Note the seeds and cell stocks to which the Master Seed concept applies (9 CFR 113.8).

b. Check the records of each Master Seed and Master Cell Stock at each passage level for accountability and identification, tracing them from acquisition to production of serials. Be sure that records are complete. Note which tests to check later.

c. Determine if the Master Seeds and Master Cell Stocks being used in production agree with those listed in the corresponding Outlines of Production.

d. Determine if the licensee's system of identification is adequate to ensure that the proper Master Seed or Master Cell Stock has been used at the proper passage level in production. Verify that the Master Seeds, Working Seeds, Production Seeds, and Master Cell Stocks used in producing the product serial each have the same identity as those used in developing prelicense testing data. Also verify that the passage levels of the Master Seeds, Working Seeds, Production Seeds, and Master Cell Stocks used in producing the product serial are all acceptable based on the corresponding passage levels used in developing the prelicense testing data.

e. 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.

f. 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.

g. Review Master Seed production and testing records. Review immunogenicity test and repeat immunogenicity test records. Determine if the bench records for each serial of product are complete and clearly trace to the Master Seed. Determine if required repeat immunogenicity tests have been done.

h. Review bench records or other data files from field trials of new products. Determine if summaries of the data correctly reflect all the field reports.

2. *Observations:*

a. Observe any production or testing procedures in progress for compliance with the Outline of Production or regulations. Note if the seeds are checked regularly for virulence, how they are maintained, how frequently they are passed, how they are stored, how much current inventory, etc.

b. Determine where Master Seed, Working Seed, and Production Seed are prepared. Only Master Seed may be prepared in separate and apart researchfacilities; Working Seed and Production Seed must be prepared on licensed premises in acceptable facilities.

c. Observe methods of maintenance, storage, and inventory of Master Seeds and Master Cell Stocks.

d. Check if there are separate storage facilities for virulent or dangerous microorganisms.

H. Production (through batching)

1. *Audits:*

a. List serials and production lots examined, noting which were checked by observation or record audit or both.

b. Review records of preselected production procedures for accountability and identification by tracing serials and production lots from raw ingredients to filling. Check that records are complete and that each major step is listed in the Outline of Production. 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.

c. 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 prepared; compare the date of production with the date on the outline used for reference. Check to see that each step listed in the outline is shown in the records. 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.

d. Determine if the manufacturer's recordkeeping system provides for the unique identification of each ingredient and if safeguards are in place to prevent errors in the preparation of the product.

e. Determine how serial numbers are assigned and what system is used. Ask the firm to update CVB if necessary.

f. Determine how annual outline reviews are done and by whom.

2. *Observations:*

a. Check any production procedure in progress for compliance with the most recent Outline of Production and blueprint legends.

b. Determine if the identity of in-process material is maintained. Note the manner of identification used and the consistency of its use, e.g., color coding, lot numbers, product name.

c. Observe whether proper laboratory techniques and sterile practices are followed by laboratory personnel where required.

d. Observe the preparation of equipment and media and other ancillary procedures in the service area for compliance with applicable special outlines.

e. 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, and used by, line supervisors.

f. Look for any production procedures that may adversely affect the product.

I. Final Production (filling through packaging)

1. *Audits:*

a. Check filling records for recorded losses or gains, fill checks, and filling problems. Determine the firm's standard fill range and the maximum-minimum range for each fill size. Determine how over-filled or under-filled vials are handled and if the firm has a written policy covering this.

b. 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.

c. Determine if all reprocessing was authorized, i.e., if further procedures were conducted on serials of liquid product after bulking and identification (other than filling and labeling) only when provided in the Outline of Production or when authorized by CVB.

d. Check 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.

e. Determine if losses incurred through breakage, loss of vacuum, etc., are noted in the serial records.

f. Determine if the firm attaches copies of the container label, the carton label, and the enclosure to the serial record.

2. *Observations:*

a. Observe and evaluate actual filling procedures, including aseptic technique, fill checks, proper mixing during fill, and maintenance of concurrent records. Determine if employees know the fill limits and how to handle unacceptably filled vials. Observe if fill limits are posted.

b. Check lyophilization procedures. Note stoppering devices. Note if different container sizes are mixed in one lyophilizer and if temperature varies on different shelves. Determine if placement of probes is adequate.

c. Note in-house procedures for vial and label inspection, sampling, identification of unlabeled vials, and how product is controlled until released.

d. Check handling of diluent, how and where it is stored, and how it is accounted for.

e. Check freezing procedures. Note the time interval from filling to start of freezing and the rate at which product temperature is lowered.

f. Observe several selected serials for product uniformity, color, volume, texture, opacity, labeling, packaging, serial number readability, and expiration date. Check Markem or silk screen labels to ensure they have not rubbed off and are legible.

g. 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 non-licensed product is maintained during filling, packaging, and labeling.

h. Observe how long serials are out of the cooler during finishing procedures. Check if observed time is routine or an exception. Determine if this time may be detrimental to the product.

J. Labels

1. *Audits:*

a. Check the files of the firm's label controller for inactive, superseded, or obsolete labels.

b. Check labels for which there are special requirements in 9 CFR 112. Determine if these labels are in compliance.

c. Determine who assigns expiration dates and how it is done.

d. Determine how the label control person knows when a new label has been approved.

e. Check the label stock against the label file for accuracy. Check stock labels for color, style, printing, etc., and determine if there is any distinct difference from approved labels. Determine if stamped copies of approved labels are readily available to the person approving new label stock.

f. Check that the firm maintains accountability for all labels printed for use on licensed products. Check inventory records, and compare with actual inventories. How does the firm account for labels that are damaged or destroyed? Determine how the firm accounts for roll labels and if actual inventories are made by the firm.

2. *Observations:*

a. Check that labels are not left unattended where they could be pilfered or inadvertently used on the wrong product. Determine if unused imprinted roll labels are voided at the end of the labeling run.

b. Check security of labels in storage. Remember to check cartons, enclosures, and bottles that have been labeled prior to use.

c. Observe by whom and when imprinted serial numbers and expiration dates are inspected.

