

# United States Department of Agriculture Regulatory Requirements and Guidelines

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## Introduction

The regulation of veterinary biological products in the United States began in 1913 with the passage of the Virus-Serum-Toxin (VST) Act. An investigation of the veterinary biologics being produced in the United States at that time had revealed that they were not of acceptable quality. The VST Act was therefore enacted by Congress to prevent the importation and interstate shipment of worthless, contaminated, dangerous, or harmful veterinary biological products. The VST Act was amended by the Food Security Act of 1985 to expand this authority to include all products shipped into, within, or from the United States. Although the regulations and procedures used to implement this act have changed as needed to deal with new methods of production, new products, and expanding scientific knowledge, the need to assure the purity, safety, potency, and efficacy of veterinary biological products has remained constant.

## Authorities and Organization

The VST Act of 1913 as amended by the Food Security Act of 1985 and regulations published in Title 9, Code of Federal Regulations (9 CFR) Parts 101-118 provide the United States Department of Agriculture (USDA) the authority for the regulation of all Veterinary biological products shipped into, within, or from the United States. The regulations in 9 CFR 101.2 (w) define veterinary biological products to be "all viruses, serums, toxins, and analogous products of natural or synthetic origin, such as diagnostics,

antitoxins, vaccines, live microorganisms, killed microorganisms, and the antigenic or immunizing components of microorganisms intended for use in the diagnosis, treatment, or prevention of diseases of animals."

The VST Act as amended makes it unlawful to sell worthless, contaminated, dangerous, or harmful veterinary biologics or to ship veterinary biologics in or from the United States unless they are prepared in a licensed establishment in compliance with USDA regulations. An exemption from this licensing provision is given for products prepared by (1) a person solely for administration in that person's own animals, (2) a veterinarian for use in his or her own licensed practice under a veterinarian-client-patient relationship, and (3) a person operating a State licensed facility solely for distribution of product within the state of production in a State that has a State regulatory control program for veterinary biologics that has been reviewed by USDA and found to be acceptable. The Act as amended also gives USDA the authority to make and issue regulations to prevent the preparation and marketing of worthless, contaminated, dangerous, or harmful veterinary biologics and for the inspection of manufacturing facilities, manufacturing processes, and the veterinary biological product itself. It requires the issuance of a permit by USDA prior to the importation of a veterinary biological product and gives the Department the authority to test veterinary biological products prior to importation if desired. The VST Act as amended also provides for the issuance of conditional or special licenses for products on the basis of purity, safety, and a reasonable expectation of efficacy in order

to meet an emergency condition, limited markets or local situation, or other special circumstance.

In case of violation, the Act as amended permits USDA to remove or suspend establishment and/or product licenses provided the licensee is given the opportunity for a hearing prior to such action. It also gives authority for detention, seizure, and condemnation of products and injunction against products or establishments. Criminal action that could lead to a fine or imprisonment also can be taken against violators.

Within USDA the authority for administering the VST Act as amended has been delegated to the Animal and Plant Health Inspection Service (APHIS). There are four units within APHIS, each with specific responsibilities, that must coordinate their activities for program delivery. These units are:

(1) Veterinary Biologics (VB), a staff located in Hyattsville, MD that is responsible for the development of licensing and permit requirements; review of license and permit applications; development and publication of program policy and procedures in regulations, standard requirements, memorandums, and notices; program planning and budgeting; and coordinating informal hearings concerning violations that could lead to suspension or revocation of licenses.

(2) Veterinary Biologics Field Operations (VBFO), A line unit located in Ames, IA that has responsibility for inspection of licensed establishments and establishments seeking license, coordinating investigations of suspected violations of the Act as amended, receiving consumer complaints due to unsatisfactory field performance of products and determining when these are product related that require appropriate action by APHIS, and reviewing the testing of each serial of product to assure compliance with established requirements prior to authorizing release for marketing.

(3) National Veterinary Services Laboratories (NVSL), containing Veterinary Biologics Laboratories also in Ames, IA, has responsibility for developing

new test methods for assuring the purity, safety, and potency of veterinary biologics; developing and providing references for use in such tests; conducting surveillance testing to monitor the licensed manufacturers' quality control; conducting prelicense testing on all products prior to licensing; serving as a source of scientific consultation on products during the licensing process; and testing products involved in consumer complaints when requested by VBFO.

