

# Regulatory requirements for vaccine authorisation

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## Summary

Vaccines are one of the most important tools available in the prevention and control of diseases in animals. It is therefore of the utmost importance that when vaccines are used, such use should meet with the requirements of the World Organisation for Animal Health *Terrestrial Animal Health Code* and must be authorised by the recognised licensing body in the country/region where the vaccines are to be used, in accordance with the three key criteria of quality, safety and efficacy.

This article provides a comprehensive and comparative description of the regulatory requirements in place for veterinary vaccines in major regions of the world, highlighting the similarities and pointing out also where there are differences. Recent advances in harmonisation of such testing requirements achieved through the International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products (VICH) are also described. The contents will provide a valuable guide to those engaged in the research and development of vaccines globally, and reassure those involved in the prevention and control of animal diseases that veterinary vaccines, when fully authorised and used according to the label instructions, are safe and efficacious.

## Keywords

Efficacy – Harmonisation – International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products (VICH) – Quality – Regulatory requirements – Safety – Veterinary vaccine.

## Introduction

Vaccines for animals, like all other veterinary medicines, have to be licensed by the relevant authorities charged with that responsibility in the country or region where the products are to be marketed. The authorisation process has to ensure that the medicinal product is of adequate quality and purity, that it is safe and that it works in the target species as claimed, for the indication/treatment for which it is intended.

Whilst society rightly demands that medicines, including vaccines, are licensed according to very high standards, the regulatory environment should not be so risk-averse in the demands made on sponsors of new products that innovation and investment in research and development are stifled, and the availability of adequate veterinary medicines compromised.

Veterinary vaccines, like those produced for human use, are therefore authorised according to high standards of

quality, safety and efficacy (taking account of the risk/benefit balance for each product under consideration) and these three major criteria are mostly defined in a similar way in the major markets around the world. However, there is variation between different countries, such that regulatory dossiers have often to be tailored for different markets. This adds to the already considerable expense which companies incur when researching and developing a new medicine, which can take over a decade and cost as much as 50 million euros.

These high costs are often the cause of additional problems in the veterinary sector, which differs considerably from the human medicine sector. Because the investment needed to bring new products to the market place is so large, vaccines for so-called minor species, where the potential market size is small (e.g. rabbits, goats and some species of poultry) rarely get developed, because the return on investment is not attractive enough for the animal health companies involved in marketing them. As a result many vaccines needed for use in minor species are just not available and licensed vaccines for one species may not be suitable for use in another species, which can result in a potential conflict for practising veterinarians in their duty of care and welfare to their patients.

During the development of a new vaccine the marketing authorisation holder must subject the vaccine to various tests defined in the legislation and guidelines, and these are sometimes revised. If such changes arise when a new product is well into its development phase, the consequences can be grave, with further costs being incurred to generate additional data to satisfy the newly imposed changes in requirements.

Such unpredictability certainly drains reserves for investing in new products and curbs investment in new technology and innovation as well. Fortunately, regulatory authorities are now more aware of such constraints, and are prepared to collaborate with the animal health industry to set more realistic requirements that facilitate the development of new medicines, whilst at the same time removing hurdles that can delay the time it takes to bring badly needed new products to market.

## Procedures for licensing veterinary vaccines

This section describes the procedures which potential applicants wishing to license vaccines in the major animal health markets around the world need to follow. The conditions under which the different authorities will consider applications for licensing, and the requirements which have to be satisfied are also covered to a degree that

will provide the reader with a good understanding of the rigorous regulatory systems in place to ensure that only high quality, safe and efficacious vaccines come onto the market place.

Safety is of course of paramount importance. The determination of safety is fundamentally a determination that the benefits of the product outweigh any potential risks, not only to the target species being vaccinated, but also to the user/administrator of the vaccine, the environment, and in the case of animals from which food is derived, the consumer as well.

The major regulatory authorities essentially have similar guidance on how to apply for a licence and a synopsis of the actual data required with reference to the differences between the various regions is provided in the next section.

Applications are generally submitted to the authority in charge of licensing medicines and these can be separate veterinary regulatory departments within the Ministry of Agriculture, stand-alone agencies within governments or even parts of a joint regulatory department with responsibility for human medicines as well. The applicant, normally a pharmaceutical company, has to be legally established in the country/region concerned and constituted under civil or commercial law to ensure that obligations for compliance with the legal-regulatory pharmaceutical framework are fully adhered to.

What follows is a summary of the systems in place, the authorities responsible and the type of information required.

### Japan

Veterinary drugs are under the control of the Ministry of Agriculture, Forestry and Fisheries (MAFF), which issues the licence/market approval for each vaccine following a review of the application dossier by various committees charged with assessment of the data. The standard approval time for a new vaccine is up to one year, excluding any time required for responding to requests from the Ministry for additional data from the applicant. The approval of a conventional vaccine listed as a monograph in the Standards of Veterinary Vaccines for National Assay does not require renewal, whereas the approval of a vaccine containing a new class of antigen or new combination of antigens requires renewal after six years following the initial approval.

### United States of America

Applications for licensing have to be submitted to the Center for Veterinary Biologics (CVB) which is part of

Veterinary Services (VS), a division of the Animal Health and Plant Inspection Service (APHIS) of the United States Department of Agriculture (USDA). The agency allows phased filing, which allows for the submission of results from studies as they become available instead of having to assemble a complete dossier for submission. Documents needed for phased filing are described in Veterinary Services Memorandum No. 800.50 and consist of three major packages: Application for Product License, Supporting Data for Product License Application, and Requests to Conduct Field Studies. As stated in this memorandum, the applicants are encouraged to interact with CVB personnel as necessary, to facilitate submissions. The licence has no expiration date and does not need to be renewed as long as product is produced on a regular basis. The CVB supports a serial release system; each serial produced is submitted to the CVB for review, possible testing and official release.

