

Regulations for vaccines against emerging infections and agrobioterrorism in the United States of America

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Summary

The Virus-Serum-Toxin Act of 1913, as amended in 1985, provides the legal basis for the regulation of veterinary vaccines and related biological products in the United States of America (USA). The regulatory authority for the issuance of licences and permits that allow the shipment or importation of pure, safe, potent, and effective veterinary biological products lies with the Center for Veterinary Biologics (CVB), an agency of the United States Department of Agriculture (USDA). Under the standard licensing or permitting process, a manufacturer must develop and completely characterise and evaluate a product prior to licensure, and the CVB must review and evaluate the submitted information, audit and inspect the manufacturing facilities and methods of production and testing, and confirm key product test results through independent testing of product. This complete and comprehensive evaluation may not be possible in emergency situations, so processes and mechanisms are in place that allow for the more rapid availability of veterinary vaccines. Next generation vaccine development against foreign animal diseases such as foot and mouth disease is actively in progress in the USA and the authorities must ensure that there is an adequate supply of these vaccines in the National Veterinary Stockpile.

Keywords

Bioterrorism – Disease – Emergency – Emerging – Licensing – Regulatory – Vaccine – Veterinary.

Introduction

Regulation of veterinary biological products in the United States of America (USA) began in 1913 with the passage of the Virus-Serum-Toxin Act by the United States Congress. The United States Department of Agriculture (USDA) is responsible for regulating veterinary biological products,

including, but not limited to, vaccines, bacterins, toxoids, antibodies, and antitoxins which are intended for use in the treatment of animals and which act primarily through the stimulation, supplementation, enhancement, or modulation of the immune system or the immune response. Because the term treatment, by definition, includes the prevention, diagnosis, management, or cure of diseases of animals, diagnostic test kits are also under

regulatory control by the USDA. The current USDA regulatory programme consists of:

- review of all data developed by manufacturers in support of each product and product claim
- inspection of manufacturing processes and practices including equipment, facilities, materials, personnel, production, quality control, and records
- confirmatory testing of manufacturers' biological seeds, cells, and product
- a post-licensing monitoring system of inspection and random testing of product
- post-marketing epidemiological surveillance of product performance under normal conditions of use.

This combination of regulatory oversight before and after licensure assures the availability of pure, safe, potent, and effective veterinary biologics to veterinarians and animal owners. Under the standard licensing process, this spectrum of evaluation and review includes the complete characterisation, identification and purity testing of seed materials, product ingredients and the final product; environmental, laboratory, and host animal safety and efficacy studies; stability studies, and post-licensing monitoring of field performance. All aspects of this comprehensive conventional evaluation may not be possible during the emergence of a new animal disease agent or in an animal disease emergency such as in the intentional (agrobioterrorism) or unintentional introduction of a significant exotic animal disease agent. In these situations, the USDA has various mechanisms for expedited product approval. In addition, the USDA may also provide exemption of products from some or all of the regulatory requirements for conventional product approval. Implementation of these existing mechanisms and perhaps, the identification of other novel avenues for product approval will be critical for the acceleration and timely development of next generation foreign animal disease (FAD) vaccines and immune-based biotherapeutics.

Recently, to expedite emergency disease response capabilities, the Center for Veterinary Biologics (CVB), an agency of the USDA, has partnered with other authorities in the USA, such as the USDA's National Veterinary Stockpile (NVS), and foreign regulatory authorities, such as the Tripartite Canada-Mexico-USA North American Foot and Mouth Disease Vaccine Bank, to purchase vaccine antigen concentrates and/or finished emergency use vaccines. In addition, the NVS is entering into contractual agreements with biologics manufacturers to ensure immediate access to existing stocks of licensed emergency-use vaccines. These emergency preparedness products may be licensed and distributed under standard processes or

with exemption from some or all of the normal regulatory requirements.

Regulatory framework

The Virus-Serum-Toxin Act of 1913 (Title 21 of the United States Code Parts 151-159) provides the legal basis for the regulation of veterinary biologics in the USA; the CVB has the regulatory authority for the issuance of licences and permits for such products. The law was amended in 1985 by the Food Security Act to include the distribution of all veterinary biologics (both interstate and intrastate) in the USA as well as those intended for export. Administrative regulations and standards appear in Title 9 of the Code of Federal Regulations (9 CFR) Parts 101-118, with additional programme guidance found in CVB Notices, Veterinary Services Memoranda, General Licensing Considerations and other guidance documents. Veterinary biologic products are defined in the regulations as 'all viruses, serums, toxins (excluding substances that are selectively toxic to microorganisms, e.g. antibiotics), or analogous products at any stage of production, shipment, distribution, or sale, which are intended for use in the treatment of animals and which act primarily through the direct stimulation, supplementation, enhancement, or modulation of the immune system or immune response.' This includes, but is not limited to, vaccines, bacterins, allergens, antibodies, antitoxins, toxoids, immunostimulants, certain cytokines, antigenic or immunising components of live organisms, and diagnostic components that are of natural or synthetic origin or that are derived from synthesising or altering various substances or components of substances such as microorganisms, genes or genetic sequences, carbohydrates, proteins, antigens, allergens, or antibodies.