K. Testing

1. *Audits:*

a. For each test, list the product name, the serial or lot number, and whether the test was reviewed by examining records or by observation. Give special attention to tests that are not routinely confirmed by CVB Laboratory.

b. Records of testing done as required by the Outline of Production or regulations must show when observations are made and must be authenticated by the individual making the observations. Evaluate records for evidence of falsification. Review records of selected tests of ingredients, bulk lots, serials, Master Seeds, Master Cell Stocks, and diluents for compliance.

c. Note if tests contain the proper controls and if critical components, reagents, and equipment are monitored for quality before and/or during the test.

d. Make sure that all tests summarized on APHIS Form 2008 reports are supported by daily records.

e. Review any tests conducted by the firm that are not reported on the APHIS Form 2008. Determine whether or not these results indicate that the product may require special attention.

f. Evaluate whether retests are conducted according to regulations and/or the Outline of Production.

g. 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.

2. *Observations:*

a. Observe testing procedures to determine if they are in compliance with the Outline of Production and the regulations.

b. Observe testing procedures to determine if the firm is using proper laboratory technique along with proper recordkeeping.

c. Observe if proper testing controls are used.

L. Animals

1. *Audits:*

a. 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 inspection report to see if there were any deficiencies. Determine if they have been corrected.

b. For animals used in production and testing, check procurement and test records for completeness, for accuracy, and for 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.

c. Check 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.

d. 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.

2. *Observations:*

a. 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.

b. Note whether animals are adequately identified.

c. Determine if a firm has post mortem facilities for animals used for production and test purposes.

d. 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.

e. Determine whether there is any preconditioning or treatment of animals that might adversely affect testing or production.

M. Distribution

1. *Audits:*

a. Evaluate the method of reconciling estimated and actual inventories.

b. Determine whether distribution records are adequate for inventory control.

c. 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.

d. Review documentation of any recent product recall or stop sale. Determine if the actions taken were appropriate and in accord with APHIS policy and guidelines (VS Memo 800.57).

e. Review the firm's recall/stop sale policy to be sure that it is in accord with APHIS requirements.

2. *Observations:*

a. Evaluate the physical system of control and identification on pre- and post-release serials. The system should prevent inadvertent distribution of unreleased serials.

b. Review the release system with the firm to ensure adequate documentation and control. Verify who is designated to receive releases from Inspection and Compliance.

c. Compare the marketable inventory as reported on APHIS Form 2008 with the actual inventory. Record any significant changes in inventory.

d. Check if cooler space is adequate for licensed products at the normal level of production.

e. Observe for returned goods on premises. Determine how these goods are handled and disposed of. Check recordkeeping on returned goods.

N. Miscellaneous

1. *Audits:*

a. Discuss the firm's consumer complaints with the responsible official. Review the complaint files as indicated in CVB files or as required by license provisions.

b. 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.

c. Verify that products found unsatisfactory by the firm were destroyed and reported destroyed on an APHIS Form 2008.

d. Check the blueprint legends for notation of storage of reserve samples.

2. *Observations:*

a. Inspect storage areas to verify that products reported destroyed by the firm are not still being retained by the firm.

b. Inspect the quarantine area for separation and security.

c. Observe that only authorized samplers are selecting samples for APHIS testing.

d. Review sampling techniques. Be sure samples collected are representative. Check the methods of authentication and modify them if necessary. Check the method of packing samples for shipment.

e. Review APHIS Form 2020 preparation with the sampler. Countersign the APHIS Form 2020, and request testing according to the Inspection and Compliance Biologics Program Manual.

f. Check reserve samples for proper authentication and security.

g. Check 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. Check the inventory and accounting of any samples retained from unsatisfactory serials.

/s/ Karen A. James for

Alfonso Torres
Deputy Administrator
Veterinary Services

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United States Department of Agriculture
Center for Veterinary Biologics

Standard Operating Policy/Procedure

The Inspection Proper

Date: **August 30, 2012**

Number: ICSOP0013.03

Supersedes: ICSOP0013.02, December 27, 2010

Contact: Renee M. Schnurr, (515) 337-6103

Approvals:

/s/Steven A. Karli Date: 25Sep12
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/s/Rebecca L.W. Hyde Date: 25Sep12
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Table of Contents

The Inspection Proper

1. Purpose and Scope

This document describes the Inspection Proper. The Inspection Team must determine that the products have been produced and tested by competent people using acceptable facilities, equipment and methods; that products being marketed are not worthless, contaminated, dangerous, or harmful; and that reports and records of production and testing of products are accurate and complete.

2. Rules of Conduct

The ideal relationship is one of mutual understanding, confidence, and respect. Although this ideal cannot always be reached, the inspector should observe these rules of conduct and procedure which will approach the ideal as nearly as possible. There are certain specific rules to be followed by all inspectors.

- The inspector is in the position of an observer and should in no way assume a note of supervision or enter into operational management.
- The inspector should be reasonable in demands on the time of laboratory personnel by limiting questions and conversation to that directly related and necessary to the inspection.
- The inspector should not discuss possible exceptions with sub-supervisory laboratory personnel or engage in conversations concerning controversial subjects.
- The inspector shall be aware that all information obtained is privileged and shall not be conveyed in any manner or form except to those officially authorized by the Center for Veterinary Biologics Inspection and Compliance (CVB-IC) Director.
- The inspector should observe all organisms and vector control requirements of the laboratory.

3. Established Inspection Techniques

The following techniques are commonly used in inspection: 1) selective audit; 2) observation; 3) perambulation; 4) evaluation of internal control; 5) completion of worksheets; and 6) issuance of a formal report.

3.1 Audit

The inspector selects certain records for an in-depth review. Related records are reviewed to establish the validity of the entries on the master records selected. Exceptions are noted.

3.2 Observation

The inspector personally substantiates that the information provided to the Animal and Plant Health Inspection Service (APHIS) and records kept by the firm are in agreement with what was found at the actual situation or site at the establishment.

3.3 Perambulation

This is a special class of observations. The inspector unobtrusively watches ongoing operations for a sufficient time to observe unusual or uncharacteristic occurrences, especially regarding techniques of manufacture.

3.4 Internal Control

Well-managed enterprises have checks and balances built into their methods of operation to minimize and/or expose errors. The inspector, using experience and judgment, explores the adequacy of these controls. These findings may determine further inspection actions to accomplish a comprehensive inspection.

3.5 Worksheets

The inspector personally makes a record of the findings in such a logical and systematic manner that this record may be later admissible as evidence of the audit and findings in a court of law.

3.6 Formal Reports

The inspector communicates the findings in a written form that can be used later for discussions with supervisors, licensee representatives, other team members, subsequent teams, and others properly authorized to use the information gathered.

