

CHAPTER 2.3.2.

THE ROLE OF OFFICIAL BODIES IN THE INTERNATIONAL REGULATION OF VETERINARY BIOLOGICALS

SUMMARY

The official control of veterinary biologicals is vested in various national and regional organisations that differ in their approach to ensuring the quality, safety and efficacy of the products. International harmonisation of regulations concerning biological products did not begin until well after those concerning chemically defined products. The first biological products for veterinary use were not manufactured and distributed until the end of the nineteenth century. They were often produced under unsophisticated conditions, and distributed or sold without any control other than those of their manufacturers. Later, each manufacturer developed its own standards. In Europe, these were subject to State controls as early as 1895 for certain diagnostic products (e.g. mallein, tuberculin) or vaccines. Gradually the conditions for international harmonisation of standards evolved, beginning with the comparative testing of products being issued by different European laboratories. It was only in the second half of the twentieth century that national laws covering veterinary biologicals were imposed. These demanded that precisely defined techniques be followed before biological products for veterinary use could receive relevant regulatory approval. This was followed by considerable efforts to harmonise these national regulations, first at the regional level (notably in Europe and the Americas) then at the global level, notably by the World Organisation for Animal Health (WOAH, founded as OIE) with the publication of the first edition of the WOAH Manual of Standards for Diagnostic Tests and Vaccines in 1989.

World-wide harmonisation of standards for veterinary biologicals will be of help to Chief Veterinary Officers who must follow the instructions given in the WOAH Terrestrial Animal Health Code, as they apply to all biological products for use in international trade. It will also be of assistance to vaccine producers, who have expressed their wish for world-wide harmonisation of rules for relevant regulatory approvals so as to simplify and facilitate marketing of their products. Evidently, it will also be of interest to farmers and to consumers, who would benefit from the fact that the quality, safety and efficacy of the products that they use would have been assured to a uniformly high level.

The different sections of this chapter will review and compare regulations from the regions of the world that have made most progress in this field and will describe current attempts at harmonising these regulations on an international scale.

Note: *In this chapter the term 'veterinary biological' will be taken to include vaccines for use in animals, antisera for use in animals, and in-vivo diagnostic preparations.*

A. REGULATION OF VETERINARY BIOLOGICALS: PRESENT SITUATION

1. In Japan

1.1. Introduction

Medicinal products that are exclusively used for animals, including veterinary biologicals, are under the jurisdiction of the Ministry of Agriculture, Forestry and Fisheries, and securing their quality, efficacy and safety is stipulated in the Law on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical devices (the Pharmaceutical and Medical Device Law) (Government of

Japan, Act No.145 of 10 August, 1960). Since 1972, registration procedures have been developed with the aim of rationalising the examination procedure and facilitating the acquisition of approval. These procedures are stipulated in the Pharmaceutical and Medical Device Law and other related regulations. Consequently, a speedy and simple examination procedure has been achieved with emphasis on the assurance of quality, safety and efficacy. The Food Safety Commission was established in the Cabinet Office, Government of Japan, in July 2003. In the case of approval examination, re-examination and re-evaluation, all veterinary vaccines, except products of dogs and cats, must comply with the Food Safety Basic Law.

1.2. Regulations governing the approval and quality assurance of veterinary biologicals

1.2.1. Application for relevant regulatory approval

A person intending to distribute veterinary biologicals shall obtain the license for marketing approval holders and the marketing approval for each biological from the Minister of Agriculture, Forestry and Fisheries after an intensive reviewing process by the National Veterinary Assay Laboratory (NVAL). The application for the marketing approval should be submitted with designated appended documents, such as those on clinical studies. Of the latter, the safety studies and clinical studies using the target animal species should have been performed in compliance with GLP (Good Laboratory Practice) and GCP (Good Clinical Practice). It is also required, as a condition of approval, that the manufacturing and quality control of the product complies with GMP (Good Manufacturing Practice). A marketing approval holder shall comply with the standard of GQP (Good Quality Practice) and the GVP (Good Vigilance Practice).

Regulatory approval to manufacture veterinary biologicals is issued by the Minister of Agriculture, Forestry and Fisheries and must be renewed every 5 years.