The USDA is authorised to issue *licences* to veterinary biologics manufacturers in the USA. In addition to what are variously referred to as the 'conventional', 'regular' or 'full' veterinary biological product licences in the USA, conditional biologics licences and autogenous biologics licences may be issued for use in specific situations or under certain conditions. Thus, some consideration should be given to use these identified mechanisms for licence approval of next generation vaccines and immune-based biotherapeutics in order to reduce their overall time to operational readiness.

The USDA is further authorised to issue three types of *permits* to allow the importation of veterinary biologics into the USA. A Permit for Transit Shipment Only is required for a biological product shipped from one non-US country to another non-US country by way of the USA. A biological product issued a Permit for Transit Shipment Only may not be used in the USA. A Permit for Research and Evaluation

may be issued if the manufacturer provides adequate information for the USDA to assess the product and the product's impact on the environment and the product investigator (user) demonstrates scientific capabilities adequate to safeguard domestic animals (all animals, other than man, including poultry) and protect public health, interest, or safety from any deleterious effects which might result from the use of such product. For this permit type, the user could be the Department of Homeland Security (DHS) Science and Technology (S&T) Directorate Foreign Animal Disease Biological Countermeasure Program at Plum Island Animal Disease Center (PIADC). This government facility, located off the north-eastern tip of New York's Long Island, is specifically designed to conduct research and development studies on FADs and thus is in a unique position to further evaluate experimental biologicals that may be of value for further development and licensure. A Permit for Distribution and Sale may only be issued if the manufacturer and the permittee can insure that the product is pure, safe, potent, and effective. A Permit for Distribution and Sale is essentially equivalent to a conventional Veterinary Biological Product License in the USA. For this permit type, DHS S&T could coordinate activities between the foreign vaccine manufacturer and biological company in the USA with a veterinary establishment licence.

The USDA's Animal and Plant Health Inspection Service (APHIS) Administrator may also specifically exempt any veterinary biological product from one or more of the normal regulatory requirements under certain circumstances, e.g. if the product is to be used experimentally (see section entitled 'Exemption of biological products from licensing requirements') or if this product will be used by or under the supervision of the USDA in the prevention, control, or eradication of animal diseases in conjunction with:

- a) an official USDA programme, or
- b) an emergency animal disease situation, or
- c) a USDA experimental use of the product.

DHS S&T can play an integral role in this exemption policy by leading in the testing and evaluation of experimental vaccine product candidates for FADs. The scientific data generated can be used, for example, to better inform foot and mouth disease (FMD) modelling studies. In addition, DHS S&T can directly test or facilitate the testing of FAD vaccines currently licensed and manufactured in foreign countries. Examples include licensed veterinary vaccines for FMD, highly pathogenic avian influenza, rinderpest, Rift Valley fever, and classical swine fever. These current products can be characterised to yield new scientific data (e.g. days to onset of protection, virus shed/spread, vaccine dose sparing, etc.) that are

important in a decision process immediately following outbreak diagnosis.

All licences and permits issued by the CVB may include restrictions on the distribution and use of the product (this also applies to products that have been exempted from certain other requirements by the APHIS Administrator). In an animal disease emergency such as in the intentional (bioterrorism) or unintentional introduction of a significant exotic animal disease agent, these restrictions would include, but not be limited to, the following:

- 'Domestic distribution and use shall be under the supervision or control of USDA, APHIS, Veterinary Services, as part of an official USDA animal disease control program.'
- 'Distribution in each State shall be limited to authorized recipients designated by proper State officials—under such additional conditions as these authorities may require.'

DHS S&T can serve a coordinating role in obtaining scientific data that can be used by APHIS-Veterinary Services to help underpin decisions on the specific restrictions under which these exempted products would be used. Examples include data on the ability of test material to reduce pathogen shed (including the duration of reduction) and the ability of the product to be used in a Differentiating Infected from Vaccinated Animals (DIVA) diagnostic recovery phase programme.

The CVB's Inspection and Compliance (CVB-IC) section is responsible for determining whether licensed and permitted companies are being properly inspected and whether the products they manufacture are being prepared, tested, and distributed according to all applicable regulations and requirements. Major CVB-IC activities include on-site inspections of manufacturing and quarantine facilities, control and release of product batches (serials), and post-licensing product monitoring (pharmacovigilance). Licensed and permitted manufacturing establishments are subject to comprehensive in-depth inspections at one to three year intervals. In-depth inspections include 14 categories of inspection, each of which includes numerous items suggesting records to audit and items for observation. The categories of inspection considered in all in-depth inspections include licences, personnel, facilities, equipment, sanitation, research, seeds and cells, production, final production, labels, testing, animals, distribution, and miscellaneous (including pharmacovigilance). Special inspections of establishments are also utilised to address issues such as:

- observation of pivotal pre-licence efficacy or safety studies
- auditing of production, quality control, or animal test records

- inspection of new facilities or equipment
- review of product distribution or pharmacovigilance records.

Each licensee or permittee is required to furnish the CVB with representative samples of every vaccine master seed organism and master cell stock proposed for use in the preparation of veterinary biological products, and samples of each serial or subserial of finished veterinary biological product manufactured in or imported into the USA. The APHIS Administrator is authorised to cause these samples to be examined and tested for purity, safety, potency, and efficacy. A master seed organism or master cell stock found unsatisfactory by any test may not be used to prepare veterinary biological products. A serial or subserial found to be unsatisfactory by a required test prescribed in an approved Outline of Production or Standard Requirement is not in compliance with the regulations, and may not be released for distribution.