(4) Regulatory Enforcement and Animal Care, a staff and field unit within APHIS is responsible for investigation of alleged violations and assuring compliance with the Act as amended and the regulations.

## Licensing Procedures

In order to produce and market a veterinary biological product in the United States, a producer needs two kinds of licenses, as described in 9 CFR Part 102:

(1) A United States Veterinary Biologics Establishment License for each production facility and

(2) A United States Veterinary Biological Product License for each product produced in a licensed establishment.

Procedures for the issuance of establishment and product licenses in the United States are designed to define and document what is being licensed and who will be responsible for the production and distribution of product that is being authorized. They are also intended to assure the purity, safety, potency, and efficacy of each product and the accuracy of labeling.

A staff reviewer is assigned to work with each license applicant and to guide them through the licensing process. Staff officers also will review protocols of proposed research to be conducted to support product license applications to assure the study design is valid, statistically sound, and acceptable for the purpose intended.

Materials submitted in support of license applications are considered to be confidential business information and not

subject to release under the Freedom of Information Act. However, licensees are requested to identify their submissions as confidential and to indicate why release of the information would cause substantial harm to the competitive position of the firm.

To obtain a United States Veterinary Biologics Establishment License, an application (APHIS form 2001) must be filed with APHIS that identifies the name and address of the applicant and any subsidiaries or divisions that will be doing business under the license. The application also identifies the responsible person for the license including corporate officers for corporations. The application must be supported by:

(1) an application for a U. S. Veterinary Biological Product License.

(2) a copy of the articles of incorporation if the applicant or subsidiaries are incorporated,

(3) plot plans and blueprints of the facilities to be licensed and a legend that provides a brief description of the activities performed in each room including decontamination procedures and other precautions against cross contamination,

(4) a certificate from the appropriate water pollution control agency, that the establishment is in compliance with applicable water quality control standards, and

(5) a short resume of training and experience of employees at the establishment that will be responsible for essential steps in production, testing, and initial distribution of product.

Prior to the issuance of a license for the establishment, VBFO personnel will conduct a prelicensing inspection of the facilities. Inspectors will review the adequacy of record keeping systems to document each step in production. They also will review the construction and operation of the establishment to validate that they are as represented in the blueprints and legends and also assure they are in acceptable condition for production of the veterinary biological products intended to be licensed. Laboratory practices will be observed to

assure the facilities are being operated at an acceptable standard, and they will train a person at the establishment to collect and submit valid samples from each serial of product for testing at NVSL. Quality control testing and other compliance requirements also will be reviewed at this time. The report of the prelicense inspection is forwarded to VB for consideration in the licensing process. If found satisfactory in all regards, the establishment license will be issued with the first product license.

A U.S. Veterinary Biological Product License is required for each product produced in a licensed establishment. An Application for U.S. Veterinary Biological Product License (APHIS Form 2001) must be filed for each product in accordance with 9 CFR 102.5. If an establishment is not already licensed, an application for an establishment license must accompany the application for a product license. Product license applications must be supported by: (1) an outline of production, (2) legend changes, (3) sketches and/or final labels, and (4) supporting data.

The outline of production is the detailed protocol for manufacturing and testing the product and should be prepared and submitted in accordance with 9 CFR 114.8 and 114.9. The outline includes information such as:

For each microorganism---the source and date of accession, the isolation and passage history, strains and proportion of each; Cultures---the method of identification of each microorganism, virulence and purity data, all media composition, seed culture storage, inoculation technique; Harvesting---handling of cultures and media, time from inoculation to harvest, technique for harvesting microorganisms; Product preparation---stepwise description from harvest of antigen to the finished product in final containers; Testing---stages at which samples are collected, reference to applicable Standard Requirements, details of additional tests giving minimum requirements for each satisfactory test;

Other information---final container sampling, calculation of expiration date, recommendations for use, dosage, and route of administration.

Data must be provided to support the purity, safety, potency, and efficacy of product produced in accordance with the outline of production. The use of a Master Seed as the source of all seed for production assists in maintaining uniformity of production. In most cases final product must not be more than 5 serial passages from the Master Seed. Master Seed, Master Cell Stock, primary cells, ingredients of animal origin, and final product are tested to assure compliance with standard test procedures.

