Present systems and future needs for risk assessment of biologicals in the United States of America: the perspective of the regulator

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Summary: The authority for regulating veterinary biologicals in the United States of America (USA) is provided in the Virus-Serum-Toxin Act, enacted in 1913 and amended in 1995. The Act authorizes the Secretary of Agriculture to prescribe regulations governing the preparation and marketing of veterinary biologicals shipped into, within or from the USA. The mandate of the United States Veterinary Biologics Program is to ensure that all veterinary biological products under Government jurisdiction in the USA are pure, safe, potent and effective. The Program is based on licensing, inspection and testing.

Risk assessment techniques, and effective strategies for risk management and risk communication, are essential tools for regulatory officials charged with the responsibility of developing requirements for licensing veterinary biological products and production facilities.

To accommodate scientific advances, heightened consumer awareness and the international harmonisation of requirements, regulatory agencies must continually review and update programme requirements. The author discusses programme updates initiated to address future needs of the United States Veterinary Biologics Program.


REGULATING AUTHORITIES

The United States Code of Federal Regulations, Title 9, Part 101.2 (9 CFR 101.2) defines biological products as ‘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’ (1). The Virus-Serum-Toxin (VST) Act (enacted in 1913 and amended in 1995) makes it unlawful to sell worthless, contaminated, dangerous, or harmful veterinary biologicals, or to ship veterinary biologicals in or from the United States of America (USA), unless they are prepared in a licensed establishment in

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compliance with United States Department of Agriculture (USDA) regulations (2). The following types of products are exempted from this licensing provision:

- products prepared by a person solely for administration to animals owned by that person
- products prepared by a veterinarian for use in his/her own licensed practice under a veterinarian/client/patient relationship
- products prepared by a person operating a State-licensed facility solely for distribution of a product within the State of production, in a State which has a USDA-approved State regulatory control programme for veterinary biologicals.

The VST 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 biologicals, and to inspect manufacturing facilities, manufacturing processes and the veterinary biological product itself. The Act (as amended) requires a USDA permit to be issued prior to the importation of a veterinary biological product, and gives USDA the authority to test such products prior to importation, if desired. The Act also provides for the issuance of conditional or special licences for products on the basis of purity, safety and a reasonable expectation of efficacy, to deal with an emergency situation, limited market, specific local situation, or other special circumstance.

In case of violation, the Act (as amended) permits USDA to revoke or suspend licences for establishments and/or products, and product permits, provided that the licensee or permittee is given the opportunity for a hearing prior to such action. The Act also gives authority for detention, seizure and condemnation of products, and injunctions against products or establishments. Violators are also liable to criminal action, which could lead to a fine or imprisonment.

**ORGANIZATION OF AUTHORITIES**

Within USDA, the authority for administering the VST Act (as amended) has been delegated to the Animal and Plant Health Inspection Service (APHIS). Within APHIS, the following units each have specific responsibilities and coordinate their activities within this context:

a) Veterinary Biologics (VB) – a technical ‘staff’ located in Hyattsville, Maryland – is responsible for the following:

- development of licensing and permit requirements
- review of licence and permit applications
- development and publication of policy and procedures in the form of regulations, standard requirements, memoranda and notices.

b) Veterinary Biologics Field Operations (VBFO) – a ‘line’ (executive) unit located in Ames, Iowa – is responsible for the following:

- inspecting licensed establishments and establishments seeking a licence
- conducting and coordinating investigations of suspected violations
- receiving consumer complaints of unsatisfactory field performance of products and determining when complaints require appropriate action by APHIS
- reviewing the testing of each batch of product to ensure compliance with established requirements prior to authorizing release for marketing.

c) The National Veterinary Services Laboratories (NVSL) – containing Veterinary Biologicals Laboratories – are also located in Ames, Iowa, and are responsible for the following:

- developing new test methods to ensure the purity, safety and potency of veterinary biologicals
- developing and providing references for use in such tests
- conducting surveillance tests to monitor the quality control procedures of the licensed manufacturer
- conducting pre-licensing tests on all products
- providing scientific consultation on products during the licensing process
- testing products involved in consumer complaints when so requested by VBFO.

d) Regulatory Enforcement and Animal Care, which comprises a technical ‘staff’ and a field unit within APHIS, is responsible for investigation of alleged violations involving unlicensed persons, and ensuring compliance with the VST Act (as amended) and the regulations.