## European Union

Potential applicants have a choice of routes to authorisation of vaccines in the European Union (EU). If the vaccine is derived from biotechnology then the application must be filed with the European Medicines Agency (EMA) in London, through the so-called 'centralised procedure' and the dossier is assessed by the Committee for Medicinal Products for Veterinary Use (CVMP) within a legislative time frame of 210 days, excluding the time taken for companies to provide additional data to the Committee if requested to do so. If the Committee is in favour of the application it issues a positive opinion which is then transferred into a Community marketing authorisation by the European Commission in Brussels, giving the company the commercial advantage of allowing it to market the vaccine in all 27 member states of the EU. This route to licensing is also open to non-biotech vaccines if they are innovative and/or can be shown to have particular advantages for animal health. Shortly after the Community Authorisation is published in the *Official Journal* of the EU, the EMA publishes on its website a European Public Assessment Report (EPAR) which provides a detailed summary of the CVMP assessment, excluding proprietary information about the product considered to be confidential. EPARs of all vaccines authorised through this procedure are to be found on the EMA website ([www.ema.europa.eu](http://www.ema.europa.eu)).

Alternatively, if the vaccine is not derived from biotechnology or is innovative, but the applicant only wishes to market the product in a few of the 27 EU member states, then the submission of the dossier can be made through a national procedure followed by the mutual recognition of this approval by other EU member states or through the new decentralised procedure, in which the applicant selects the member states in which they wish to

market the product and these are all included in the assessment procedure from the outset, with one regulatory agency acting as the reference member state that leads the procedure. With mutual recognition procedures the dossier is submitted to the regulatory authority of one member state (the reference member state), who undertakes the assessment, and once approved, the authorisation to market is mutually recognised by the other member states where the company has filed the dossier (the concerned member states). Public Assessment Reports for vaccines authorised through this route are also soon to be made public.

## Australia

All vaccines must be registered by the Australian Pesticides and Veterinary Medicines Authority (APVMA) in accordance with the Agricultural and Veterinary Chemicals Act 1994 and the Agricultural and Veterinary Chemicals Code Act 1994 and other supporting legislation. Once APVMA registration is granted, state by state registration is not required.

## Presentation of dossiers

Details of the responsible authorities and the appropriate legislation for authorisation of vaccines in the various major markets are provided in [Table I](#).

With all these authorities, the dossier is presented and submitted according to the local requirements. However, the submission is generally required to be formatted in a structured manner and must include an administrative part which will include detailed information on the applicant company, the provision of samples if required, information on the manufacturing site, evidence of conformance to Good Manufacturing Practice (GMP), and details of marketing authorisations/licences granted elsewhere. Details on the product itself and its characteristics are included in this section, as is information on the proposed packaging and labelling of the vaccine.

The main part of the dossier is the technical section consisting of manufacture and control, followed by safety, preclinical and clinical documentation, respectively.

## Post-authorisation requirements

Regulation of vaccines does not, however, end with the issuing of a marketing authorisation. The post-authorisation phase is just as important in the product's life cycle as that prior to its introduction: the requirement to monitor for any potential adverse reaction to a vaccine

**Table I**  
**Summary details of the responsible bodies and the legislation in place for authorising vaccines**

Country	Department responsible	Pharmaceutical legislation
<b>Japan</b>	National Veterinary Assay Laboratory, Ministry of Agriculture, Forestry and Fisheries, Tokyo	Pharmaceutical Affairs Law No. 145 Series of 1960
<b>United States of America</b>	Center for Veterinary Biologics, Animal Health and Plant Inspection Service, United States Department of Agriculture	Title 21 of the United States Code (Nos 151-159), with implementing regulations in Title 9 of the Code of Federal Regulations (Nos 101-122)
<b>European Union</b>	Innovative and biotechnology vaccines: European Medicines Agency, Unit for Veterinary Medicines, London, United Kingdom  Conventional vaccines: European Union Member State Competent Authorities*	Regulation No. 726/2004 of the European Parliament and of the Council  Directive 2004/28/EC of the European Parliament and of the Council
<b>Australia</b>	Australian Pesticides and Veterinary Medicines Authority	Agricultural and Veterinary Chemicals Act 1994 and the Agricultural and Veterinary Chemicals Code Act 1994

\* see <http://www.hevra.org/directory.asp>

once licensed is an integral part of the regulatory system for most authorities.

In most countries, therefore, the licence holder is required to have in place an appropriate means of monitoring the vaccine in the field, i.e. they must carry out pharmacovigilance/vaccinovigilance. With marketing and use of a product in large numbers of animals under normal field conditions, valuable information about the safety profile of the product is gathered. This post-marketing monitoring assists in the detection of adverse events that occur infrequently in large populations and would not ordinarily be recognised in pre-authorisation safety studies. If any potential safety problems are detected, the product sponsor and the regulatory authority collaborate on the appropriate measures to address identified issues. For this purpose the regulatory systems in force have very specific guidelines enshrined in law as to the obligations for reporting adverse drug reactions, the content and timing of such reports, and the actions incumbent on the licence holder in following up with the appropriate investigations.

## Technical data requirements

What follows is a detailed presentation of the testing requirements in the major regions of the world for authorising vaccines, which enables a comparison to be made of the differences which may exist, and which are extremely important for companies who may be intending to register and commercialise products on a global basis. Details of the registration requirements are provided for the EU, the United States of America (USA), Japan and Australia, thus providing a global overview of the

framework of the systems for authorising vaccines in different parts of the world.

It is important first of all however to draw attention to efforts that have been ongoing for a number of years to harmonise such requirements. The International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products (VICH) was officially launched in April 1996. This is a trilateral programme between Japan, the USA and the EU aimed at establishing harmonised technical requirements which meet quality, safety and efficacy standards, minimising the use of test animals and reducing the costs of product development. A number of guidelines have been established or are in the process of being established to harmonise the requirements for biologicals, and details of these can be found on the VICH website ([www.vichsec.org](http://www.vichsec.org)). Australia, Canada and New Zealand are observers to VICH and also implement the adopted guidelines in their regulatory systems.