1.2.2. National assay

After receiving the marketing approval, each batch of the veterinary biological must be examined by the NVAL according to the procedures of the Assay Standard for Veterinary Biological Products, except for those approved as “seed-lot system”-based products (Anon, 2002b; Makie, 1998). A marketing approval holder must apply it to the national assay.

1.2.3. Re-examination and re-evaluation

Re-examination is performed on newly approved veterinary biologicals. Usually a field assessment of the veterinary vaccines is conducted over a period of 6 years following initial approval of the veterinary vaccines. During this investigation, the efficacy and the safety are re-examined.

Re-evaluation is performed on availability of approved products after marketing by order of the Minister of Agriculture, Forestry and Fisheries. This may happen when it is suspected that a veterinary biological does not conform to the latest standards of veterinary biological products.

1.2.4. Minimum requirement of veterinary biological products

The examinations provide information about the consistency of the manufacturing process and the quality of the product: manufacturing methods, properties of strains used for manufacturing, methods of quality control, methods of storage and shelf life, according to the standards given in the ‘Minimum Requirement of Veterinary Biological Products’ (Anon, 2002a). Any product that does not conform to these product standards cannot be manufactured, imported or marketed.

1.2.5. Cases of rejection of approval

When the quality of the veterinary biological that has been submitted for approval is found to be unsatisfactory, or its adverse effects are marked as compared with its indications, the product is judged to be of little value and approval is not given.

1.2.6. Cancellation of approvals

At the time of granting approval to market, the quality, safety and efficacy of the product are carefully examined with reference to the latest available technology. However, if scientific

knowledge acquired since the granting of approval indicates that there could be a health hazard associated with the product, re-examination and re-evaluation are performed and an order of 'cancellation of approval' may be made.

1.3. Procedure for marketing approval

When a person intends to market veterinary biologicals, an application for approval to market the veterinary drug must be submitted on a designated form to an official in charge of veterinary biologicals at the Ministry of Agriculture, Forestry and Fisheries. If the documentation is satisfactory, the application for approval to market, together with appended documents, are sent to and reviewed by the Secretariat of the Ministry of Agriculture, Forestry and Fisheries. At that time, a hearing may be conducted if necessary. The application is then discussed in the Pharmaceutical Affairs Sub-council, Pharmaceutical Affairs and Food Sanitation Council, and if any problems are not found, notice of approval to market the veterinary product is sent to the applicant.

2. In the European Union

2.1. Introduction

The pharmaceutical legislation of the European Union (EU), which has evolved over a 45-year period, covers both medicinal products for human and veterinary use. Harmonisation of requirements in the area of veterinary medicines began in 1981 with the adoption of Directives 81/851/EEC and 81/852/EEC, laying down common requirements for manufacturing and marketing authorisations, based on the evaluation of the quality, safety, and efficacy of the product. These Directives, and subsequent veterinary and human pharmaceutical legislation, were consolidated into Directive 2001/82/EC and 2001/83/EC for veterinary and human products, respectively. A series of detailed guidelines were first published in 1994 entitled 'Rules Governing Medicinal Products in the EU' (European Union, 1999). These have since been updated and describe in detail the legal basis for obtaining marketing authorisations, how dossiers should be compiled and how they should be assessed. These rules serve as extremely useful reference publications for any authority that is setting up a system for authorisation of veterinary biologicals. The rules were formally adopted and applied specifically to veterinary biologicals from 1993. Many additional measures were taken to further harmonise the procedures and the criteria for the evaluation of veterinary medicinal products, such as framework requirements and interpretive guidelines for their testing, principles and guidelines of GMP, and a Community procedure for the evaluation of high-technology products. However, granting of authorisations remained at the national level. As a consequence, although applications were evaluated on the basis of these harmonised criteria and procedures, and in some cases simultaneously by the authorities of the Member States, there were differences in the decisions reached by the Member States on individual products. This was why in 1990 the Commission proposed a new system for marketing authorisation for medicinal products, which was adopted by the Council of Ministers in 1993 and entered into force on 1 January 1995.

One of the first consequences was the creation of the European Medicines Evaluation Agency (EMEA), now the European Medicines Agency (EMA).