PERMITS FOR IMPORTATION OF PRODUCTS

Importation of a biological product into the USA requires that the importer first obtain a United States Veterinary Biological Product Permit, issued by APHIS. APHIS is authorized to grant three types of permits for this purpose, as follows:

- for research and evaluation
- for transit shipment only
- for distribution and sale.

Most importation permits are issued for research and evaluation; very few are issued for distribution and sale. In general, products manufactured in the USA and then exported may not be imported back into the USA. Under special circumstances, however, small quantities of such products may be imported under a permit issued for research and evaluation to conduct in vitro tests. Permits are issued to a person or firm within the USA: foreign producers do not receive a permit or licence. The permittee must be a legal entity within the USA. The label for such products must include the permit number issued by APHIS. Both the foreign producer and the permittee importing the product are listed on the label and are clearly distinguished.

A separate permit is required for each shipment of biological product to be imported for transit shipment or for research and evaluation. A permit granted for distribution and sale, however, allows importation on a continuous basis for marketing under the same conditions as a licensed product.

The regulations concerning the issuance of permits in 9 CFR 104 state that: ‘A permit shall not be issued for a biological product from countries known to have exotic diseases, including but not limited to foot and mouth disease, rinderpest, Newcastle
disease and African swine fever, if in the opinion of the Administrator, such products may endanger the livestock or poultry of this country. Conservative implementation of this regulation has severely limited the sources of veterinary biologicals entering the USA, as incidence of these diseases is widespread. In general, it has been easier to import killed products than live products, and it has been easier to import diagnostic products than products which are directly inoculated into animals.

RISK ASSESSMENT

The increased interest in the international marketing of veterinary biological products, as well as the Canada/USA Free Trade Agreement, the North American Free Trade Agreement, and other negotiations – such as the General Agreement on Tariffs and Trade (GATT; now World Trade Organisation: WTO) – have forced APHIS to focus on the harmonization of regulatory requirements and the need for fair competition in the marketing of animals, animal products and veterinary biological products. As a result, APHIS has developed regionalization and risk assessment procedures to facilitate international trade.

Formal risk analysis procedures have been used since 1986 to assess the risks associated with the release of live organisms into the environment. These principles are now being used to develop a risk analysis model applicable to assessing the risks associated with the importation of biologicals. Products evaluated by this model and found not to represent a risk to the health of livestock in the USA will be considered for importation under permit.

Informal procedures for risk assessment have been an integral part of the United States Veterinary Biologics Program since its inception. The VST Act identifies worthless, contaminated, dangerous or harmful products as the hazards to be addressed by the Program. Regulatory authorities must identify the risks associated with the production and use of veterinary biological products. Each product and its method of production must be evaluated during the licensing process and monitored after licensing, to determine the likelihood that these hazards will occur and the consequences if they do occur. If a significant risk is identified, risk management procedures must be established to mitigate such risks. APHIS uses data and other materials submitted in support of licence or permit applications to conduct this informal risk assessment.

PERMITS FOR DISTRIBUTION AND SALE

Products which enter the USA for distribution and sale must meet the same requirements as products prepared and licensed in the USA. However, the permittee must formally agree to cover all costs associated with a VBFO inspection of the production facilities in the foreign country and also any testing required at Plum Island Animal Disease Center.

As with licences for establishments and products, permits for importation of products for distribution and sale in the USA are designed to define and document what is being authorized and who is responsible for the production and distribution of the product to be marketed. Such permits also define the risk management procedures established to ensure the purity, safety, potency and efficacy of each product, and the accuracy of labelling.
Materials submitted in support of permit applications are considered to be confidential business information and are not subject to release under the Freedom of Information Act. However, applicants 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 their firm.

To obtain a United States Veterinary Biological Product Permit for Distribution and Sale, an applicant must file an application to APHIS (on APHIS form no. 2005). The application should indicate the type of permit desired, the name and address of the applicant who will be doing business under the permit, the actual name of the product, and the point of entry.