Data and review requirements for conventional product licences or permits for distribution and sale

All regulations pertaining to product licences or permits for distribution and sale (data requirements, confirmatory testing by the CVB, inspection and compliance requirements – see following sections) are contained in 9 CFR Parts 101-118. Pre-licensing data evaluation and review procedures are designed to assess the purity, safety, potency, and effectiveness of each product and support all product label claims. In order to fulfil these criteria, data from all phases of product development are evaluated against these key elements. This spectrum of evaluation includes complete characterisation and identification of seed material and ingredients, laboratory and host animal safety and efficacy studies, demonstration of stability, and monitoring of field performance. Specific purity, safety, potency, and efficacy requirements are described in the following paragraphs.

Purity

All product components and ingredients must meet standards of purity and quality. Master seed, master cell stock, primary cells, ingredients of animal origin, and final products must be tested and shown to be free of extraneous microorganisms. This requirement is especially important in a scenario in which veterinary vaccines licensed and produced overseas would be considered for

use in an animal disease emergency. DHS S&T PIADC can provide a proactive, coordinating role in the testing of master seed, cell stocks, and formulated vaccines for the presence of foreign animal disease agents. Eggs used in production of biological products must be acquired from specific-pathogen-free flocks. Purity and identification of master seed and master cell are confirmed by testing at the CVB. In addition to the first serials (batches of completed product) prepared under licence, a random sample of serials are subjected to pre-release purity testing at the CVB to verify manufacturer's quality assurance/quality control on final product.

Safety

Products must be shown to be safe through a combination of safety evaluations. Master seeds and master cell stocks must be fully identified and characterised. Production passage levels (limits) are established for both seeds and cells. Master seeds for live products are tested for shed, spread, and reversion to virulence through backpassage studies in the host animal. Following a minimum of five passages in the host, recovered isolates are fully characterised using the same procedures used for the master seed. Demonstration of an acceptable level of attenuation must be shown. Other safety studies are required as appropriate (e.g. safe use in pregnant animals, environmental safety, safety of adjuvants in products for food-producing animals). Field safety studies designed to detect unexpected reactions that may not have been detected in product development are required before licensure. The CVB and DHS S&T must decide if the next generation FAD vaccines currently under development will be exempt from this requirement or if field safety vaccine trials in foreign countries with reported FAD will be required. Host animal tests are conducted at a variety of geographical sites using large numbers of susceptible animals representing all ages and husbandry practices for which the product is intended. Final product serials are subjected to safety testing primarily through *in vivo* animal tests.

Efficacy and potency

All products must be shown to be effective according to the claims indicated on the label, and each batch (serial) of each product must demonstrate potency at least equal to that of the reference serial(s). As defined by regulations in the USA, efficacy is a product characteristic, demonstrated at least once prior to licensure, while potency is a batch measure, and is intended to confirm that a serial will be at least as effective as a known immunogenic serial. The two terms can be distinguished as follows:

- efficacy is the specific ability or capacity of a biological product to effect the result for which it is produced, when

used under the conditions recommended by the manufacturer

- potency is the relative strength of a biological product as defined by test methods or procedures established by APHIS in the 9 CFR Standard Requirements or in the approved Outline of Production for the product.

Efficacy is generally demonstrated by statistically valid host animal vaccination-challenge studies and must be correlated to the product potency assay. The following general considerations are applied to efficacy studies:

- immunogenicity studies must be conducted using minimum levels of antigen at the highest passage level from the master seed that is permitted for production;
- product must be prepared in production facilities on a scale representative of normal production;
- challenge methods and criteria for evaluating protection will vary with the immunising agent, but in general, tests are conducted under controlled conditions using seronegative animals of the youngest age recommended on the label;
- duration of immunity data is required for some existing products (e.g. for rabies) and for all newly licensed antigens;
- field efficacy studies may be considered where laboratory animal challenge models are not well established. Similarly, serologic data may be used to establish efficacy only when serology is indicative of protection;
- data is required for each species for which the product is recommended and for each route, dose, and regimen of administration;
- for products with two or more fractions (components), data demonstrating no antigenic interference is required;
- stability studies are required to set the expiration date on the label;
- potency tests correlated to host animal vaccination and designed to measure the relative strength of each serial must be developed prior to full licensure. In addition, each serial must be formulated and tested prior to marketing to ensure effectiveness and reproducibility of activity (potency) according to standards set at the time of licensing. Generally, this is accomplished through an established immune-mediated animal or *in vitro* assay or by using microbiological counts or virus titrations for live bacterial or viral products.

Risk analysis

The CVB uses risk analysis procedures to evaluate licence applications for all 'new' live conventionally-derived

vaccines and biotechnology-derived veterinary biologics, and to assess proposals to import veterinary biologics into the USA. To facilitate the preparation of scientifically valid and credible risk analyses, the CVB has developed Summary Information Formats (SIFs) and Risk Assessment (RA) outlines to provide guidance to interested parties. The SIFs and RA outlines identify the relevant information that should be evaluated in veterinary biologics risk analysis, and may be downloaded from the CVB website.