4. Division of Responsibilities

Following the assignments made during the pre-inspection meetings, each team member proceeds to obtain information and evaluate the information obtained from the various sources. Findings are reviewed with the team to assure a coordinated effort. If necessary, the team leader reassigns individual activities to maximize the effectiveness of the inspection. The team leader evaluates, coordinates, and finalizes the actions that are taken.

5. Conducting the Inspection

The inspection proper has three phases: 1) an initial meeting with the licensee representative(s) for making introductions, contacts and schedules, and explaining the purposes of the inspection;

2) the inspection activities themselves; and 3) a wrap-up meeting with the licensee to discuss the inspection findings.

5.1 Introductions

Upon arrival do the following so senior management officials will know what to expect:

5.1.1 The inspector should identify themselves to the licensee's receptionist. A printed card is useful.

5.1.2 Ask for the firm's official government liaison by name. If the liaison is not available, ask for the designated alternate. If none of the designated official representatives are available, ask to see the individual in charge.

5.1.3 The inspector should identify themselves again to the official representative showing his/her official government badge and identification card. This should be a deliberate act even if the inspector is well known to the representative. Section 157 of Title 5, U.S. Code, gives authority to make the inspection only when it is shown that the inspector is duly authorized. The official identification may be delayed until the initial meeting with the management staff, but must be done before any inspection activities.

- Do not trade the official government badge or identification card for a firm's identification badge.
- Do not allow the firm to copy the inspector's numbered badge. In some cases, the firm may photocopy the inspector's VS1-4 identification card.
- Do not provide the firm with any personal identification, such as a driver's license or Social Security card.
- Do not sign a confidentiality agreement connected in any way related to the duties as an inspector for the Center for Veterinary Biologics. The obligations under Veterinary Services Memorandum No. 800.2, *Confidential Information Concerning the Veterinary Biologics Program*, may be explained to the firm. If necessary, contact the IC Section Leader or the CVB-IC Director.

5.1.4 The licensee representative should be informed that the inspector is on the premises to conduct an inspection. Arrange a meeting with the representative, the individual in charge, and with as many of the supervisory or management staff as may be necessary to have present at the initial meeting. If this meeting cannot be done in a timely fashion (within the first 15 to 20 minutes upon arrival), then the inspector may request to forgo the meeting until a later time that day and begin the tour of the facilities.

5.2 Refusal of Entry

If, after proper identification (see **Section 5.1**), the firm denies the inspector access to the licensed premises, areas of the premises, or documents that are germane to the inspection, then the inspector should proceed as described in the current version of **ICSOP0028,** *Refusal of Entry for Inspection, Assault, and Bribery Procedures*.

5.3 Initial Meeting

Go over the following points in the initial meeting, being brief, businesslike, and courteous:

5.3.1 State the purpose. Explain what an inspection means. Go over the inspection categories in a general manner.

5.3.2 Develop a preliminary schedule with the licensee. Allocate time for:

- An orientation tour of the facilities
- License/blueprints/legends review
- A product review (Review of production records can include all records from the acquisition of seed material to the last container of product leaving the plant including operating procedures and records.)
- An equipment records and equipment operation review
- Review or experimental, field trial, and consumer complaint records
- Review of labels and packaging procedures and records and
- Wrap-up discussion session.

5.3.3 Discuss the APHIS Biologics Program Inspection Policy which is as follows:

- Will go anywhere it is felt is necessary but will respect licensee policy as nearly as possible and will not interfere with operations if it can be possibly avoided.
- Will accept individual to observe and accompany the inspector at any and all times. The firm may designate whomever they wish.
- Will discuss policy matters only with individuals specifically designated by the firm to do this.
- Will not instruct or admonish any employee.
- Will discuss findings only with employees that management designates. The items discussed will be repeated to management later.

5.3.4 Discuss what the inspectors need to help them in their inspection.

- How will inspectors move about the plant?
- Obtain the names of observers, if any, who will accompany inspectors. Establish the ground rules for observers.
- What are the working hours? Does the company work in shifts?
- Obtain a schedule of activities that will be occurring while inspectors are in the plant. This may include:

    - filling room schedules
    - test starting dates, animal challenge dates, observation times
    - inoculation or harvesting schedules
    - batching schedules

- Determine the locations where records are kept. This should include the following types of records:

    - labels and label files
    - animal acquisitions and disposals
    - production and testing records
    - sterilizer, lyophilizer and filling records
    - outlines of production
    - stock culture and master seed records--testing
    - distribution records
    - inventory records

- Where may inspectors work? Obtain working space in a location convenient to the records area and to production and testing facilities if possible.

5.4 Worksheets

The preliminary work sheets prepared during pre-inspection review are utilized during the inspection proper. Examples of typical worksheets that may be used in the inspection are as follows:

- Daily Inspection Notes
- Additional Daily Inspection Notes
- Inspection Product Check-Off Sheet
- Additional Product Inspection Notes
- Product Destruction Record (APHIS Form 2045)

All worksheets, other notes, schedules, copies of documents, exhibits, and employee statements become part of the notes. These must be usable as supporting evidence for all exceptions noted.

- Make notes legible, clear, and indelible.
- Cross-index or number so sequences can be maintained and any omissions made apparent.
- Identify by date or by person preparing.

5.5 How to Evaluate Exceptions

There are three types of exceptions: Minor, less serious, and serious

5.5.1 Minor exceptions. Are not apt to affect quality of product but indicate laxity or error that could become more serious if not corrected. If numerous minor exceptions are noted during the inspection, it is indicative of poor management and should be considered as having cumulative effect.

5.5.2 Less serious exceptions. By repetition or very nature, may affect quality of a product. They may require evaluation at the CVB-IC office before final action is taken.

Holding release of serials or products may be required.

5.5.3 Serious exceptions. Violations of this degree will probably affect the quality of the product or products or may be willful. This type of violation will require more thorough documentation and referral to higher authority. Either stop sale or temporary suspension of license should be considered.

Each exception must be related to the Virus-Serum-Toxin Act (VSTA) or to the regulations issued pursuant to the Act. An inspector must not go beyond this authority and should develop the habit of carefully determining what regulation might be violated when a possible exception is noted. This will insure that the inspector has not exceeded the delegated authority and that the inspector will be continually increasing the effectiveness of work.