## Requirements for the registration of veterinary vaccines in the European Union

### Categories of veterinary vaccines

Vaccines exist against viral, bacterial, fungal or parasitic infections. These can be based on live, attenuated, or inactivated agents. Within these categories complete causative agents (whole cell vaccines) or parts of an agent (subunit or vector vaccines) may be used to obtain protection. Because the vast majority of existing vaccines

are used against viral or bacterial infections this article will mainly focus on the requirements for live and inactivated vaccines of these types.

## Basic registration requirements

Although regulations may differ, in general, all authorities aim at licensing only those products that meet a number of basic requirements. Only vaccines whose quality, safety and efficacy have been proven obtain a marketing authorisation in the EU. A vaccine licence is initially issued with a five-year validity. After re-evaluation of the risk/benefit balance the marketing authorisation is renewed and is thereafter valid for an unlimited period of time. Apart from direct EU law, companies should also take into account other legislation that is applicable in Europe, e.g. the European Pharmacopoeia (Ph. Eur.). In the Ph. Eur. general requirements as well as specific tests for starting materials or the final product (vaccine monographs) are laid down.

The current EU criteria which veterinary vaccines must meet are outlined below.

## Quality

### Manufacture

Since licensing of veterinary vaccines was formally introduced in the EU in 1981 it has been a requirement that both the active ingredient (antigen) and the finished product (vaccine) must be manufactured according to GMP. Even before that time, some national regulatory agencies already insisted on GMP for the manufacture of veterinary vaccines.

In addition to a marketing authorisation for each country in which the product is to be marketed, a manufacturing licence must be obtained for each production facility where the vaccine (or part thereof) is being produced. Data must be presented to show that the manufacturer is able to produce the vaccine in a consistent manner.

Regular internal and external audits aim at surveying the quality control procedures in place. Moreover, a vaccine producer must employ at least one qualified person who is, without prejudice to his relationship with the holder of the manufacturing authorisation, personally responsible for release of vaccine onto the market.

The quality of starting materials used for production, whether bought from a commercial supplier or produced in-house, must be evidenced. In the case of ingredients purchased from external suppliers, the commercial supplier has his own quality assurance system. In addition, controls on incoming-goods are performed by the vaccine manufacturer (e.g. growth promotion assays for serum batches used to cultivate certain vaccine strains) to further

guarantee the quality of the material. The vaccine manufacturer must declare a specification for each starting material and ensure that each batch purchased meets the acceptance limits of the specification. Many starting materials are listed as monographs in the Ph. Eur. Even these must be tested to ensure compliance with the current monograph. Additionally, requirements exist for starting materials of biological origin which are commonly used for vaccine production (e.g. exclusion of extraneous agents).

Seed stocks of the vaccine strain are laid down in a seed lot system, making passages from the master seed to establish a bank of working seed from which all production batches are produced. The history of the isolation and previous passages of the initial master seed must be known in order to minimise the risk of transmission of spongiform encephalopathies (TSE).

### Testing

#### Purity

A veterinary medicinal product must be sterile, i.e. free from any contamination with live microbiological agents. In the specific case of live vaccines the product should not contain live microbiological agents other than the vaccine strain(s). In order to achieve this, the master seed stock from which all subsequent vaccine batches will derive must be absolutely free from extraneous agents.

For virus vaccines this means freedom from contaminating bacteria, fungi, *Mycoplasma* species, and extraneous viruses; for bacterial vaccines it means freedom from contaminating bacteria and fungi. The expression used to determine freedom from contamination for bacterial vaccines is 'purity'. To confirm the absence of extraneous agents in virus vaccines, validated assays must be used, i.e. spiking of the seed virus with a series of extraneous agents should reveal positive test results.

#### Identity

In addition to purity, the vaccine strain must be tested to ensure it is identified as the correct strain. Identification is pursued beyond the strain and species to subtypes or serotypes as appropriate.

#### In-process and finished product testing

To ensure that each batch of a commercial vaccine is equivalent in quality and will therefore be safe and efficacious, the manufacturer must register all relevant in-process tests as well as tests to be performed on the finished product, giving limits of acceptance that must be met before the batch can be released for sale. Once these test methods and limits have been approved by the regulatory agencies, they become mandatory tests for placing the vaccine on the market. The type of tests performed may include:

- sterility/purity tests for absence of contamination

- antigen quantification tests (e.g. titre, cell count, optical density, enzyme-linked immunosorbent assay [ELISA], etc.)
- tests for complete inactivation (inactivated vaccines only)
- physico-chemical tests, e.g. pH, viscosity of emulsion, quantity of residual inactivant, etc. (mainly valid for inactivated vaccines)
- adjuvant content tests, if an adjuvant is included in the formulation
- tests to determine the titre (live vaccines) or potency (inactivated vaccines) of finished product (see the section on 'Potency' below)
- tests to verify the safety of the product in the target species.

Each batch of vaccine must be tested for absence of local and systemic effects in animals of the target species using an overdose ( $2 \times$  for inactivated vaccines and  $10 \times$  for live vaccines) administered by a route recommended on the label. The marketing authorisation holder may apply for a variation to the licence to withdraw this test following satisfactory results from at least ten batches and satisfactory pharmacovigilance reporting.

In addition, the manufacturer must prove that the quality of the vaccine is guaranteed until the end of its shelf life. To demonstrate this, stability testing must be performed on at least three batches of vaccine in the final container. The vaccine must be tested at regular intervals throughout the proposed shelf life. If a preservative is included in the vaccine (multidose containers only), its effectiveness during the shelf life must be tested using a method described in the Ph. Eur.

## Safety

Clearly, the product must be safe for the target animal, but it must also be documented that the product does not pose a danger to humans or to other animals that may come into contact with the product, or to the environment. Experimental data obtained with batches with the highest potency or titre (see below) must be generated in specially designed experiments, i.e. in accordance with European Good Laboratory Practice (GLP) standards.