Legislation for veterinary products (Regulation 726/2004 and Directive 2004/28/EC) was published in May 2004. This legislation, for the main part, came into force in 2005 and resulted in a number of changes aimed at strengthening public and animal health, and environment protection by reinforcing requirements and controls. Directive 2001/82/EC already stated that the competent authorities cannot grant a marketing authorisation (MA) without having conducted a benefit-risk analysis. The document in the MA dossier must "demonstrate that the benefit bound to efficacy outweighs potential risk". But the relation between benefit and risk was not defined in that Directive. The new Directive gives the definition of the "risk-benefit balance": an evaluation of the positive therapeutic effects of the veterinary medicinal product in relation to the risk".

The risks concern:

- i) The animal;
- ii) The user of medicinal product;

- iii) The consumer liable to ingest animal food containing medicinal products residues;
- iv) The environment.

With the revision of the Directive, if no medicinal product is available for 3 consecutive years, its MA is secluded. Before the revision, the MA was renewed every 5 years. Now, a single renewal is required. The pharmacovigilance is reinforced.

Title IV of regulation 726/2004 related to responsibilities and administrative structure of the European Agency came into force in April 2004 in order to face the consequences of the enlargement of the EU.

Annex I of Directive 2001/82/EC was further amended to take account of scientific and technical progress. In particular, two new systems were introduced for particular immunological veterinary medicinal products and by derogation from the provisions of Title II, Part 2 Section C on active substances:

- i) The first was based on the concept of a master file (vaccine antigen master file, VAMF), becoming a stand-alone part of the marketing authorisation application dossier for a vaccine, which contains all relevant information on quality concerning each of the active substances that are part of the veterinary medicinal product. The stand-alone part may be common to one or more monovalent or combined vaccines presented by the same applicant or marketing authorisation holder.
- ii) The second was aimed at permitting authorisation of vaccines against antigenically variable viruses in a way that ensures that the most effective measures can be taken swiftly by the Community against the incursion or spread of three epizootic diseases (foot and mouth disease, avian influenza and bluetongue), leading to the concept of a multi-strain dossier. A multi-strain dossier means a single dossier containing the relevant data for a unique and thorough scientific assessment of the different options of strains or combinations of strains permitting the authorisation of vaccines against antigenically variable viruses.

In September 2015 the European Commission launched a revision of the legal framework for veterinary medicinal products in EU (i.e. directive 2001/82/EC). The purpose of this revision was to increase the availability of veterinary medicinal products, to reduce the administrative burden on commercial producers, to improve the functioning of the internal market for veterinary medicinal products and to assess the possibilities of having an improved response to antimicrobial resistance related to the use of veterinary medicines. The revision will contribute to the realisation of certain actions in the Animal Health Strategy.

2.2. The role of the European Medicines Agency

In 1995, a new European system for the authorisation of medicinal products came into force. After 10 years of cooperation between national registration authorities at the EU level and 4 years of negotiations, the Council of the EU adopted, in June 1993, three directives and one regulation, which together form the legal basis of the system (Brunko, 1997).

The EMEA was established by Council Regulation 2309/93/EEC of 22 July 1993 (*Official Journal* No. L214, 24.8.1993). In December 2009, the EMEA officially launched a new organisational structure and visual identity, and became the European Medicines Agency (EMA). This was the second major reorganisation of the Agency's services since it was established in 1995, and resulted from the expansion of the Agency's responsibilities and tasks, giving it a reinforced role in the protection of public and animal health in Europe.

This agency formulates opinions and, apart from the administrative staff and the management board, is composed of two scientific committees: the CHMP (Committee for Human Medicinal Products) in charge of medicinal products for humans and the CVMP (Committee for Veterinary Medicinal Products) in charge of medicinal products for use in animals.

The CVMP is responsible for the evaluation of applications for marketing authorisation for products derived from biotechnology, for productivity enhancers, new chemical entities and other innovative new products. In addition, the CVMP makes recommendations regarding MRLs (maximum residue limits) for substances used in food-producing animals, and manages referrals when EU issues such as

concerns over the safety or benefit–risk balance of a medicine or a class of medicines need to be resolved. To support its activities, the CVMP relies on a pool of experts put at the disposal of the agency by the EU Member States. These experts may participate in any of the CVMP working parties. Among the working parties, the Immunologicals Working Party (CVMP/IWP) advises the CVMP on general policy issues such as the elaboration and revision of guidelines on immunological veterinary medicinal products (IVMPs). A scientific advice working party foreseen in regulation 726/2004 has been created. The aim of this working party is to advise applicants during the development phase of a veterinary medicinal product. The CVMP prepares scientific guidelines in consultation with the national competent authorities of the EU Member States, to help applicants prepare marketing authorisation applications for medicinal products for veterinary use.