6. Inspection Notes

Inspection notes are the true inspection report. The typed report is just a summary. Everything in the summary report must be taken directly from notes or attachments. Nothing can appear in the summary that is not documented in notes or attachments. Remember, notes are confidential business information and must be kept secure or in the inspector's possession at all times.

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6.1 Some of the uses of notes are:

- Writing the summary (formal) report
- Reference for the next inspection
- Reference to support action relating to special requests, complaints and testing
- Reference to support regulatory action
- Legal evidence for court proceedings (Notes will always accompany personnel to court.)
- Documenting what was done for supervisory or program review

6.2. Following are a few reminders to assist in preparing notes:

- Use preprinted forms (Daily Inspection Notes and Daily Inspection Notes Continued). If the form is not available, be sure to include the same basic information as called for on the preprinted form--initials, date, page X of Y, etc.
- Write legibly. Prepare notes with care. Notes may be the most important writing ever done in this job.
- Complete notes include **who, what, where, when, why** and **how.**
- Use indelible ink and only one color.
- Where possible, tie statements to a specific product and serial number.
- Document the source of information:
- Describe observations – in addition to **what** was seen, include **when, where**, and **who** was involved.
- Person – always identify **who** told the information – then confirm everything told from records or observations. The weakest way to confirm information is from another person.
- Immediately mark all exhibits or other documents received with the name of the person they were received from, the date and inspector's initials on the back of each page. Attach them to the notes and make reference to them in the notes.

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- Document the times at the firm. Show clock hours including time left for lunch or other breaks.

- Document that the inspector identified themselves (identification card) and stated that the purpose is to inspect. (This validates the inspection per VSTA and the Code of Federal Regulations, Title 9 (9 CFR) Part 115.1.)

- Document the time, building number, floor, and who guided any tours that were taken.

- Document agreements or anything else the firm volunteers to do and the name of the firm official making the agreement.

- The notes should be in complete sentences, phrases or bullet statements. Remember that two years from now, the inspector must be able to look at what was written and know exactly what it means.

- Notes should be concurrent – completed within 24 hours. Stop frequently during the day to complete notes. Put down the date the notes were completed to show compliance with above.

- Notes must be facts only – what is seen, read, heard, smelled, or touched. Opinions or judgments may not be included in notes. Notes should be clear enough for the reader to make their own judgment or opinion concerning an issue. (Informed scientific opinions or judgments may be used in the summary report or memos recommending action, only if supported by details in the notes.)

- When violations are seen, do not put down just the 9 CFR number – document in detail exactly what is observed. Always list findings; never what should be done to correct the problem.

- Anything that appears to be a noncompliance or violation should be documented in much more detail than general observations. Write down every detail. Go back if something is found missing.

- Error correction should be done by making a single line through the error and initialing.

- Number or otherwise separate paragraphs in notes so particular items can easily be found later.

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7. Inspection Routines

Use of a planned routine to gather information on the compliance status of specific items or procedures is the best assurance that necessary information will be discovered. There is no way that all of the routines that are needed can be described. The following, however, are several routines of major importance covering the areas of records, products, production procedures, and controlled equipment. During the course of use of these planned routines, it is almost certain that items will be discovered that need further comprehensive investigation. The information that will subsequently develop as these "leads" are pursued will be almost wholly dependent upon ingenuity and resourcefulness as an inspector.

8. Serial Record Audit

For a complete serial record review, start with the bulk/batch assembly record.

8.1 Complete Serial Audit

- Review selected serial assembly records against the appropriate outline. These should include complete identification of all added ingredients and account for each step in final processing through completion of the bulk serial.
- Observe for losses or gains in volume, actual or estimated measurements, authentication of critical steps, and identification of the operator.
- Identify each bulk lot, raw ingredient, major equipment, procedure, or test.
- Certify the procedures against the outline at this point.
- Determine if major equipment is identified and has been properly sterilized.
- Hold other identified items for checking later.

8.2 Production Lot Audit (antigen production)

- Review the selected production lot or batch records of raw biologics and compare each step against the outline.
- Determine record keeping compliance.
- Trace back to appropriate seed or culture and forward to the serial assembly.
- Identify all ingredients, cell cultures and tests for later checking.

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- Review selected ingredient records against the outline, special outline or standard laboratory procedure.
- Note record keeping compliance.
- Identify tests run and raw materials used. Be sure to note special requirements for certain ingredients (e.g., E.I.A. test for horse serum).
- Review selected cell culture production records against outline and regulations.
- Identify raw materials and tests run on cell cultures.
- Review selected diluent production records for compliance – the same as listed for serial audit (see **Section 8.1**).
- Review each selected test procedure and compare each step against the outline or 9 CFR.
- Identify ingredients of test materials or animals used (for further audit at a later time). This includes all ingredients of animal origin.
- Determine if identification is adequate.
- Check to see that special testing equipment is operating properly.
- Review each selected animal record and compare with outline, special outlines or 9 CFR testing requirements.
- Check to see that identification of the animals is adequate.
- Determine compliance with appropriate Animal Welfare regulations and 9 CFR Part 117 regulations.
- Review animal health program with responsible official including routine medications given.
- Consult with the veterinarian-of-record to see how often care or advice is required.

8.3 Compliance Criteria for Records

Records are defined in 9 CFR 116.1 as "detailed records of information necessary to give a complete accounting of the activities within each establishment." The records will contain sufficient detail so that any person familiar with the production of the product can clearly understand each step in production.

8.3.1 Check on chronology. There should be no evidence that entries are being recorded at any other time than at the time essential steps of production, testing and destruction are actually being done. The steps should follow the same sequence that has been approved in an outline of production.

8.3.2 Check identity of items. Records should sufficiently identify ingredients, cell passages, seed cultures, etc., so entries reflect precisely what is processed.

8.3.3 Check on dates. Records show the time and date(s) applicable to each step required. Be sure records are dated. Be sure time is recorded when essential to accurately assess the process as filed in the outline of production.

8.3.4 Check on quantity. Identity and quantity of ingredients, material, or product added or removed at each important step must be shown. Unusual gain or loss from start to finish must be accounted for.

8.3.5 Check on identity of personnel. Designated individuals shall initial or sign the records as they make measurements or judgments. These initials must be later identifiable.

8.3.6 Check on location of items. Locations of products in storage or in distribution shall be recorded so the items can be traced and located.

8.3.7 Check on legibility and indelibility of records. All records must be legible and indelible and kept for at least 2 years after the expiration date of the product. Records common to two or more lots of product should be traceable. All records must be available upon request.