This application must be supported by the following additional materials concerning the establishment:

a) a copy of the articles of incorporation (if the applicant is a legal corporation)

b) plot plans and blueprints of the foreign production facilities and of the receiving, storage and distribution facilities in the USA, with a legend which provides a brief description of the activities performed in each room, including decontamination procedures and other precautions against cross-contamination

c) a certificate from the appropriate water pollution control agency, indicating that the facilities in the USA are in compliance with applicable water quality control standards

d) a short résumé describing the training and experience of those employees who will be responsible for essential steps in the production, testing and initial distribution of the product

e) written authorization from the manufacturer for unannounced inspections of the production facility and of all production records.

Prior to the issuance of a permit for distribution and sale of a product, VBFO personnel must inspect the foreign production facilities. Inspectors review the adequacy of record-keeping systems to document each step in production. They also review the construction and operation of the establishment to confirm that they are as represented in the blueprints and legends, and to ensure that conditions are acceptable for production of the veterinary biological products intended to be imported. Laboratory practices are observed to ensure that facilities are being operated at an acceptable standard. Quality control testing and other compliance requirements are reviewed.

VBFO personnel also inspect the facilities for receiving, storing and distributing the product in the USA. At this time, they train a person at the establishment to collect and submit valid samples from each batch of product for testing at the NVSL. The report of these inspections is forwarded to VB for consideration in the permit decision.

One permit is issued for each establishment, listing each of the products which may be imported. In accordance with 9 CFR 104, a fresh application must be filed and approved for each new product to be imported.

Permit applications must also be supported by the following information concerning each product:

- 'Outline of Production'
- changes to the legends which refer to the blueprints of the production establishment and describe where each step in production will take place
- sketches and/or final labels
- supporting data (which demonstrate the purity, safety, potency and efficacy of the product).

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

a) for each microorganism:
   - source and date of accession
   - isolation and passage history
   - strains present and proportion of each strain;

b) cultures:
   - method of identification of each microorganism
   - virulence and purity data
   - composition of all media
   - seed culture storage
   - inoculation technique;

c) harvesting:
   - handling of cultures and media
   - time from inoculation to harvest
   - technique for harvesting microorganisms;

d) step-by-step description of product preparation, from harvest of antigen to the finished product in final containers;

e) testing:
   - stages at which samples are collected
   - reference to applicable Standard Requirements (e.g. for tests conducted to ensure purity, safety, potency and efficacy of the product)
   - details of additional tests, giving minimum requirements for each satisfactory test;

f) other information:
   - final container sampling
   - calculation of expiration date
   - recommendations for use, dosage and route of administration.

The Outline of Production, plot plans, blueprints and legends which are produced and filed during the licensing process must be complied with. These describe the risk management procedures needed to ensure the purity, safety, potency and efficacy of products, and form the basis for a contract on the means of production. After the permit is issued, these documents and the regulations serve as the basis of in-depth inspections conducted at both the foreign production facilities and the establishment run by the permittee in the USA.
DATA REQUIREMENTS

Data must be provided to demonstrate the purity, safety, potency and efficacy of products manufactured in accordance with the Outline of Production. The use of a master seed, as the source of all seed for production, helps to maintain uniformity of production. In most cases, no more than five serial passages may intervene between the master seed and the final product.

Tests are conducted on master seed, master cell stock (i.e. primary cells or cell-lines used for the production of master seed), primary cells, ingredients of animal origin and the final product, to ensure compliance with standard test procedures in 9 CFR 113 (1).

Product ingredients must meet accepted standards of purity and quality. Master cell stock and ingredients of animal origin must be shown to be free of extraneous bacteria, fungi, mycoplasma and viruses.

Immunogenicity of the product must be demonstrated by statistically-valid vaccination and challenge studies in the target species. The vaccination must be conducted using the minimum level of antigen indicated in the Outline of Production, and using product at the highest passage level from the master seed which is permitted for production. The precise challenge method and the criteria for determining protection vary, depending on the immunizing agent.

Field efficacy studies have been accepted in the licensing of products, when an applicable 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 some cases, a combination of laboratory and field efficacy studies is needed to demonstrate efficacy.

The validity of each label indication must be established. In other words, each route or method of administration, each species of animal for which the product is recommended, and any claims for degree of protection must be substantiated prior to approval.