Ingredients of animal origin must meet accepted standards of purity and quality. Master cell stock, i.e., primary cells or cell lines used for production of Master Seed and animal ingredients, must all be shown to be free of extraneous bacteria, fungi, mycoplasma, and viruses.

Product immunogenicity must be demonstrated by statistically valid host animal vaccination and challenge studies. The vaccination must be conducted using the minimum level of antigen indicated in the Outline of Production, with product produced at the highest passage level from the Master Seed that is permitted for production. The precise challenge method and the criteria for determining protection vary with the immunizing agent.

A minimum of 20 vaccinates and 5 controls are required for immunogenicity testing. In most cases 19 of 20 vaccinates must be shown to be protected against a challenge that kills 4 of 5 controls, with the fifth control demonstrating severe signs of the disease. In the case where 95 percent efficacy cannot be expected for the product or the challenge organism is not pathogenic enough to cause death, other parameters, such as the scoring of clinical signs or pathology, are used in the evaluation of the test.

Field efficacy studies have been accepted in the licensing of products when a meaningful laboratory challenge model

cannot be established. Field efficacy studies must include valid controls and an adequate number of animals to demonstrate a significant effect from the use of the product. In our experience it is usually much more difficult to obtain valid efficacy data under field studies than in the laboratory. The level of challenge is highly variable under field conditions; many studies fail to produce valid data because the lack of adequate exposure to an appropriate challenge results in a low incidence of disease in the nonvaccinated controls. In other cases, exposure to other disease-producing organisms that cause a similar disease in the test animals make valid interpretations of the data difficult. In some cases, a combination of laboratory and field efficacy studies is needed to assure efficacy.

The efficacy of each label indication must be established. That is, each route or method of administration, each species of animal for which the product is recommended, and any claims for degree of protection afforded must be supported prior to approval.

Potency tests are designed to correlate with the host animal vaccinate-and-challenge studies. Prior to release, each serial, i.e., production lot, is tested for potency. For killed viral or bacterial products, potency tests may be conducted in laboratory or host animals or with quantitative *in vitro* methods. For release of live vaccines, bacterial counts or virus titrations are used. The bacterial count of a live bacterial vaccine for release must be sufficiently greater than that used in the immunogenicity test to assure that when tested at any time within the expiration period the titer will be at least twice that used in the immunogenicity test.

Stability studies (based on an acceptable potency test) are required to establish the validity of the expiration date given on the product package. For preliminary stability studies the product may be incubated at 37° C for a short time (e.g., a week), but these results should be confirmed by potency tests through the period of time indicated by the expiration date, and 6 months beyond.

Safety testing can be a combination of various studies. Mouse intracranial, subcutaneous, or intraperitoneal tests are acceptable for the final product. For anaerobes, the guinea pig appears to be very sensitive for evaluating safety. Host animal safety data also are required.

Environmental safety is an important issue for live viral or live bacterial vaccines, and in particular for live recombinant products. Live products must be characterized to determine if they have the ability to shed from the host and transmit to contact animals. Back passage studies are required to provide information on genetic stability and on what can be expected when that vaccine is put into animals in the field. Once laboratory characterization studies are completed, field tests provide additional safety data.

Licensees are required to produce three consecutive satisfactory serials of final product in their licensed establishment in accordance with the approved Outline of Production. Samples of these serials are forwarded to NVSL for prelicense testing to confirm the producer's test result.

Upon satisfactory completion of all requirements, including review and acceptance of labels and circulars, a U.S. Veterinary Biological Product License may be issued.

### **Field Safety Tests**

All veterinary biological products must be tested for safety in the field before licensure. Field safety studies are designed to detect unexpected reactions, including mortality, that may not have been observed during the development of the product. The firm applies for authorization to do field safety studies after the firm has prepared and tested the three prelicense serials and after VB has approved the results of the efficacy test. The firm must meet the requirements indicated in 9 CFR 103.3 for shipping experimental products; this includes obtaining permission from the proper animal health authorities for each State where the tests will take place.

The tests are conducted on the host animal, at a variety of geographical locations, using large numbers of susceptible animals that the firm does not own. The test animals should represent all the ages and husbandry practices for which the product is indicated. The product tested should be one or more of the three prelicense serials. A detailed protocol for the field safety test is submitted to VB for review. The protocol should indicate the observation methods and the recording methods.