8.3.8 Check for deviations from approved methods. Any deviations must be explained in enough detail to allow APHIS inspectors to judge whether purity, safety, efficacy, or potency of the product was affected. If products were judged to be adversely affected, a record from APHIS permitting the deviation must also be on file.

Two things must be stressed in record audit:

- Accountability
- Identity

8.4 Use of Outlines of Production

The inspectors complete their review of the products that were tentatively selected and of worksheets prepared during the pre-inspection review.

- Request the officially stamped copy of the product outline or special outline for the product, procedure, or equipment selected for examination.
- Check the page dates against the pre-inspection notes.
- Request completed detailed licensee records for the serial or other procedure selected.
- Review the records and compare with requirements in the outline.
- Observe procedures and compare with requirements in the outline.
- Make notes on the product check-off sheets. Record all exceptions.
- Check supporting records to substantiate the validity of the primary records.

8.5 Routines in the Observation of Production Procedures

The inspector will schedule their observations of production procedures from the production schedule provided by the firm and from pre-inspection notes.

- Consult pre-inspection notes to assist in selecting critical procedures to observe and make actual selection.
- Consign observation to one or more team members taking into consideration their field of specialization.
- Check with the firm for production schedules, schedule changes and request to observe procedures.
- Determine and follow specific restrictions necessary to enter limited access areas.
- Take the assigned product and physically follow the route of movement from room to room within the facility. Compare with the blueprint check-off sheet; note if each activity is where pre-inspection notes indicate.
- Spend enough time at each phase being observed to thoroughly understand exactly what movements are being made in what sequence. Mentally be able

The Inspection Proper

to do the complete sequence of movements. Return to the outline and recheck correct procedure. Record any deviations.

- Maintain an awareness of potential contamination; be aware of people's personal habits, environment factors affecting sterility, air movement, proximity to other organisms in use, etc.
- Watch if routines for strict sterility are being broken, particularly harvest, bulk mixing, and fill.
- Watch for deviations in proper lab procedure – placement of a sterile item on a non-sterile surface, then reusing.
- Observe if all surfaces of sterile rooms are being cleaned, walls and ceilings, as well as floors and lab tops.
- Notice if the line supervisor is aware of the conditions or restrictions of the outline. Often outlines are written and filed by management without line supervisor involvement.
- Watch measurement of ingredients – compare with allowed amounts in the outline.
- Watch the recording of each step as it is done, verifying it is concurrent with operations.
- Watch for evidence of reprocessing – watch steps taken post-incubation – compare with that allowed in the outline. Keep sufficient notes on the observation to enable proof as to whether or not a procedure is according to the outline.
- Call other inspectors to witness alleged exceptions. If procedure is dangerous to product or production people, call a team conference and request immediate review by firm personnel. TAKE ACTION.
- Go into coolers; check if unlabeled serials can be mixed up. Check if unreleased serials can be mistakenly sold or distributed.
- Recognize anything that is unlabeled or unidentified and require it be immediately identified and properly labeled, otherwise quarantine it and destroy under APHIS supervision.

- Be on the lookout for organisms in abnormal amounts or in abnormal places as signs of possible research or extra testing in production areas--maintain an awareness of what organisms are authorized where.

- Watch for activity in rooms where not so indicated in blueprints or legends.

- Watch if proper lab clothing and if safety equipment is in use or only present on a token basis.

- Watch for movement of people through a restricted area who are on official business but are not observing the restrictions (maintenance men, firm executives).

- Watch for nuisance things – food in coolers, lunching in laboratory rooms, desks and files in sterile rooms, lounging of idle employees in sterile rooms (often these are hidden and make good places to avoid the supervisor).

- Make notes on product check-off sheet. Record all exceptions and failures to follow good manufacturing practices.

8.6 Inspection of Controlled Equipment

The inspector checks the operating condition and regulation compliance of all automatically controlled equipment.

- Review team assignments for observing firm's equipment.

- Review the pre-inspection list of firm's equipment. Add any new equipment found at the firm.

- Observe working schedules and determine periods of high and low equipment use. Areas with constant temperature control should be checked during both the high and low activity periods and on several different days.

- Schedule observation time with appropriate firm supervisory personnel. Determine and follow special procedures for entering limited access areas.

- Check CO_2 incubators and determine if appropriate CO_2 percent atmosphere is being provided. Determine how the CO_2 levels are monitored and how often they are double checked by the licensee.

- Observe controlled freezing of completed product and note the time elapsing from harvest to reaching the final storage temperature. Compare freezing rate and time elapsed to outline requirements.

- Observe sterilizers for loading that provides for circulation of heat or steam.

- Observe pasteurizers for temperature of both serum and water bath. The firm should be checking their pasteurizing recording equipment against accurate thermometers once a week or once every run if operated less often.

- Observe lyophilizer and determine if each vial in the serial or subserial is being held and lyophilized under essentially identical conditions. Watch for shelf temperature variations, non-uniform stoppering, mixed container sizes in a unit, a subserial in more than one drying chamber, etc. If breakdowns have occurred, how are the vials handled? What do the records show? What precautions are taken?

- Observe fermentors and bioreactors and determine if the environment provided the product is in accord with that specified in the outline. Review records and note breakdown, manual operation, sterilization, automatic additions, and maintenance of sterility.

- Determine if the automatic controlling equipment is providing the environment within limits required by the outline or regulations. Note time, temperature and recovery time after doors are opened, hot or cold material added, etc.

- Determine how often the firm checks their equipment manually or with standardized measures.

- Review the record keeping system. Be sure manual or standardizing checks are recorded.

- Make notes on all equipment checked and record all exceptions to outline or regulation requirements.

9. Daily Team Review

The team leader may assemble all members of the team daily.

- Meet at a location where privacy is assured. This permits free discussion and prevents disclosures of privileged information.

- Review the activities of each member of the team.

- Discuss each exception found.

- Tentatively rate each exception as minor, less serious or serious. Look for guidelines in special circumstances. Contact IC Management if unable to mitigate.

- Check the documentation of each exception to be sure it can be substantiated. Have it ready for the wrap-up session.

- Discuss the next day's activities and modify assignments if indicated.