In addition to the safety of a single dose, the safety of an overdose and repeated doses of the vaccine must be shown. The rationale for demonstrating the safety of a repeated dose is because some vaccines, especially inactivated ones, have a primary vaccination course consisting of two doses, followed by a booster dose six or twelve months later. For a vaccine with this recommendation, demonstration of the safety of repeated

administration of the product will consist of monitoring the safety (e.g. injection site reaction, clinical symptoms) following three administrations of the vaccine with appropriate intervals between each administration.

There are additional special requirements for live vaccines. A live vaccine strain must be stable, i.e. should not revert to virulence during consecutive passages. Depending on the agent, recombination or genomic reassortment needs to be evaluated. In general, vaccine is produced within a limited number of passages from the master seed stock. Usually this is limited to five passages for virus vaccines, however, there is no limit for bacterial vaccines. The safety of the vaccine strain at the lowest passage number is shown in animal studies using the most sensitive target animal/species. Issues such as the spread of the vaccine strain and dissemination in the vaccinated animal need to be taken into account where appropriate. In addition, studies on the immunological functions may have to be carried out where the vaccine might adversely affect the immune response.

If the vaccine is intended for administration to pregnant animals, safety during pregnancy must be shown using a batch of vaccine at its highest potency or titre. It must be demonstrated that vaccination has no adverse effect on the reproductive performance of the target animal.

Depending on the starting materials used for manufacturing the vaccines, studies may need to be carried out on possible residues if they are considered to be present at levels having pharmacological activity. Negative effects on the environment must also be assessed.

Additional requirements have to be met for vaccines containing genetically modified organisms.

## Efficacy

Data must be provided that support the efficacy claims. In other words: a product must be able to do what is claimed on the label (e.g. reduce virus shedding, control clinical signs, etc.). Preferably, these data are obtained from field trials performed under Good Clinical Practice-veterinary (GCPv) conditions and from laboratory studies in which, if possible, validated experimental challenge models are used. Data showing efficacy from laboratory studies must be provided using batches with the lowest potency or titre (see below).

## Potency

The manufacturer must provide data that guarantees the immunising capability and thereby protective effect of a product over the entire shelf life. This is a major hurdle in the development of inactivated vaccines. Confirmation of the protective effect of a specific immunogen is usually established by vaccination-challenge experiments.

Such experiments are preferably not used as routine batch potency tests as these involve animal experimentation and are normally of several weeks duration. An alternative test should ideally be developed which is carried out on each batch of finished vaccine and has predictive value as to the efficacy of that particular batch. As the efficacy of the vaccine batch has to be guaranteed over its entire shelf life the batch potency test must provide assurance that the vaccine will remain potent throughout its shelf life. This assurance is provided by testing the vaccine's stability over the period of the shelf life plus an additional three months beyond for a minimum of three batches. The pass level for batch release is set at the minimum level that was shown to be efficacious in the target animal. If the protective mechanism of immunity against a specific pathogen is not known, it may take years before an accurate potency test can be developed.

## Special requirements

### Registration of the label claim

In the EU, each marketing authorisation is granted with an approved Summary of Product Characteristics (SPC). This document reflects the results of the supportive data provided in the registration dossier. It includes a description of the composition of the vaccine, the target species, the route of administration, the supported vaccination schedule, the claims, any contra-indications or adverse effects that might be seen, the shelf life and a description of the vaccine containers and storage conditions. If the marketing authorisation holder wishes to change any of the statements made on the SPC, this can be achieved by varying the licence with the appropriate supporting data.

#### *Target animal*

The animal species for which the product is intended must be specified and it should be clearly stated if the vaccine is designed for use in a specific category of animal, e.g. broiler chickens not breeder chickens. The suitability of the product for use in pregnant animals should also be stated. An important factor may be the presence of maternal immunity in young animals. If this may affect the induction and onset of vaccine-induced immunity then it must be studied. Results may prompt the manufacturer to recommend not vaccinating animals below a certain age.

#### *Route of administration*

Some products can be administered through different routes, e.g. oral application or injection. For each of these routes of administration safety and efficacy experiments must be performed to support the claims made. These claims may differ depending on the route of administration, and this must be clearly stated in the dossier and on the label and leaflet (known as the 'circular' in US regulations).

### *Onset and duration of immunity*

Apart from the information requirements imposed by regulatory authorities, most of the label information relating to the onset and duration of immunity is included on the label because of market demand. All claims must be documented and supported, either by existing literature or by experimental data. This may take years of research, particularly if, for instance, one claims that a product has a shelf life of three years. Specific efficacy claims must also be supported by data. If, for example, the label claims that the duration of immunity is one year and that a yearly vaccination will sustain this level of immunity, data must be provided that show that one year after the primary vaccination course, animals are significantly protected (in some cases by experimental challenge infection) and also that animals that receive a single booster vaccination one year after initial vaccination are still protected one year later. This involves more than two years of experimentation.

### *Compatibility*

If the label claims that the vaccination may be carried out within two weeks of vaccination with another product (concurrent use) then this must also be documented with supportive data. This can become a complicated task depending on the target animal. For example, the life span of the average broiler chicken is 6 to 7 weeks and these animals very often need to be vaccinated against a series of pathogens (amongst others, Marek's disease virus, Newcastle disease virus, infectious bronchitis virus, Gumboro disease virus) very early in life, i.e. before the age of 14 days. Compatibility of the new product with all of these vaccines must be shown if this use is claimed. This will involve safety studies as well as efficacy studies. Obviously, if it is claimed that a vaccine can be physically mixed with another product and subsequently administered, data from safety and efficacy studies must be presented to support such a claim.

### *Recommendations*

Specific recommendations have to be provided that aid in the most efficient use of the product. Such recommendations vary with the particular product. Obvious recommendations are to only vaccinate healthy animals in the case of vaccines for prophylactic use. Apart from vaccines against cattle ringworm, no therapeutic vaccines are currently licensed, but they are envisaged for the future (e.g. for the treatment of leishmaniasis). In the case of live vaccines against pathogens that can be controlled by chemotherapeutics, it may be important to recommend a withdrawal period after chemotherapeutic treatment before administering the live vaccine. Likewise, it may be sensible to advise minimisation of the risk of concurrent infections during the vaccination period, as these could interfere with the induction of the proper immune response.