The SIF for conventionally-derived live vaccines is designed to identify the appropriate information that should be provided to properly characterise the vaccine microorganism, based on its microbiological and biological properties, and those of the parental microorganism from which the vaccine strain was derived.

The SIF for Category I biotechnology-derived veterinary biologics is designed to identify the appropriate information that should be provided to properly characterise the recombinant microorganisms for inactivated biotechnology-derived veterinary biologics. Subcategories for inactivated biotechnology-derived veterinary biologics are as follows:

- I-A-1, bacterins, killed virus vaccines, and subunit vaccines
- I-A-2, recombinant antigens for use in diagnostic test kits
- I-B-1, monoclonal antibodies for therapeutic or prophylactic use
- I-B-2, monoclonal antibodies for use in diagnostic test kits
- I-C-1, synthetic peptides for therapeutic or prophylactic use
- I-C-2, synthetic peptides for use in diagnostic test kits
- I-D-1, nucleic acid-mediated vaccines
- I-D-2, nucleic acid-mediated diagnostic test kits.

Inactivated biotechnology-derived microorganisms can be used in the manufacture of 'killed' vaccines, subunit vaccines, and diagnostic kits. The characterisation of the inactivated microorganism centres on its molecular properties, as well as on those of the parental microorganism and on any deleted or donor genes. Obviously, it is not anticipated that inactivated microorganisms will pose a threat to the environment. Accordingly, for inactivated biotechnology-derived products, the veterinary biologics risk analysis process is used to ensure that the biotechnology-derived microorganism is properly characterised and inactivated. Risk analyses to evaluate proposed environmental releases of inactivated products are not conducted.

The SIF for Category II biotechnology-derived veterinary biologics is designed to identify information needed to properly characterise microorganisms for biotechnology-derived live vaccines containing gene deletions and/or heterologous marker genes. The characterisation of the gene-deleted microorganism includes the molecular and biological properties of the vaccine microorganism, and of the parental microorganism receiving the genetic modifications.

The SIF for Category III biotechnology-derived veterinary biologics is designed to identify information needed to properly characterise the vaccine microorganisms for biotechnology-derived live vector vaccines containing heterologous genes encoding immunising antigens and/or other immune stimulants. The characterisation of biotechnology-derived vector vaccines includes the molecular and biological properties of the recipient, the donor, and the recombinant master seed microorganism. The characterisation of the donor microorganism includes the properties of both the donated structural genes and their regulatory elements. It is anticipated that the majority of next generation molecular vaccines and/or immune-based biotherapeutics for FADs currently under development by DHS S&T will fall under this risk classification.

A risk analysis prepared by the licensee or permittee must be submitted to the CVB for pre-licence evaluation of every Category I, II, or III biotechnology-derived product. The risk analysis should contain the most current version of the SIF and a risk assessment based on safety characteristics of the vaccine. A risk assessment outline for use in the preparation of risk analyses for biotechnology-derived products is available from the CVB.

Risk analyses for environmental release must be prepared by licensees or permittees for new live conventionally derived and biotechnology-derived veterinary vaccines. The risk analysis needs to include environmental release assessments, which evaluate the safety characteristics of the vaccine microorganism within the context of the target environment. A SIF which identifies the information that should be included in release assessments for proposed environmental releases is available from the CVB. Prior to the first release of a live biotechnology-derived veterinary vaccine determined not to have a significant impact on the quality of the human environment, the CVB prepares an environmental assessment and advises the public of plans for field testing the vaccine. The CVB also provides public notice of their intent to issue a product licence or permit for the vaccine, provided the field test data support the conclusions of the environmental assessment and the issuance of a finding of no significant impact and the product meets all other requirements for licensing.

The veterinary biologics risk analysis model for importing veterinary biologics centres on the risk of introducing

FADs into the USA through the importation of a contaminated veterinary biological product. This requires a thorough evaluation of all potential sources of contamination during the development and manufacture of the product. The SIF for importation of veterinary biological products identifies the information regarding the facilities, reagents, production procedures, and testing procedures that should be evaluated when preparing risk analyses for proposals to import veterinary biological products into the USA. As previously discussed, DHS S&T PIADC can play an important coordinating role in generating additional, scientific data that can be used in the risk analysis model, such as BSL3 Ag (biosafety level 3 for agricultural hazards) safety testing in animals of veterinary biologics that may be candidates for importation.

Licensing data should be developed and submitted for licensure in a logical sequence representing successive steps in product development (e.g. master seed purity and identity, laboratory safety, immunogenicity, initial production serials [usually three], purity, safety, potency testing, and field safety). All data generated in product development is required to be reported to the CVB.

Confirmatory testing by the Center for Veterinary Biologics laboratory for conventional product licences or permits for distribution and sale

The laboratory staff within the CVB conduct assays on veterinary biological products and key biologics manufacturing materials (master seed bacteria, master seed virus, and master cell stocks) as required in 9 CFR parts 101-118. Primary activities include:

- pre-licence testing
- test development and standardisation (including reagent activities)
- post-licence quality control monitoring.