- Prepare a summary of findings and assemble a rough form of the inspection report as the inspection is winding up. Present findings logically. Usually use the general inspection category outline in presenting exceptions. Cite 9 CFR references, note these may change upon policy review by the Inspection Section Leader. Note where dates must be set for corrections or where supervisors must be told of significant items. Have the rough form ready for verbal presentation at the plant wrap-up session.

10. The Wrap-up Session

Identification of an exception is only a beginning. Compliance with regulations is the desired end result. Many exceptions can be satisfactorily handled through meeting with representatives of management at the conclusion of the inspection.

- Record the names of the individuals attending the wrap-up session.

- Use the summary of exceptions prepared at the last team review session as the format for the verbal presentation.

- Allow each team member who worked on the category in which the exception was found to present the findings and exception(s) found. The team leader maintains responsibility for developing all actions to be taken as a result of the discussion on each category.

- Encourage an exchange of opinions with the representatives of the firm. Be sure any misconceptions or misunderstandings are resolved.

- Record the important points that are brought out in the discussion. If some differences cannot be reconciled, tell the firm representatives that final actions will be determined after consultations with the appropriate APHIS personnel.

- Ask the firm representatives to suggest a date by which each exception will be corrected. If a date is not reasonable, try to set one by negotiation. If these approaches fail, assign a date by which corrections must be made.

- Attempt to have written confirmation of all agreements made at the meeting returned to the licensee within 15 days of the conclusion of the inspection.

- Keep three questions in mind during all negotiations, discussions and actions:

    - Is the action consistent with regulations?
    - Is the action consistent with APHIS policy?
    - Is the action reasonable?

- Discourage tape recording the sessions. Taping tends to inhibit open and candid discussion. If a firm's secretary transcribes all or portions of the proceedings, insist that a copy be sent to the team leader.

- Make favorable, as well as unfavorable, comments.

11. Guidelines for Actions in Special Circumstances

Inspectors will discover things which seem to indicate serious violations or willful noncompliance.

Document suspected or proven major violations using photocopies of records, employee statements and such other information as will stand legal scrutiny. See **ICSOP0016,** *Investigation and Processing of Alleged Violations of the Virus-Serum-Toxin Act*, for more information. Consult with the CVB-IC Director to confirm action.

Impose a stop sale or hold release on products involved in a major violation(s). Do this only after exploring all aspects of the situation and after contacting CVB-IC Management. Do not use this option too quickly.

Do not rescind a stop sale or hold release until the alleged violation is disproved or the need for it is clearly removed by subsequent events or instructions.

Maintain security on evidence of willful violations so the results of the investigation will not be compromised. Discuss evidence only with those who need to know.

11.1 Verbal Abuse of Veterinary Biologics Inspectors

A question has arisen as to what recourse there is when an inspector is subjected to verbal abuse by the owner or manager of a licensed or permitted facility. Based on a case involving Animal Welfare inspectors, the Office of the General Counsel has determined that if the harassment is of a nature which compromises the inspector's ability to properly inspect the facility, the inspection should be terminated and alleged violation initiated for failure to comply with the provisions of the VSTA. Consult the CVB- IC Director for advice.

11.2 APHIS Employees' Safety Responsibilities While Conducting Inspections

In 1991, after a tragic loss of life to fire at a food processing plant in North Carolina, the Administrator issued a memorandum on employee responsibilities when safety violations are observed. Even though there is no regulatory authority for the safety of non-Federal employees at commercial facilities, there is a moral obligation to identify and report obvious unsafe conditions. If, during an inspection, conditions are observed that pose potentially disastrous consequences if not corrected, report safety hazards such as blocked fire exits or other workplace hazards to the owners or operators of the establishment.

12. Summary of Revisions

Version .03

- **5.1**: Additions regarding parameters concerning identification of inspector at a firm (information received from Select Agent Program for Inspectors)

Version .02

- The Contact information has been updated.
- **3.1/3.4:** These sections have been updated to use more common language.
- **5.3:** Batching schedules have been added.
- **8:** Batch has been added for clarification.
- **8.1:** The word "bulk" has been removed.
- **8.2:** Antigen production has been added for clarification.
- **9.** Noted that 9 CFR citations may be changed upon review.

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Animal and Plant Health Inspection Service

Risk Assessment and Biotechnology-derived Veterinary Biologics

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Virus-Serum-Toxin Act – 1913

- Prohibited distribution of Worthless, Dangerous, Contaminated, Harmful virus, serum, toxin, or analogous product intended for use in the treatment of domestic animals
- Restricted production to licensed establishments
- Products prepared in compliance with regulations
- Provided for inspection of establishments/products
- Prohibited importation of Worthless, Dangerous, Contaminated, Harmful products
- Gave authority to suspend licenses

USDA
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1979
First Recombinant Product Licensed

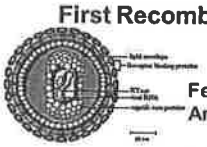


Diagram of a Retrovirus

Feline Leukemia Virus Antigen Test Kit

- FELV, a transmittable RNA that can severely inhibit a cat's immune system, was first discovered in the 1960's
- The Diagnostic Test Kit contained a monoclonal antibody, a new technology at that time
- Kittens & cats less than one year of age are most susceptible to the virus

USDA

Regulatory Authorities

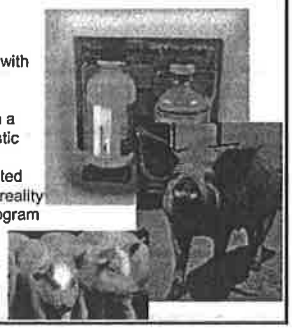
- 1913 Virus-Serum-Toxin Act (VSTA)
- 1985 Food Security Act: regulate intrastate biologics too
- 1986 Coordinated Framework for Regulation of Biotechnology
  - Encouraged biotechnology development
  - Determined that existing statutes are adequate for regulating biotechnology
- 1969 National Environmental Policy Act (NEPA)
- 1974 Freedom of Information Act
- 1995 APHIS' NEPA Procedures (7CFR Part 372)

USDA

1986
First Live Gene-Deleted Product Licensed

Pseudorabies Vaccine, MLV

- Major outbreaks in U.S., mid-1970s with introduction of total confinement, continuous farrowing operations
- 1988 - 1st gene-deleted vaccine with a companion ELISA serologic diagnostic test kit
- Differentiating vaccinated from infected animals (DIVA) concept becomes a reality
- 1989 - State-Federal eradication program initiated with new biologics tools