## Post-marketing requirements

Following the granting of a marketing authorisation in the EU, each batch of vaccine that has satisfactorily undergone all the finished product testing can be placed on the market in all European member states. In some countries, however, a batch may only be placed on the market after official release by the competent authority in the EU member state concerned. For a few vaccines, e.g. rabies vaccines, release onto the market is not authorised until an officially appointed laboratory has re-tested the batch and declared that it is in compliance with the registered specification.

As with other regions of the world, pharmacovigilance is strictly applied in the EU and has become the acceptable replacement for the previous requirement to apply to renew a marketing authorisation every five years.

# Requirements for the registration of veterinary vaccines in the United States of America

## Who regulates veterinary vaccines?

The Center for Veterinary Biologics (CVB), under the umbrella of the USDA, is tasked with implementing the provisions of the Virus-Serum-Toxin Act passed in 1913. The CVB is divided into two sections: Policy, Evaluation, and Licensing (CVB-PEL) and Inspection and Compliance (CVB-IC). The CVB regulates vaccines, bacterins and bacterial extracts, antibody products, diagnostic products, antitoxins, toxoids, and other products of biological origin. As stated in the section on EU requirements, this article will focus mainly on the requirements for viral and bacterial live and inactivated vaccines.

## Basic registration requirements

Veterinary biologics manufactured in the USA must have a US Veterinary Biologics Establishment License and a US Veterinary Biological Product License for each separate product. The requirements for labelling, for manufacturing processes, and for obtaining an establishment licence and a product licence, can all be found in Title 9 of the Code of Federal Regulations. Additional guidance can be found in published memorandums and notices. Veterinary biologics must be proven to be pure, safe, potent, and effective prior to licensure and upon release of each serial. Applicants are encouraged to interact with CVB-PEL personnel as necessary to facilitate submissions.

Contact with the CVB is via a person designated as the official (primary) liaison. The CVB sends all official mail to the official liaison. Alternate liaisons can be designated to assist the liaison in signing certain documents such as official correspondence and APHIS Form 2015, which is used for submission of labels, circulars, and 'Outlines of Production'.

## Quality

### Manufacture

Each Veterinary Licensed Establishment in the USA must submit and maintain the qualifications of supervisory personnel and facility documents, which include blueprints, plot plans, and legends. The manufacturer is required to review and update these documents annually.

A manufacturer is required to submit and obtain CVB approval of an Outline of Production detailing key steps in the manufacturing process for each licensed product. Data on three consecutive pre-licensing serials must be presented to show that the manufacturer is able to produce the vaccine in a consistent manner. Consistency of production is monitored by the agency through the use of the approved Outline of Production, release tests, and unannounced inspections.

Seed stocks of the vaccine strain are laid down in a seed lot system, making passages from the master seed to establish working seed stocks from which all production batches are produced.

As stated in the section on the European Union, the history of the isolation and previous passages of the initial master seed must be known in order to minimise the risk of transmitting TSEs. Cell lines used in the production process must also follow the seed lot system. Both master seed stocks and master cell stocks must be approved by the CVB for use in production of a licensed product.

### Testing

#### Purity

The Outline of Production for all veterinary biological products must include a description of the procedures that are to be followed in order to keep the product free from any viable contaminating microbiological agents. In the specific case of live vaccines, the product should not contain microbiological agents other than the vaccine strain(s). Consequently, it must be ensured that the master seed stock from which all subsequent vaccine serials will be derived is free from extraneous agents. Regulations require that master seed and final container testing be described in the Outline of Production. Final containers of each serial and subserial are tested as follows: for virus vaccines, demonstration of freedom from contaminating bacteria, fungi, mycoplasma, and, in some cases, specific extraneous viruses; for bacterial vaccines, demonstration of

freedom from contaminating bacteria and fungi. The word used to describe freedom from extraneous microorganisms or material is 'purity.'

### Identity

In addition to purity, master seeds for all product types and final container samples of vaccines of each serial or subserial must be tested to ensure it is identified as the correct strain. Subtypes and serotypes may also be tested if thought necessary. Identity of final container samples may be demonstrated in conjunction with potency testing by fluorescent antibody staining, serological methods, challenge of vaccinates, or other *in vitro* methods, such as ELISA techniques.

### Finished product testing

To ensure that each serial (batch) and subserial of a commercial vaccine is equivalent in quality and will therefore be safe and efficacious, the manufacturer must file in the Outline of Production all relevant tests to be performed on the finished product, giving limits of acceptance that must be met before the serial or subserial can be released. Only the CVB can release a product for distribution and sale. In the US system, a manufacturer submits a summary of all relevant tests on an official form (APHIS Form 2008) for each serial and subserial. Once a serial or subserial is produced and representative samples are submitted, the serial or subserial may be randomly picked for confirmatory testing. After the firm submits APHIS Form 2008 at the conclusion of their testing, if the serial or subserial is not chosen for confirmatory testing or if the confirmatory testing has been completed satisfactorily, the product is released by the CVB for distribution and sale. The type of tests performed may include:

- sterility/purity tests for absence of contamination
- antigen quantification tests (e.g. ELISA and tests to determine titre, cell count, optical density, etc.)
- tests for complete inactivation (inactivated vaccines only)
- physico-chemical tests, e.g. pH, viscosity of emulsion, quantity of residual inactivant, etc. (mainly valid for inactivated vaccines)
- tests to establish titre/potency (titre mainly for live vaccines) of finished product (see section on 'Potency' below)
- safety tests in target or laboratory animals.

All tests are described in Title 9 of the Code of Federal Regulations and are based on use of the final product in poultry or non-poultry, and on product type, i.e. live or inactivated (see the next section on 'Safety').

In addition, the manufacturer must prove that the quality of the vaccine is guaranteed until the end of its shelf life. To demonstrate this, several serials of vaccine must be tested at regular intervals throughout the proposed shelf life.