Potency tests are designed to correlate with the immunogenicity tests. Prior to release, each batch (production lot) is tested for potency. For killed viral or bacterial products, potency tests may be conducted using laboratory animals, target animals, or in vitro relative-potency parallel-line immunoassay methods. For live vaccines, potency tests generally involve bacterial counts or virus titration. The bacterial count of most live bacterial vaccines for release must be sufficiently greater than that required by the immunogenicity test, to ensure that when the vaccine is tested at any time prior to the expiration date the titre will be at least twice that used in the immunogenicity test. The virus titre for most live virus vaccines on release must be sufficient to ensure that, when the vaccine is tested at any time prior to the expiration date, the titre will be at least five times 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 estimates of stability, the product may be incubated at 37°C for a short time (e.g. one week), but these results should be confirmed by potency tests over a period equal to six months longer than the indicated useful life of the product.

Safety testing can consist of a combination of various studies. Intracranial, subcutaneous or intraperitoneal tests in mice are acceptable for the final product. For
anaerobes, the guinea-pig appears to be very sensitive for evaluating safety. Target animal safety data are also required.

Environmental safety must be addressed before the use of live viral or live bacterial vaccines outside of containment, in particular for live recombinant products. Live products must be characterized, to determine the potential for shedding from the host, survival in the environment and transmission to contact animals. Reverse passage studies are required to provide information on genetic stability and on what can be expected when vaccine is administered to animals in the field. Data from such studies - together with data from other studies on characterization, purity, identity and safety - should be used to complete the appropriate Veterinary Biologics Summary Information Format (3). APHIS will then use these data to conduct a risk analysis and prepare an environmental assessment. If the Administrator determines that the proposed action will have no significant impact on the environment, authorization may be given to conduct studies with the product outside of containment (3).

The risk analysis conducted by APHIS on such products includes risk communication. Copies of the risk analysis may be submitted for peer review to a special technical committee (an ad hoc committee of experts) or, if public health issues are involved, to the National Vaccine Program Office of the United States Department of Health and Human Services. The availability of the environmental assessment and the preliminary finding of no significant impact on the environment (FONSI) is announced in a Federal Register Notice, with a thirty-day comment period. Substantive comments from the public are reviewed and addressed in the final risk assessment. Alternatively, if the risk rating is low and – because of previous experience with the same type of product – APHIS has already addressed public concerns, or is confident from this experience that no public concerns of substance will be raised, the availability of the Environmental Assessment and FONSI is publicly announced in the Federal Register without a comment period. All documents related to the review process, including the risk analysis, are available to the public under the Freedom of Information Act (any confidential business information is deleted beforehand). Risk communication can be a complex, sensitive and time-consuming task, but it has been the key to successful approval of actions subject to the National Environmental Policy Act in the USA.

**FIELD SAFETY TESTS**

All veterinary biological products administered to animals must be tested for safety in the field before a licence or a permit for distribution and sale may be issued. Field safety studies are designed to detect unexpected reactions, including mortality, which may not have been observed during the development of the product. The manufacturer applies for authorization to conduct field safety studies after having prepared and tested the three pre-licence batches, and after VB has approved the results of the efficacy test. The manufacturer must meet the requirements indicated in 9 CFR 103.3 for shipping experimental products; this includes obtaining permission from the relevant animal health authorities in each State where the tests will be conducted.

The tests are performed at a variety of geographical locations, using large numbers of susceptible target animals which are not owned by the manufacturer. The test animals should represent all the ages and husbandry practices for which the product is indicated. The tested product should be from one or more of the three pre-licence batches imported under a permit for research and evaluation.
Prior to the field safety test, a detailed protocol is submitted to VB for review. This protocol should indicate the observation methods and the recording methods.

**SAMPLING**

Prior to the issuance of a permit for distribution and sale, manufacturers are required to produce three consecutive satisfactory batches of final product, in their production facilities, in accordance with the approved blueprints, legends and Outline of Production. These batches are imported to the establishment run by the permittee in the USA, under a permit for research and evaluation. Samples of these batches are then selected and forwarded to NVSL for testing to confirm the test results obtained by the manufacturer.