USDA

1990
Killed Virus Recombinant Product

Pseudorabies Vaccine, Killed Virus

- Many recombinant Killed Virus (KV) products followed: for use in porcine, feline, avian, canine, equine, and bovine species
- Inactivation provides greater assurance of safety: lack of shed/spread; no reversion to virulence

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CVB Biotech Guidelines

- VS Memorandum 800.205 - General Licensing Considerations: Biotechnology-derived Veterinary Biologics Categories I, II, & III
  - Attachments: Summary Information Format (SIF) templates for Categories I, II, III and examples
- VS Memorandum 800.300 – Stability Testing of New Biotechnological/Biological Veterinary Medicinal Products
- Risk Assessment Outline for Use in Preparing Risk Analyses (RA) for Biotechnology-Derived Products
- CVB Notice No. 07-06 – Preparation and Testing of Experimental Biological Products that are Derived from Biotechnology
- VS Memorandum 800.213 – Guidelines for Obtaining a Conditional Veterinary Biologics License for Production Platform Derived, Recombinant, Non-replicating, Nonviable Constructs (SIF Cat. IV)

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Biotech Risk Review Guidelines

- Data: Summary Information Format (SIF)
  - http://www.aphis.usda.gov/animalhealth/cvb_regsandguidance
  - The biologics firm provides the requested information using the pertinent SIF, reviewed by CVB
- Risk Assessment outline
  - http://www.aphis.usda.gov/animal_health/vet_biologics/publications/SIF_RiskAssessmentOutline.pdf
  - Completed by the firm, evaluated by CVB
- Risk analysis (RA) of proposed field safety trials
  - Environmental assessment (EA) of any potential effects
    - On animal safety, public health, or the natural environment

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Overview

- Each biotech product is evaluated individually to determine the appropriate requirements to establish purity, safety, potency, and efficacy.
- Replication proficient products must undergo an environmental risk assessment.
- Killed or inactivated (non-replication competent) biotechnology products must undergo an abbreviated risk assessment.
- Critical data/information is in the Summary Information Format

USDA

Summary Information Format (SIF)

- Data requirements & the SIF template are defined by the type of (biotechnology-derived) product
  - Veterinary Biologics: new/unique conventional vaccine
  - Category I: killed, MAb, subunit, nonviable product
  - Category II: gene-deleted live product; may have inserted marker
  - Category III: live vectored or chimeric product
  - Category IV: production platform derived nonviable product
  - Nucleic Acid-Mediated: vaccine, PCR test kit
  - Plant-based biologic
- The SIF supports the CVB laboratory characterization and the Risk Assessment

USDA

Category I: Non-replicating Recombinant Antigen(s)

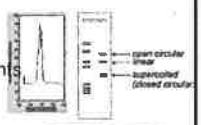
- Subunit or Killed Vaccines – examples:
  - Feline Leukemia, Porcine Circovirus
- Diagnostic Kits – examples:
  - Antibody Test Kits for EIA, IBD, AI, PRRS Viruses
  - Antibody Test Kits for Anaplasma, Babesia Equi, B. Caballi
- Nucleic Acid Vaccines - examples:
  - Infectious Hematopoietic Necrosis Virus, Canine Melanoma

USDA

2007
First Cancer Vaccine Licensed

Canine Melanoma Vaccine DNA

- Conventional requirements
- Product Purity
- Sterility
- Contaminants:
  - Endotoxin range
  - Extraneous DNA
  - RNA & cellular debris
- Nucleic acid integrity



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Category II: Live Gene-Deleted

- Salmonella Typhimurium Vaccine
  - Poultry
- Escherichia Coli Vaccine
  - Poultry
- Salmonella Dublin Vaccine
  - Bovine
- Pseudorabies Vaccine
  - Porcine

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2004 – US: Pseudorabies-Free Status

- The Eradication Program, established in 1989, was successful because of highly efficacious vaccines and companion tests
- 1977 - First Vaccine Licensed
- 1984 - First Vaccine with mutations
- 1986 - First Screening ELISA
- 1988 - First gene-altered vaccine & first diagnostic test to differentiate antibody from gene-deleted vaccine
- 1992 - First "free" State
- 2004 - All states achieve free status

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United States Department of Agriculture

Category III: Licensed Live Vectored Vaccines

- ~15 live vectored vaccines: some are made by several companies +/or are components of other products – examples:
- Antigens in fowl pox vector - from avian influenza H5, Newcastle disease virus, infectious laryngotracheitis virus
- Antigens in turkey herpesvirus vector - from Marek's disease virus, Newcastle disease virus, infectious bursal disease, infectious laryngotracheitis virus
- Rabies glycoprotein in vaccinia virus vector
- Marek's disease virus - herpes-chimera
- Antigens in canarypox vector - from canine distemper, rabies, equine influenza, West Nile, feline leukemia virus

1989
申请标可

populated area, 狂犬病口服疫苗得以使用

USDA

1994
Live Vectored Product Licensed

Newcastle Disease – Fowl Pox Vaccine, Live Fowl Pox Vector

- For use *in ovo* or after hatching
- Efficacy against virulent Newcastle disease and virulent fowlpox viruses
- Genetic and phenotypic stability after cell culture and chick passage
- Lack of reversion to virulence after passage in chicks
- No shed-spread to contacts
- Safety in other avian species

USDA

1995 - 2013
Other Live Vectored Products Licensed





- 1995 – Rabies Vaccine, Live Vaccinia Vector
- 1997 – Canine Distemper-Adenovirus Type 2-Parainfluenza-Parvovirus Vaccine, MLV, Live Canarypox Vector
- 1999 – Marek's Disease Vaccine, Turkey Herpesvirus Vector
- 2012 – Foot and Mouth Disease Virus Vaccine, Serotype A24, Live Adenovirus Vector
- 2013 – Rabies Vaccine, Live Raccoon Poxvirus Vector


Poxvirus


Herpesvirus


Adenovirus

USDA

Category IV: Production Platform

- Production platform-derived recombinant, non-replicating, nonviable constructs
  - PEDV Vaccine, RNA
    - Porcine
  - Swine Influenza Vaccine, RNA, Subtype H3
    - Porcine

非100%有效，但不减少各病毒及其变异

USDA

CVB Confirmatory Testing Based on the SIF: If Satisfactory, MS Approved for Use in Production