### Safety

It must be shown, of course, that the product is safe for the target animal, but documentation must also be provided which demonstrates that the product is safe for the environment, for other animals, and for humans that may come into contact with the product. Extensive literature searches into the background for each master seed candidate are required prior to CVB approval of that master seed. The manufacture may be required, for certain products, to conduct risk analysis to assess the potential effects of the product on the safety of animals, public health and the environment. An environmental assessment will be prepared to address the requirements of the National Environmental Policy Act of 1969. The manufacturer, in agreement with the CVB, may conduct additional tests if needed to provide additional proof of the safety of the strain used.

Prior to licensure, a target animal field safety study following product label directions must be conducted. The studies are generally performed on at least two serials and in at least three geographical locations. Animal numbers should take into account label recommendations such as age, site of administration, sex, breed, pregnancy, protection claims in neonates, and any other distinguishing features. If the vaccine is intended for administration to pregnant animals, additional data may be required.

A live vaccine strain must be stable, i.e. should not revert to virulence during consecutive passages. Depending on the agent, recombination or genomic reassortment needs to be evaluated. Vaccines are produced within a specified number of passages from the master seed stock. Usually this is limited to five passages for virus vaccines and higher for bacterial vaccines. The safety of the vaccine strain at the lowest passage number is shown in animal studies using the most sensitive target animal/species. Aspects such as spread of the vaccine strain and dissemination in the vaccinated animal need to be taken into account where appropriate. Also, studies on the immunological functions may have to be carried out where the vaccine might adversely affect the immune response.

### Efficacy

Data must be provided that support the efficacy claims. There are four predefined claims supported by the CVB: prevention of infection, prevention of disease, aid in disease prevention, and aid in disease control.

Manufacturers are encouraged to interact with CVB when planning the protocol for these studies, which are required to be laboratory controlled studies, not field performance studies. Experimental product used in the studies must be prepared from the highest passage from the master seed stock, and if cell culture is used in manufacturing it must be prepared at the highest passage from the master cell stock allowed in the Outline of Production. The studies must be conducted at or below the minimum antigen level needed for efficacy, which is also specified in the Outline of Production.

### Potency

As in the EU, the manufacturer must provide data that guarantees the immunising capability and thereby protective effect of a product. *In vivo* or *in vitro* testing can be used for this purpose. Both the CVB and manufacturers are moving away from animal testing toward *in vitro* tests.

For release of finished product, a pre-calculated titre value is added to the minimum antigen level demonstrated for efficacy. For live virus vaccines, the titre required through dating must be at least  $0.7 \log_{10}$  greater than the titre used in the efficacy study. For live bacterial vaccines, the bacterial counts required through dating must be twice those used in the efficacy study. Expected loss in stability or via steps in production should be added to these values, normally  $0.5 \log_{10}$  to the live viral products.

### Special requirements

#### *Registration of the label claim*

In the USA, the licence is granted with a CVB approved Outline of Production, label, and circular. The CVB assigns a 'true name' and a product code number that is used to differentiate the biological product from others. This true name must be listed prominently on all packaging components. The Outline of Production includes the history and test methods used to support the master seed stocks. The Outline includes the passage details, source of media used, in-house testing as well as serial release testing, expiration dating confirmation, efficacy confirmation, release titres, and description of final product containers, use of the product, and storage conditions. Changes to the Outline of Production must be pre-approved by the CVB.

#### *Target animal*

As with the EU regulations, clearly, it must be specified for which animal species the product is intended. In addition, the category must be stated, e.g. whether the product can be used safely in pregnant animals or is intended for specific use, such as for broiler chickens as opposed to breeder chickens or layer flocks. The CVB also grants an autogenous licence for inactivated viral or bacterial products. This type of product has a very special use in the flock or herd of origin.

#### *Route of administration*

Just as in the EU, studies must be performed to support the safety and efficacy claims of each route of administration (e.g. oral application, injection) and the claims must be clearly stated in the Outline of Production and on the label and circular.

#### *Onset and duration of immunity*

Special efficacy trials are designed around claims for onset and duration of immunity. Trials to test duration of immunity claims take the form of efficacy studies in which the animals are vaccinated according to the directions for use, and then challenged at a specified time, i.e. one year or three years post vaccination. Data from non-challenge studies (publications, studies not used to support licensure, etc.) must be pre-approved through the CVB before a manufacturer is allowed to make such claims.

#### *Compatibility*

For those vaccines used in combination, additional supporting data must be submitted. Combination products have two or more antigens in one vial or are prepared by mixing two or more separately licensed products in the field. Of course, the efficacy of each fraction must be proven, but a lack of interference must also be established between fractions. Challenge or serology models may be used. These studies may be used to recalculate the minimum potency level at which the product will be released.

## Requirements for the registration of veterinary vaccines in Japan

### Quality

#### Manufacture

Both the antigen and the vaccine must be manufactured according to GMP. A manufacturing licence must be obtained for each production facility where the antigen or vaccine is being produced or stocked for sale. An overseas production facility which intends to export vaccines to Japan must be accredited by MAFF in Japan in advance. This accreditation is renewed every five years. A marketing authorisation must be obtained by a marketing licence holder prior to sale of the vaccine in Japan.

As a precaution against the risk of contamination with bovine spongiform encephalopathy strict regulation is applied to the use of any raw materials of ruminant origin for production of veterinary vaccines regardless of the intended target animal species. For example, milk and

dairy products from the United Kingdom and Portugal cannot be used, and bovine serum and bovine serum products from the USA have to be certified as not originating from a TSE-affected bovine herd in the USA.

### National assay

In Japan, each batch of a veterinary vaccine is tested by the National Veterinary Assay Laboratory (NVAL) for conformance to the respective monographs published in the Standards of Veterinary Vaccines for National Assay prior to release of the batch on the market. This 'national assay' process requires the sponsor of a veterinary vaccine application to propose those testing methods which are easily practicable by the NVAL in the registration dossier. The Standards also stipulate general test methods that are used in the national assay.

While some of these test methods have been globally harmonised thanks to the VICH initiative, some other test methods remain unique to Japan and the sponsor often carries out the test according to the method used in Europe or the USA and then repeats the same test according to the Japanese method (sterility test for example) when exporting a vaccine to Japan from the USA or Europe.