Batch samples are selected for testing – prior to the issuance of the permit and from each batch imported after the issuance of the permit – in accordance with the procedures given in 9 CFR 113.3 (1). The selection is made either by an APHIS employee or, more routinely, by an employee of the manufacturer, who has been designated and trained by VBFO. In addition to samples tested by the manufacturer and samples submitted to NVSL, the selector also picks representative final containers from each batch for storage at the temperature recommended on the label. The manufacturer keeps these reserve samples until six months after the expiration date shown on the label, and makes them available to APHIS upon request.

On satisfactory completion of all requirements, including review and acceptance of labels and circulars, a United States Veterinary Biological Product Permit for Distribution and Sale may be issued, and the batches of product released for marketing. For subsequent batches of product imported under the permit, the product may not be marketed until the following requirements have been satisfied:

- satisfactory test reports (APHIS form no. 2008) have been prepared and submitted to VBFO
- product samples have been submitted to NVSL for check testing
- release authorization has been received from VBFO.

Surveillance testing is conducted on 5-10% of batches. Any product found to be unsatisfactory by a standard requirement or outline test may not be released. Performance of the product after issuance of the permit is also monitored by VBFO through consumer complaints.

**ALTERNATIVE PERMIT PROCEDURES**

Licensing products for further manufacture has permitted split manufacturing procedures, where two or more licensed establishments work together to manufacture a product. These are regular licences for products which are permitted to be shipped only 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 a second company under a licence for further manufacture. The second company finishes the product and releases it under a normal licence. Licensing in this manner has permitted the industry to take full advantage of production capacity and to expand company product lines without major development costs. Permits for further manufacture may also be issued to permit split manufacturing of products between foreign and domestic manufacturers.
Sub-licensing of a licensed product from one company to another is also permitted. In this process, the company which has a licence for the product contracts to transfer to a second company the data, technology and materials necessary to manufacture 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 the master seed and master cell stock and conduct an immunogenicity test in a reduced number of target 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, and may also be invoked to support the issuance of a permit for importation of a product for distribution and sale.

**REVIEW AND UPDATE OF PROGRAMME REQUIREMENTS**

Although current programme procedures have served APHIS well, the need to accommodate scientific advances, heightened consumer awareness and the international harmonization of requirements demand that APHIS continually review and update its programme requirements. The veterinary biologicals industry has changed significantly since 1913. As science has advanced, so have the industry and the regulatory requirements. New methods of production have had major impacts on the number, type and quality of products developed. At present, the impact of biotechnology is becoming apparent, together with the development of another new generation of products, new concepts in preventive medicine, and new approaches to the production and testing of veterinary biological products.

As the industry has changed, regulatory procedures have also changed. APHIS has progressed from a programme of resident inspectors, which focused primarily on the production process and testing conducted by the licensee, to unannounced in-depth inspections combined with review of product test results and check testing in APHIS laboratory facilities. With each new method of production adopted by the industry, APHIS has been required to identify potential hazards and, through risk assessment, to develop appropriate risk management procedures – in the form of standard test requirements and regulatory procedures – to ensure the purity, safety, potency and efficacy of products.

As a result of this review process, APHIS has recognized several areas of its biologicals programme which require change. Some of these changes are already under way. For example, APHIS has begun to develop new post-licensing monitoring procedures to improve assessment of the performance of products after licensing. VBFO has informally surveyed all licensed firms about their systems for handling consumer enquiries and complaints. Comparing the advantages and disadvantages of various procedures will help in developing the best system for APHIS. Several firms have volunteered to participate with APHIS in a pilot project to set up this new system.

On 1 January 1993, APHIS began a biological product stability survey in conjunction with the Cow-Calf Health and Productivity Audit (CHAPA) of the Veterinary Services National Animal Health Monitoring System. In this joint project with VBFO and NVSL, data were collected from producers involved in CHAPA in five States, to evaluate the use and stability of veterinary biological products under typical field conditions. APHIS expects to continue participating in this type of study, in an attempt to obtain data which are more representative of the performance of products in the field.
VBFO is in the process of reviewing all of its management records and information systems. Some 23,000 batch records are currently reviewed each year, in addition to several hundred requests to consider special situations relating to both facility operations and release of batches. VBFO is examining ways to make these systems easier for both the licensed firms and APHIS, and to ensure that the work of VBFO is really effective. The use of computerized systems for electronic transmission, review and storage of these data is being explored.