- Differentiate (MS) from parental organism(s)
- Confirm identity of MS
- Verify purity of MS
  - Lack of extraneous agents
  - Lack of extraneous sequences
- Verify genotypic and phenotypic stability at n and n+5 (or the highest passage)
- *Identify virulence properties of the MS*

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The SIF Provides Molecular Characterization

- Descriptions of parental strains
  - Backbone Biological Agent
  - Donor Biological Agent(s), DNA, or genes
- Genetic modifications to create the Regulated Biological Agent (Master Seed)
  - Detailed construction process
  - Cloning sites & identity of gene(s) at site
  - Markers, screening methods & protocols
- Protocols for purification and characterization of the Regulated Biological Agent

USDA

The SIF Provides Properties of the Master Seed (MS)

- Detailed physical and restriction maps
- Identification methods & protocols
- Biological properties and effects
  - Virulence
  - Tropism (host & lab animal; tissue)
  - Horizontal gene transfer potential
  - Recombination potential
  - Shed/spread potential
- Stability at n & n + 5 (or the highest passage)
- Expression of the foreign (target) gene(s)

USDA

SIF: Additional Data

- Environmental distribution of backbone agent
- Geographical distribution of backbone agent
- Recommended NIH biosafety levels
  - *In vitro* testing
  - *In vivo* testing
- Survivability in the environment
- Available sequence information
  - Submitted by electronic file(s)

USDA

Environmental Considerations

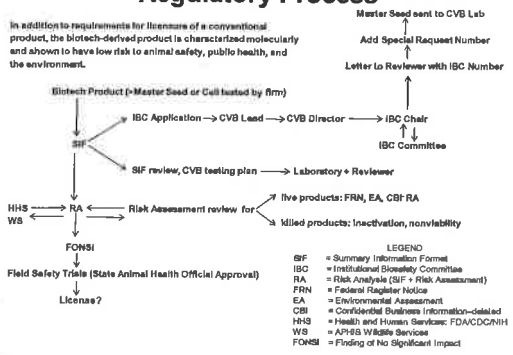
- Deliberate release of any organism containing recombinant DNA into the environment is subject to review and approval by appropriate Federal agencies.
- Under normal husbandry and laboratory practices, injected veterinary biologicals are not considered to be released into the environment if testing shows the agents are not shed.
- Any agents shown to be shed are considered released into the environment.

USDA

Requirements for Release of Live Recombinants (CVB Notice No. 07-06)

- Contained Release
  - Firm's Institutional Biosafety Committee (IBC) or equivalent: approval for R&D, licensure experiments
  - CVB approval if performed in the firm's (inspected) production facilities
- Field safety trials
  - Federal Register Notice of intent: Confidential business information (CBI)-deleted SIF/RA, and EA
  - CVB approval (9 CFR 103.3) to ship & use in animals
  - National Environmental Policy Act (NEPA) compliance

Regulatory Process



Risk Considerations

- Risk: The likelihood of an adverse event occurring and the consequences if that adverse event occurs
- Biological products are not without risk
- Mitigations of potential adverse events, contaminants, animal/human/environmental consequences
- Ensuring Quality (Pure, Safe, Potent, and Effective) biologics

Risk Assessment Objectives: Identify Hazards

- Examine genotypic and phenotypic stability in target host animals (reversion to virulence?)
- Evaluate changes in tissue tropism
- Assess shed/spread capabilities
- Assess host range specificity
- Consider recombination potential and consequences
- Identify effect of overdosing
- Assess survivability in environment

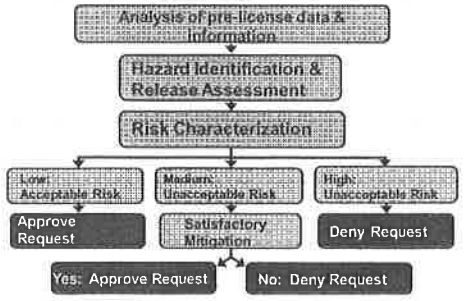
Formal Risk Review of Biotech-derived Vaccines

- Data: Summary Information Format (SIF)
  - The biologics firm provides the requested information using the pertinent SIF, as well as their testing results
- CVB: confirmatory Master Seed & prelicense serial testing
- Risk Assessment outline (includes study results)
  - Completed by the firm, evaluated by CVB
- Risk review by CVB of proposed field trials
  - Environmental assessment (EA) for any live vaccine's effects
    - On animal safety, public health, or the natural environment

Risk Analysis: Assessment, Characterization, Communication, Management

- Prelicense product testing by the Biologics Firm
- Confirmatory master seed & serial testing at CVB
  - Purity assessment
  - Molecular characterization
  - Phenotypic characterization (insert expression)
- NEPA compliance for field safety trial
  - Decision-making considers impact on environment
  - Alternative actions are evaluated
  - Potential mitigation is identified
  - The public is notified of possible risk
  - Action is taken to mitigate possible risk

Request to Ship + Test an Experimental Biologic - 9 CFR 103.3



USDA

1995 – 2013
Live Vectored Products for Use in Wildlife

- 1995 – Rabies Vaccine, Live Vaccinia Vector

Rabies virus

- 2011 – currently, field safety trial evaluation: Rabies Vaccine, Live Adenovirus Vector

- 2013 – currently, field safety trial evaluation: Yersinia Pestis Vaccine, Live Raccoon Pox Virus Vector

Yersinia pestis

USDA

Federal Register Notice for Live Biotechnology-Derived Vaccines

- The firm provides to the CVB for public viewing:
  - Confidential business information (CBI)-deleted SIF/RA
- Announcement in Federal Register: pending field trials
  - CVB-prepared Environmental Assessment (EA)
  - Public comment period
  - Finding of No Significant Impact (FONSI)
  - Approval of field trials if no significant issues arise
- Licensure
  - If the field trials showed the product to be safe and all other requirements are met

USDA

CVB Risk Review of Licensed Products

- Once licensed:
  - the firm provides to CVB test results of each serial prior to release
  - CVB conducts risk-based, random testing of serials
  - Vaccinovigilance reports important to the process
  - If potential problems, testing and reevaluation

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Risk Analysis in Summary

- Systematic interdisciplinary approach
- Ensures use of scientific information in planning and decision making
  - Includes outside review by subject matter experts as needed
- Flexible, transparent, comprehensive
- Characterization of safety risk based on qualitative and quantitative assessments
- Certain "categorical exclusions" under discussion
- Developing standards as technologies develop