MAFF is currently planning to introduce a full seed lot system in the near future and the national assay process will be simplified or eliminated depending on the type of vaccine to be tested.

### Potency test

In Japan, traditionally an *in vivo* potency test has been required as part of the batch release control procedure of practically all veterinary vaccines, including live vaccines. This is usually performed by a serological technique such as neutralisation, haemagglutination inhibition or ELISA, but sometimes a challenge test is also performed. The potency test has to be correlated with the efficacy of the vaccine. Since this is not a requirement for a live vaccine in the USA or Europe, a sponsor usually has to develop a validated *in vivo* potency test for registration of a live vaccine in Japan.

### Abnormal toxicity test

The abnormal toxicity test in mice and guinea pigs, or a toxicity limit test in either of these species, which is a modified version of the abnormal toxicity test, is required as part of the batch release control of all mammalian vaccines. The abnormal toxicity test is not routinely conducted in the USA or Europe.

### Safety test

Safety testing in the target animal species is required in the batch release control of all veterinary vaccines except for

large animal vaccines (swine, cattle and horses). In the case of poultry vaccines, reporting of non-specific mortality in the safety tests is not accepted unless the cause of death is shown to be irrelevant to the vaccine, whereas a certain number of non-specific deaths are accepted in the safety test in chickens in the USA and Europe.

### Physico-chemical and biological properties

Physico-chemical properties such as morphology of the vaccine strain and biological properties such as virulence of the vaccine strain in various cell lines or laboratory animal species, and comparison with a standard reference strain should be included in the registration dossier. In addition, data on immunogenicity, growth characteristics and, where applicable, interference between antigens should be submitted. For a live vaccine, data on identification of the marker of attenuation and the strain as well as the marker stability, shed and spread, and reversion to virulence should be submitted. An outline of production is also required. Three pilot batches should be manufactured and tested according to the proposed specification and test methods.

### Stability

In the stability test, three pilot batches are stored under the proposed storage conditions for the proposed shelf life period. Each individual vaccine sample should be within the proposed specification at all time points throughout the storage time, whereas a statistical approach is often used in the interpretation of the stability test in the USA and Europe. Stability after reconstitution of the vaccine, where applicable, and changes at room temperature should also be investigated.

### Safety

In Japan, a target animal safety study requires that a group be given a recommended dose and another group be given an overdose equivalent to 100 times the recommended dose for live vaccines or 10 times the recommended dose for inactivated vaccines, administered in divided doses to avoid causing physical harm to the test animals. The study should normally use the final vaccine, i.e. the vaccine that is to be registered. Use of target animal safety data obtained with a maximum combination vaccine for the registration of a combination vaccine containing fewer antigens is generally not accepted, unlike in the USA or Europe. For a vaccine for food-producing animals containing adjuvant, depletion of adjuvant must be investigated in addition to normal histopathology. An appropriate withdrawal period is established based on depletion of the adjuvant and resolution of the lesions at the injection site. All the target animal safety studies must be conducted in accordance with the GLP guidelines.

## Efficacy

Efficacy studies consist of basic studies supporting efficacy and field trials. Basic studies supporting efficacy should normally include:

- establishment of minimum effective antigen dose
- establishment of minimum protective antibody titre against the target disease
- determination of duration of immunity
- establishment of the relationship between the antigen dose and the antibody titre
- analysis of the relationship between local immunity and the protection induced
- comparison of response between different ages, breeds and routes of administration
- analysis of protective mechanism
- determination of the relationship between the maternally derived antibody and the protection induced.

In addition, data must be presented on onset of immunity, the effect of booster vaccination and the effect of other vaccines that are likely to be administered concurrently. Field trials, usually at two or more locations in Japan, are required to provide safety and efficacy data from a minimum of 60 animals for a mammalian vaccine or 200 birds for a poultry vaccine. Usually, all animals, or just certain individual animals, have to be monitored periodically for serological responses to each antigen contained in the vaccine. Field trial data collected in foreign countries are accepted if the epidemiology and the trial protocol are similar, but even in this case, at least one local field trial is required. Field trials must be conducted in accordance with the GCP guidelines.

## Special requirements

### Generic vaccine

In the case of a vaccine that is considered equivalent to those vaccines that are already registered in Japan (e.g. a vaccine containing a different strain but having similar biological properties, similar composition, similar dosage and administration instructions and the same indication) a sample of the vaccine has to be submitted to the NVAL for confirmation of equivalence. Once such confirmation is obtained from the NVAL, the registration process subsequently becomes much simpler compared with that of a new vaccine.

### Food animal vaccine

The dossier on a new food animal vaccine is reviewed not only by MAFF but also by the Food Safety Commission

(FSC), which reports to the Prime Minister's Office on the possible impact on human health. The review by the FSC consists of several steps, including an invitation for public comment, and it usually lengthens the regulatory approval process by 6 to 12 months.

### Recombinant vaccine

Detailed requirements for registration of a recombinant vaccine in Japan remain somewhat vague and the guidelines for application of the Cartagena Protocol to veterinary vaccines are still awaited. To date, no recombinant vaccine has been approved in Japan.

## Requirements for the registration of veterinary vaccines in Australia

Australia is considered an advanced country from the point of view of registration of vaccines. Vaccine products are registered and their accompanying labels are approved by the government regulator prior to marketing. The basis of approval of vaccines is essentially similar to that in the EU or USA, but the process of registering differs in some respects.

### Pre-marketing requirements

Australia maintains a national registration scheme for veterinary products which is administered by the federal government on behalf of the Australian States and Territories. All vaccines must be registered by the Australian Pesticides and Veterinary Medicines Authority (APVMA) in accordance with the Agricultural and Veterinary Chemicals Act 1994 and the Agricultural and Veterinary Chemicals Code Act 1994 and other supporting legislation. Once APVMA registration is granted, state by state registration is not required.