Pre-licence testing by the CVB laboratory for conventional product licences or Permits for Distribution and Sale includes assaying both parent materials (master seeds and cells) and final product. Master seeds and master cell stocks are evaluated for purity and identity (including identity of construct and expressed antigen for genetically engineered products). Prior to licensure or permitting of a product, a manufacturer is required to demonstrate their ability to consistently produce pure, safe, and potent product. This is usually accomplished through the

satisfactory production of three consecutive, independent pre-licence serials. Before a licence or permit is issued, the purity, safety, and potency of pre-licence serials will be confirmed by testing in the CVB laboratory. This testing assures that the product tests are appropriate and transferable and that the manufacturer is able to consistently reproduce quality product.

It is important to note that although all tested master seeds, master cells, and pre-licence serials have been tested by the manufacturer and submitted to the CVB as satisfactory, the CVB laboratory regularly finds a small percentage of seeds, cells, and products that are not pure, safe, potent, or effective.

Inspection and compliance requirements for conventional product licences or permits for distribution and sale

According to Title 9 of the CFR, parts 101-118, for a US manufacturer to distribute veterinary biological products, the producer must hold valid licences of two types:

- a United States Veterinary Biologics Establishment License
- one or more Veterinary Biological Product Licenses.

In order to distribute veterinary biological products manufactured outside the USA, a permittee (defined as any individual, firm, partnership, corporation, company, association, educational institution, state or local government who resides in the USA or operates a business establishment within the USA) must hold a United States Veterinary Biologics Establishment License and a United States Veterinary Biological Product Permit, For Distribution and Sale. Thus, the distribution of FAD imported vaccines that may be of interest to the National Veterinary Stockpile will require the identification of a company, individual or government authority that is willing to apply for these licences and to serve as the permittee. Partnerships between DHS S&T and private industry will most likely be required to ensure programme success, since the customer target for these imported products will be USDA APHIS and the National Veterinary Stockpile, rather than traditional meat, milk and egg producers.

Prior to the issuance of an establishment licence or permit for distribution and sale, an applicant for biologics manufacturing must address the following items:

a) the regulations require that manufacturing establishments be operated under the direct supervision of persons competent by education and experience to handle all matters pertaining to the preparation and testing of biological products. Summaries of the relevant qualifications for each supervisory employee responsible for essential steps in production, testing, and initial distribution of products must be provided to and accepted by the CVB;

b) facility documents, including plot plans for all buildings, blueprints for each building used in preparing biological products, and blueprint legends which provide a brief description of all activities in each room or area of a production facility must be submitted to and accepted by the CVB;

c) for each room, the blueprint legend should include:

- all activities conducted in a room, for example, inoculation, harvest, concentration, filling, etc.
- all microorganisms prepared, tested, or stored in the room, including an indication of whether the microorganism is viable or killed
- a listing of stationary or other essential equipment such as mills, centrifuges, mixing tanks, bottling and sealing equipment, etc.
- for rooms where products are exposed to the surroundings, a description of decontamination procedures and other precautions against cross-contamination;

d) the regulations require buildings to be constructed so that:

- the floors, walls, ceilings, partitions, posts, doors, and all other parts of all structures, rooms, or facilities used in the preparation of biologicals can be readily and thoroughly cleaned
- all rooms are located and arranged to prevent cross-contamination of products
- there are adequate air handling systems to ensure sanitary and hygienic conditions for the protection of products and personnel
- there are separate rooms or compartments for preparing, handling, or storing virulent or dangerous microorganisms
- adequate hot and cold water supplies and efficient draining and plumbing systems are provided for animals and equipment;

e) equipment cleaning, pasteurisation, sterilisation, temperature recording devices or other records of sterilisation must be acceptable;

f) all animals used in the preparation or testing of biologicals must be healthy. Animals admitted into, used in, and disposed of from biologics production areas must

meet the standards in the regulations for biologics and the Animal Welfare Act;

g) records and record-keeping systems must be adequate to give a complete accounting of all activities within each establishment, including all procedures used in all steps in the preparation, testing, and disposition of products;

h) if, at any time, there are indications that raise questions regarding the purity, safety, potency, or efficacy of a product, or if it appears that there may be a problem regarding the preparation, testing, or distribution of a product released for marketing, the manufacturer must agree to immediately notify the CVB concerning the circumstances and the action taken;

i) written assurance must be filed with the CVB that the licensed or permitted products will not be advertised so as to mislead or deceive the purchaser and that the packages or containers used in marketing the product will not bear any statement, design, or device which is false or misleading in any particular;

j) for biologics manufacturers in the USA, the entire premises of an establishment are subject to inspection, at any time, without prior notification. The regulations specifically authorise inspection of 'all buildings, compartments, and other places, all biological products, and organisms and vectors in the establishment', and all materials and equipment, such as chemicals, instruments, apparatus, and the like, and the methods used in the manufacture of, and all records maintained relative to, biological products produced at such establishments;

k) for non-US manufacturing facilities, the producer and permittee must agree to submit to periodic inspections of the production facilities, and the permittee must agree to be responsible for all costs associated with the inspections.

Before a United States Veterinary Biologics Establishment License or a United States Veterinary Biological Product Permit, For Distribution and Sale is issued, a pre-licence inspection by the CVB must confirm whether the condition, equipment, facilities, methods, etc. used to prepare biological products conform with the above items and all other requirements in the US regulations.