### **Sampling**

After completing the tests on samples of the three consecutive prelicense serials (all applicable Standard Requirement and special tests in the Outline of Production), the firm sends the results to Veterinary Biologics for review. If the test results are satisfactory, VB sends a computer message to NVSL requesting the NVSL confirm the firm's tests on samples of the three prelicense serials.

Serial samples are selected according to the procedures given in 9 CFR 113.3. The selection is made either by an APHIS employee or, more routinely, by a firm employee designated and trained by VBFO. In addition to samples tested by the firm and samples submitted to NVSL, the selector also picks representative final containers from each serial to be stored at the storage temperature recommended on the label. The firm keeps these reserve samples for 6 months after the expiration date shown on the label, and makes them available to APHIS upon request.

The outline or production, plot plans, blueprints, and legends that are developed and filed during the licensing process must be complied with and form the basis of a contract of how the product must be produced. These documents and the regulations serve as the basis of indepth inspections conducted at licensed establishments after licensing.

## Alternate Licensing Procedures

Through experience, APHIS has found the use of conditional licenses, licenses for further manufacture, and sublicensing procedures to be very beneficial. In order to meet an emergency condition, limited market or local situation, or other special circumstance, APHIS may issue a conditional (special) license under an expedited procedure on such conditions as are considered necessary to assure the purity, safety, and a reasonable expectation of efficacy. The issuance of conditional licenses permits an expedited licensing process for biological products needed to meet an emergency disease outbreak. It also provides a mechanism for the licensing of products for minor species and other limited market situations where the cost of establishing full efficacy before marketing would prohibit the development of needed products. This type of license may also be used to license needed products when host animal efficacy has been established but difficulty in the development of a fully satisfactory potency test would result in undue delay in the issuance of a regular license. Conditional licenses are issued for a period of one year. Before reissuance, the licensee must demonstrate acceptable progress toward completion of host animal efficacy and/or potency tests in accordance with protocols filed with APHIS. Labels for conditionally licensed products must bear a statement that the product is under conditional license and that potency and efficacy studies are in progress. Conditional licenses are not issued for any product already issued a regular license.

Licensing products for further manufacture has permitted split manufacturing procedures where two or more licensed establishments can work together to produce a product. These are regular licenses for products that are only permitted to be shipped from one licensed establishment to another licensed establishment or for export. This procedure permits one company to prepare the product to a certain stage of production and ship it to the second company under a license for further manufacture. The

second company finishes the product and releases it under a regular license. Licensing in this manner has permitted the industry to take the best advantage of its production capability and to expand company product lines without extensive developmental costs.

Sublicensing of a licensed product from one company to another also is permitted. In this process the company that has a license for the product contracts to transfer to the second company the data, technology, and materials necessary to produce the product. The outline of production must be transferred along with Master Seed and any Master Cell Stock. The receiving company must repeat purity testing of Master Seed and Master Cell Stock and do an immunogenicity test in a reduced number of host animals to confirm previous data. Additional field safety studies are not required.

This process has been useful in the transfer of products and technology from one company to another.

## State and Federal Interaction

As currently written, the VST Act does not have preemptive authority over State laws concerning the regulation of veterinary biological products. Veterinary biological products cannot be shipped in or from the U.S. unless they meet Federal standards; however, States may impose additional requirements if they desire. The biologics program therefore requires an active interaction with State authorities. Usually this interaction involves requesting of State approval for the distribution of products, such as requiring firms to obtain State approval before the authorization of field trials with experimental products, before authorizing the use of autogenous biologics in non adjacent herds, or before marketing a conditional licensed product in the State. Some regular licensed products also have restrictions on the license that require firms to obtain approval from the States before distribution of their product. State and Federal responsibilities for placing restrictions on the distribution of product are clarified in the regulations and

provide a procedure whereby any person may request that Federal restrictions be imposed on a product. APHIS establishes restrictions needed to assure the purity, safety, potency, and efficacy of products, whereas States are permitted to restrict the distribution of products based upon local disease conditions.

## **Conclusions**

Procedures for assuring the purity, safety, potency, and efficacy of veterinary biological products in the United States have been reviewed. Licensing, testing, and inspection activities assure the development of and compliance with program standards and that biological products of high quality are available to the consumer.

## **References**

21 United States Code 151-159, December 23, 1985.

Title 9, Code of Federal Regulations, Parts 101-118, January 1, 1994.