All registered vaccines must be manufactured in a facility approved by the APVMA under the Manufacturer's Licensing Scheme. Mutual Recognition Agreements exist between the APVMA and some other countries and others are recognised under the Overseas GMP Scheme.

Although the APVMA has its own format for the presentation of data for the registration of vaccines, the content is essentially the same as that for other advanced countries (it is particularly similar to the data required in the EU). Data presented in the format of another country is generally acceptable so long as effective cross-referencing is provided in an Australian format dossier. The APVMA does not accept phased filing in the same way as the USDA. Australia has so far adopted all VICH guidelines without

any modification in the case of vaccines. It is a default requirement that local efficacy data is presented for vaccines, but this is negotiable with the APVMA on the basis of scientific argument; this requirement is more strongly enforced for economic animals than for companion animals.

A summary of each application for registration is published on the APVMA website at the start of the review process together with, for some applications, a list of supporting trial data for the purposes of establishing data protection. All new active ingredients (including new antigens) are subject to public comment before registration is finalised. At the time of registration, a summary is published of advice on the application received from other authorities or external assessors.

Imported vaccines or locally produced vaccines containing animal-origin materials of overseas origin require prior clearance by the Australian Quarantine and Inspection Service (AQIS) (see the section on 'Biosecurity' below).

Vaccines derived from biotechnology require prior clearance or exemption by the Office of the Gene Technology Regulator.

The APVMA publishes guidelines for the time frame for registration review to which it aims to adhere. The final act in the registration process is the submission and approval of the final product label, which must conform to local guidelines.

### **Post-marketing requirements**

Finished-product testing and release is carried out by the licensed manufacturer. The maintenance of appropriate records is a requirement of GMP compliance and is subject to periodic inspection. There is no requirement for batch release by the regulatory authority (but see 'Biosecurity' below).

All registrants are required to maintain a pharmacovigilance programme and lodge annual or, in some cases, real-time reports.

An annual renewal fee for each registered vaccine is payable to the APVMA, together with a levy on sales. Periodic re-submission of data is not a requirement unless requested by the APVMA under its Existing Chemical Review Program.

### **Biosecurity**

Australia enjoys a fortunate freedom from a number of infectious animal diseases and guards this status jealously. Its strict quarantine regulations and policies are established by Biosecurity Australia and policed by AQIS. An *in vivo* permit must be obtained from AQIS for each vaccine, or animal-derived raw material intended for use in a vaccine, imported to Australia. All imports are checked at the border for correct documentation. Application for such a permit requires submission of a substantial body of biosecurity data and a potentially prolonged review period (no published time frame). Permits issued for the import of vaccines are generally for a finite period and usually require a compliance audit to be conducted by AQIS on each serial imported. The stringency of these requirements should not be under-estimated.

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## Exigences réglementaires liées à l'agrément des vaccins

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### Résumé

Les vaccins sont l'un des principaux outils pour prévenir et maîtriser les maladies animales. Dès lors, il est d'une importance capitale que les vaccins soient utilisés conformément aux prescriptions du *Code sanitaire pour les animaux terrestres (Code terrestre)* de l'Organisation mondiale de la santé animale (OIE) après avoir été évalués par l'organisme chargé de délivrer les autorisations de mise sur le marché dans le pays/la région où les vaccins doivent être utilisés, en respectant les critères fondamentaux de qualité, de sécurité et d'efficacité.

Les auteurs examinent et comparent les exigences réglementaires en vigueur pour les vaccins vétérinaires dans les principales régions du monde, en soulignant les similitudes ainsi que les différences constatées. Ils décrivent également les derniers progrès accomplis dans le domaine de l'harmonisation des exigences relatives aux tests, grâce à la Coopération internationale sur l'harmonisation des exigences techniques applicables à l'enregistrement des médicaments vétérinaires (VICH). Cet article fournit des orientations utiles pour tous ceux qui s'occupent de recherche et de développement de vaccins dans le monde, tout en apportant aux personnes chargées de la prévention et de la lutte contre les maladies animales la garantie que les vaccins vétérinaires, dès lors qu'ils sont dûment autorisés et utilisés suivant le mode d'emploi prescrit, sont sûrs et efficaces.

### Mots-clés

Coopération internationale sur l'harmonisation des exigences techniques applicables à l'enregistrement des médicaments vétérinaires (VICH) – Dispositions réglementaires – Efficacité – Harmonisation – Qualité – Sécurité – Vaccin vétérinaire.



## Requisitos de las reglamentaciones relativas a la autorización de comercialización de vacunas

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### Resumen

La vacunación es uno de los instrumentos existentes más eficaces para prevenir y controlar las enfermedades animales. Por consiguiente, es indispensable que su administración se conforme a las disposiciones del *Código Sanitario para los Animales Terrestres* (denominado también "*Código Terrestre*") de la Organización Mundial de Sanidad Animal (OIE) y haya sido autorizada por el organismo habilitado para la concesión de licencias de comercialización del país o región interesados, de conformidad con los criterios clave relativos a la calidad, inocuidad y eficacia.

Los autores exponen las exigencias sobre las vacunas veterinarias de las reglamentaciones en vigor en las principales regiones del mundo de manera pormenorizada y comparada, destacando sus similitudes y diferencias. También reseñan los últimos avances realizados por la Cooperación Internacional para la Armonización de los Requisitos Técnicos relativos al Registro de Medicamentos de Uso Veterinario (VICH) en la armonización de los requisitos que han de atenderse durante las pruebas. Este artículo, que constituye una valiosa guía para quienes trabajan en la investigación y el desarrollo de vacunas en todas partes del mundo, demostrará a quienes participan en la prevención y el control de las enfermedades animales que las vacunas de uso veterinario, una vez aprobadas y administradas conforme a las instrucciones del fabricante, son inocuas y eficaces.

### Palabras clave

Armonización – Calidad – Cooperación Internacional para la Armonización de los Requisitos Técnicos relativos al Registro de Medicamentos de Uso Veterinario (VICH) – Eficacia – Inocuidad – Requisito reglamentario – Vacuna veterinaria.