Expedited processes for veterinary biologics in the United States of America

Ideally, a fully licensed or permitted vaccine is available for use in the USA to aid in the control of a new or emerging animal disease or when vaccine is immediately required to

aid in a response to an intentional (bioterrorism) or unintentional introduction of a significant animal disease agent not normally found in the USA. If not, the processes and mechanisms described in this section have been used in the USA to allow for the more rapid availability of veterinary vaccines in an emerging or emergency animal health situation.

Conditional product licences

Conditional licences (regulated by 9 CFR Part 102.6) are authorised under very specialised circumstances to meet an emergency condition, limited market, local situation, or other special circumstance. Licences are issued under an expedited procedure which assures purity and safety, and provides a *reasonable expectation* of efficacy and/or potency for the vaccines involved. The data generated by a manufacturer to provide this reasonable expectation varies, and is evaluated on a case-by-case basis, but licences have been issued in the following situations:

a) efficacy data was adequate, but correlation to the proposed potency assay was not determined or validated

b) clinical or experimental efficacy studies suggested a protective effect against disease, but did not provide definitive data

c) a scientifically accepted correlate of efficacy, such as a virus, toxin or similar neutralising antibody titre or level was available.

It is important to note that approvals allowing the preparation of vaccines under conditional licences are time-limited, and manufacturers must actively pursue data to support full licensure. It is also important to note that the CVB may not issue 'Conditional Permits.' Conditional licences may only be issued to biologics manufacturers in the USA.

Vaccine prepared under a conditional licence must be in compliance with all other applicable licensing regulations and standards. This will involve, for example, conducting pre-licence field safety studies, following data and risk analysis procedures, advising the public prior to release of live biotechnology-derived vaccines, obtaining satisfactory results from confirmatory testing of seeds, cells, and pre-licence serials by the CVB laboratory, and complying with facility and other CVB inspection requirements.

Use of conditional licences for new FAD vaccines should be contemplated in strategic countermeasure programmes in which funds for full licensing may be limited and/or the specific advanced price or purchase commitments by the National Veterinary Stockpile are not well established. This will ultimately translate to biologics manufacturing capacity incentives.

Autogenous product licences or permits for distribution and sale

Regulations concerning autogenous product licences and permits are contained in 9 CFR Part 113.113. Autogenous biologics are prepared from cultures of microorganisms which have been inactivated and are non-toxic. Such products are to be used only by or under the direction of a veterinarian within a veterinarian-client-patient relationship. The microorganisms used as seed to prepare autogenous biologics must be isolated from sick or dead animals in the herd of origin and there must be reason to believe they are the causative agent(s) of the current disease affecting such animals. Autogenous isolates may not be modified by biotechnology methods. Normally, microorganisms from one herd are not to be used to prepare an autogenous biologic for another herd. However, under certain circumstances, preparation of an autogenous biologic for use in herds other than the herd of origin, when those herds are considered to be at risk and have an epidemiologic link, may be authorised. In general, the microorganism(s) used for the production of autogenous biologics must be used within 15 months of the date of isolation, or within 12 months of the date of harvest of the first serial of product produced from the microorganism(s), whichever comes first. Testing requirements for autogenous products include testing of final container samples for purity (sterility) and mouse and/or guinea pig and/or host animal safety tests. Master seed testing by the manufacturer is not required, nor is any CVB laboratory confirmatory testing of the seeds or cells conducted. Products must include a label precaution that potency and efficacy have not been established. A licence to produce, distribute or ship autogenous products includes the restriction that the licence does not authorise production, distribution, or shipment of autogenous vaccine/bacterin for the following:

- foot and mouth disease
- rinderpest
- any H5 or H7 subtype of avian influenza
- any subtype of avian influenza if the vaccine is intended for use in chickens
- swine vesicular disease
- Newcastle disease
- African swine fever
- classical swine fever
- *Brucella abortus*
- vesicular stomatitis
- rabbit haemorrhagic disease
- any other disease that the USDA determines may pose a risk to animal or public health.

Autogenous FAD vaccines are not an attractive option for a countermeasure programme due to the high risk involved in manufacturing the live pathogen prior to inactivation and the increased investment that would be required to build separate, dedicated manufacturing facilities to produce these vaccines.

Vaccine prepared under an autogenous licence or permit must be in compliance with all other applicable licensing regulations and standards, including risk analysis procedures. Manufacturer's purity and safety test results may be confirmed by testing in the CVB laboratory. All manufacturing establishments are thoroughly inspected (personnel, facilities, production processes, record-keeping) as CVB compliance requirements must be met.