Veterinary Biologics Staff is continuing its efforts to develop procedures along the lines of established good laboratory practice to provide greater assurance of the integrity of data submitted in support of licensing requests. These efforts are a response to inspection findings suggesting deficiencies in record-keeping in the conduct of field and laboratory studies by the industry.

VBFO has been asking industry to suggest some incentives for companies to install quality assurance/quality control programmes for the internal monitoring of compliance with APHIS requirements. Industry is showing a keen interest in the wider implementation of such programmes. VBFO feels that such procedures would provide an effective supplement to the current inspection and testing programme.

APHIS has relied on Outlines of Production, blueprints, legends, in-depth inspection procedures and general regulations, to ensure that good production procedures are used in the manufacture of products. Review of this process suggests the need to develop a system of good manufacturing procedures to provide consistent high standards of production throughout the industry.

VB has initiated a programme of developing documents on general licensing considerations and on specific product licensing considerations. The purpose is to provide guidance to staff officers involved in the licensing process, in an effort to achieve greater uniformity of staff review of licence applications. A ‘purged’ form of these documents (with confidential business information removed) will be made available to the industry. New summary information formats have also been developed to provide guidance for licensees in the submission of risk assessment data in support of licence applications for some modified live products and all recombinant-derived products. These formats should assist licensees in the preparation of their applications, as well as making the review of data more efficient.

Major efforts will be made in the next few years to prepare and publish new Standard Requirements for killed products, incorporating the use of in vitro testing based upon relative-potency parallel-line immunoassays. These standards will include master seed immunogenicity testing for the certification of references, as well as procedures for the maintenance and re-certification of these references. Some of the first standards to be published will be for Escherichia coli bacterins, Leptospira bacterins and tetanus antitoxin. Others will follow, as resources permit.

In response to consumer complaints suggesting poor duration of immunity for licensed Erysipelothrix rhusiopathiae bacterins, NVSL initiated studies on the duration of immunity of this product, and also the preparation of a new reference standard for potency testing. A new Standard Requirement will be published, which includes procedures for establishing duration of immunity as part of the target animal immunogenicity test.

Other products are also being reviewed to determine whether problems exist concerning duration of immunity, and whether labelling should be amended to provide more complete information on the re-vaccination intervals required to maintain immunity. All applications for the licensing of products which have not previously been licensed must be supported by duration of immunity data.
CONCLUSIONS

The authors have examined the requirements for the issuance of permits for importing veterinary biological products into the USA and the use of risk analysis and risk assessment procedures in conducting and updating the biologicals programme. APHIS is moving towards higher and more appropriate standards based on current scientific knowledge. Risk assessment procedures can assist efforts to develop regulatory requirements which ensure the availability of pure, safe, potent and effective products to the consumer.
establezcan los procedimientos de preparación y comercialización de productos biológicos de uso veterinario, tanto en lo que concierne a la exportación como a la importación o el mercado interior. El mandato del Programa sobre Productos Biológicos Veterinarios de los Estados Unidos es asegurar que todos los productos de este tipo que circulen bajo la jurisdicción gubernamental estadounidense sean puros, seguros, activos y eficaces. El programa está basado en la concesión de licencias y en la realización de inspecciones y pruebas.

Las técnicas de evaluación de riesgos, junto a estrategias efectivas de manejo de riesgos y de comunicación, constituyen herramientas esenciales para los funcionarios de la oficina reguladora, encargados de definir los requisitos para la concesión de licencias a productos biológicos veterinarios y a las instalaciones de fabricación de tales productos.

Con objeto de adaptarse a los progresos científicos, al creciente grado de conciencia de los consumidores y ala armonización internacional en cuanto a los requisitos a cumplir, las oficinas encargadas de la reglamentación deben revisar y actualizar continuamente el contenido de sus programas. El autor comenta el proceso de actualización iniciado con el fin de satisfacer las futuras necesidades del Programa sobre Productos Biológicos Veterinarios de los Estados Unidos.


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REFERENCES