Experimental product approvals

Regulations pertaining to experimental product approvals are contained in 9 CFR Parts 103.3 and 104.4. Under very specific circumstances the experimental production, distribution, and evaluation of biological products by manufacturers in the USA may be authorised prior to full licensing or permitting. For the benefit of licence applicants and to permit and encourage research, a person may be authorised to ship unlicensed biological products for the purpose of evaluating such experimental products by treating limited numbers of animals. Conditions must exist to ensure the experiment is conducted in a manner to prevent the spread of disease, with special restrictions imposed in the case of products containing live organisms. Requests for authorisation to ship an unlicensed biological product for experimental study and evaluation shall be accompanied by certain information including the following:

- a permit or letter of permission from the animal health authorities of each US state or foreign country involved;
- a tentative list of the names of the proposed recipients and quantity of experimental product that is to be shipped to each individual;
- a description of the product, recommendations for use, and results of preliminary research work;
- labels or label sketches which show the name or identification of the product and bear a statement, 'Notice! For Experimental Use Only – Not For Sale', or equivalent. The US Veterinary License legend shall not appear on such labels;
- a general plan covering the methods and procedures for evaluating the product and for maintaining records of the quantities of experimental product prepared, shipped and used;
- data demonstrating that use of the experimental biological product in meat animals is not likely to result in

the presence of any unwholesome condition in the edible parts of animals subsequently presented for slaughter;

- a statement from the research investigator or research sponsor agreeing to furnish, upon the Administrator's request, additional information concerning each group of meat animals involved prior to their movement from the premises where the test is to be conducted. Such information must include the owner's name and address; number, species, class and location of animals involved; date the shipment is anticipated; name and address of consignee, buyer, commission firm or abattoir;
- information in order to assess the product's impact on the environment.

Permits are not issued for biological products from countries known to have exotic diseases – including, but not limited to, FMD, rinderpest, highly pathogenic avian influenza, swine vesicular disease, Newcastle disease, and African swine fever – if such products may endanger livestock or poultry in the USA.

Recently, DHS S&T has partnered with the CVB and industry to secure permission for the shipment of experimental FMD vaccine candidates to PIADC for efficacy studies in livestock. Continuation of this partnership will be important to allow for the timely identification of lead candidates for further development.

Exemption of biological products from licensing requirements

The APHIS Administrator may exempt any veterinary biological product from any or all of the licensing or permitting requirements (9 CFR Part 106.1) if the products will be used by the USDA, or under the control and supervision of the USDA, for the prevention, control, or eradication of animal disease in any of the following circumstances:

- a) as part of an official USDA programme
- b) in an emergency animal disease situation
- c) as part of a USDA experimental trial.

DHS S&T can provide value-added information for decisions regarding product exemption by conducting scientific studies designed specifically to characterise the product in the context of its effectiveness as an emergency-use countermeasure tool.

Homeland Security Presidential Directive 9 and the National Veterinary Stockpile

The economic and social impacts of an outbreak of a highly contagious animal disease in the USA, such as FMD,

would be dramatic. In the event of such an outbreak, the lost export markets for live animals and meat products and the multiplier effect of lost production would be felt throughout the US economy.

On 30 January 2004, Homeland Security Presidential Directive 9 (HSPD-9) established a national policy to defend the agriculture and food system in the USA against terrorist attacks, major disasters, and other emergencies. This directive noted that this would be done by:

- identifying and prioritising sector-critical infrastructure and key resources for establishing protection requirements
- developing awareness and early warning capabilities to recognise threats
- mitigating vulnerabilities at critical production and processing nodes
- enhancing screening procedures for domestic and imported products
- enhancing response and recovery procedures.

As a part of response planning and recovery, HSPD-9 directed the creation of a National Veterinary Stockpile (NVS) containing sufficient amounts of animal vaccine, antiviral, diagnostic, or therapeutic products to appropriately respond to the most damaging animal diseases affecting human health and the economy. The NVS is mandated to be capable of deployment within 24 hours of an outbreak. The ability to respond to the intentional, simultaneous introduction of disease agents in multiple locations (i.e. an act of terrorism) is a particular focus for the NVS.

The NVS is the national repository of vaccines, personal protective equipment, and other critical veterinary products. It exists to augment state and local resources in the fight against dangerous animal diseases that could potentially devastate American agriculture, seriously affect the economy, and threaten public health.

The NVS reflects two significant changes in the way APHIS is able to respond to and eradicate animal diseases, as follows:

- a) previously, functional groups of specialists responding to an outbreak managed their own logistics support. This fragmentation has caused several problems:
 - groups duplicate the efforts of others
 - planning before an event is more complex and potentially incomplete
 - coordination of resources during an event is more difficult when products come from multiple sources managed by multiple groups

– costs of responding are higher because each group purchases supplies in smaller quantities and at high prices

b) in the past, APHIS eradicated disease outbreaks primarily by destroying infected and potentially exposed animals. However, given both changes in agricultural practices in the USA (e.g. herd sizes are much larger than in the past), and the availability of animal disease control models and scenarios involving multifocal disease outbreaks, planning disease control options beyond quarantine and depopulation is prudent. Vaccine in the NVS gives APHIS another option.

Within five years, the NVS intends to acquire vaccine, diagnostic testing capabilities, and therapeutic countermeasures against a variety of the most significant animal diseases, including highly pathogenic avian influenza, FMD, Rift Valley fever, exotic Newcastle disease, and classical swine fever. Within ten years, NVS plans to acquire countermeasures against all of the most dangerous diseases of animals. In order to rapidly deliver large quantities of critical veterinary supplies and equipment to the right place, at the right time, for as long as is necessary, the NVS is:

- directly obtaining, stockpiling and managing finished vaccines and other ready-to-use supplies for delivery by the NVS within 24 hours
- contracting, for delivery within 24 hours, for stocks of vendor-managed vaccines, diagnostic tests and reagents, and other perishable supplies
- developing both government and vendor-managed biologics precursors suitable for long-term storage and rapid formulation into needed products (e.g. vaccine antigen concentrates for highly pathogenic avian influenza and FMD).

Veterinary biologics acquired by or contracted to the NVS may be any licensed, permitted, experimental, or exempted product, as is deemed prudent by risk analysis.

DHS S&T can function as the single point of authority for either leading or coordinating the development of veterinary biodefence countermeasures for procurement

by the NVS. DHS S&T can provide a permanent funding source through which the federal government can co-develop next generation vaccines or novel immune-based biotherapeutics with private industry. Industry development costs can be off-set and minimised by forming strategic partnerships with DHS S&T. This approach is currently being used to establish a pipeline of next generation molecular vaccines for FMD. Expansion of this approach for other high priority foreign disease agents of threat to agriculture will be critical to enable the NVS to reach its five-year and ten-year objectives.

Conclusion

The procedures reviewed above provide a regulatory framework and outline general purity, safety, potency, and efficacy requirements for licensing of products for traditional animal diseases, emerging animal diseases, and the accidental or intentional introduction of animal diseases. Supplementary procedures may be required for certain products. These regulatory processes demonstrate the flexibility of the current regulatory system to accommodate a variety of animal health situations while providing the data-driven, performance-based oversight necessary to assure that only quality biologicals are available for use. DHS S&T, USDA-CVB and other government agencies of the USA must work together in a coordinated fashion to ensure the successful development and availability of highly efficacious, biological-based countermeasures for the US National Veterinary Stockpile.



Réglementation applicable aux vaccins contre les maladies infectieuses émergentes et à l'agro-bioterrorisme aux États-Unis d'Amérique

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Résumé

Aux États-Unis d'Amérique, la loi de 1913 sur les virus, les sérums et les toxines (Virus-Serum-Toxin Act) telle qu'amendée en 1985, constitue le fondement juridique de la réglementation relative aux vaccins vétérinaires et aux produits biologiques à usage vétérinaire. L'autorité réglementaire chargée de délivrer les autorisations de mise sur le marché et les autorisations d'expédition ou d'importation de médicaments vétérinaires purs, sans danger, puissants et efficaces est une agence sous tutelle du Département américain de l'Agriculture, le Center for Veterinary Biologics (CVB). Conformément à la procédure normalisée d'autorisation, les fabricants doivent développer, caractériser intégralement et évaluer les produits candidats avant de présenter une demande d'autorisation ; ces informations sont ensuite examinées et évaluées par le CVB, puis celui-ci procède à un audit et à une inspection des établissements du fabricant et de ses méthodes de production et de test ; les principaux résultats des tests relatifs au produit sont ensuite vérifiés lors d'un examen indépendant. Cette évaluation exhaustive n'étant pas toujours possible dans les situations d'urgence, des procédures et des mécanismes particuliers sont prévus afin que des vaccins vétérinaires soient rapidement disponibles dans ces situations. Des vaccins de nouvelle génération contre des maladies animales exotiques telles que la fièvre aphteuse sont en cours de développement aux États-Unis, et il appartient aux autorités compétentes de s'assurer que la réserve nationale de vaccins vétérinaires en contienne un stock suffisant.

Mots-clés

Autorisation de mise sur le marché – Bioterrorisme – Maladie – Maladie émergente – Réglementation – Urgence sanitaire – Vaccin – Vaccin vétérinaire.



Reglamentación sobre vacunas contra infecciones emergentes y bioterrorismo en los Estados Unidos de América

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Resumen

En los Estados Unidos de América (EE.UU.), la ley relativa a los virus, sueros y toxinas (Virus-Serum-Toxin Act) de 1913, modificada en 1985, constituye la base legal de la reglamentación sobre las vacunas de uso veterinario y los productos biológicos conexos. El Centro de Productos Biológicos de Uso Veterinario (CVB, Center for Veterinary Biologics), un organismo del Departamento de Agricultura de ese país, es el ente regulador de la concesión de autorizaciones de exportación e importación de productos biológicos de uso veterinario puros, inocuos, potentes y eficaces. De conformidad con el procedimiento normalizado de otorgamiento de licencias y permisos, es preciso que los fabricantes hayan desarrollado, caracterizado y evaluado totalmente un producto antes de que se le otorgue la homologación. A su vez, el CVB ha de revisar y evaluar la información presentada, examinar los métodos de producción y prueba, realizar una inspección de las plantas de elaboración, y someter los resultados de los ensayos de los productos clave a un organismo independiente para su verificación. En situaciones de emergencia puede carecerse de tiempo suficiente para efectuar esa evaluación global y exhaustiva; por consiguiente se han establecido procedimientos y mecanismos para disponer de vacunas de uso veterinario con mayor rapidez. El desarrollo de la nueva generación de vacunas contra enfermedades animales foráneas, como la fiebre aftosa, avanza con rapidez en los EE.UU. Las autoridades deben asegurarse de que se suministren cantidades suficientes de esas vacunas a la Reserva Nacional Veterinaria.

Palabras clave

Autorización de comercialización – Bioterrorismo – Emergencia – Emergente – Enfermedad – Regulación – Vacuna – Veterinaria.



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