Guidelines are intended to provide a basis for the practical harmonisation of the manner in which the EU Member States and the Agency interpret and apply the detailed requirements for the demonstration of quality, safety and efficacy contained in the Community directives. They also help to ensure that applications for marketing authorisation are prepared in a manner that will be recognised as valid by the Agency.

Immunological guidelines are provided, for instance, for general items, quality, stability, efficacy, summary of product characteristics (SPC), multi-strain dossiers and availability (minor uses or minor species), and are available on the EMA website at: www.ema.europa.eu

2.3. Current European procedures for marketing authorisation

At the time of the revision of the Community Code in 2004, the difficulties encountered in practice as well as jurisprudentially precise details were taken into account and modifications to various Community procedures were adopted: tightening of the conditions of examination and the safeguard clause, official recognition of the coordination group for mutual recognition and decentralised procedures (veterinary), arbitration and creation of a new procedure (decentralised procedure, see below). These provisions were introduced by the Directive 2004/28/EC amending Directive 2001/82/EC.

Four registration procedures for human and veterinary medicinal products have become available through this new legislation:

1. The centralised procedure allows a unique marketing authorisation (MA) to be obtained and made available in all the Member States. This applies to high technology products defined in the annex to the Regulation. It is optional for innovative medicinal products. This procedure was extended to veterinary vaccines covering animal diseases that are subject to Community prophylactic measures.
2. The national procedure allows an MA to be obtained for a medicinal product in a single country or in a country that will be the origin of a mutual recognition procedure.
3. The mutual recognition procedure: applications for authorisation of a product may still be obtained in a single Member State (the 'Reference Member State') by means of a national procedure. Following approval in the Reference Member State, applications may be made, if desired, to other 'Concerned' Member States for identical authorisations to be granted on the basis of '*mutual recognition*'.
4. The decentralised procedure, which was introduced in Directive 2004/28/EC, is the addition of the national one and the mutual recognition procedure, i.e. it is based upon the principle of mutual recognition of national authorisations. At the beginning of this procedure, all Member States are associated, but assessment is conducted by one reference Member State chosen by the applicant.

The most important change is the compulsory aspect of *arbitrage* in the case of a disagreement between Member States during the mutual recognition or the decentralised procedures. If a Member State considers that there is a serious risk to public health, a pre-arbitrage procedure must be carried out. In such a situation, an MA holder cannot remove his/her demand. The arbitrage allows a decision to be made on whether there is a "serious risk" with the use of the medicinal product. Finally, the decision (to grant or refuse the MA) is harmonised throughout the community.

2.4. Manufacturing authorisation and batch release control

In accordance with Directive 2001/82/EC, authorisation is also required for the manufacture of veterinary medicinal products, including immunologicals. This directive provides for regular inspections and stipulates that manufacture must be supervised by a 'qualified person', who certifies that each batch is in conformity with the approved specifications for the product. For the implementation of these requirements, the Commission has adopted Directive 91/412/EEC relating to the principle and guidelines of GMP, and published a detailed guide on GMP developed by a group of pharmaceutical inspectors from the Member States (European Union, 1999: Volume 4).

The directive also establishes GMP for active starting materials for medicinal products. This provision is reinforced through the provision of the opportunity for Member States to carry out inspections of active materials destined for the manufacturers of veterinary medicinal products.

Manufacturers are required to have the services of a qualified person at their disposal to certify that each batch of product has been manufactured and checked in accordance with the conditions for marketing authorisation. This is a basic requirement of the pharmaceutical legislation. In the case of batches imported from third countries, each batch has to undergo a full qualitative and a quantitative analysis of at least the active ingredients in the first Member State of import into the EU, under the supervision of a qualified person. Until this control by the qualified person has been carried out, a batch cannot circulate within the EU without further control. When the certificate is released, no more controls are necessary. In the special case of immunological veterinary medicinal products, an additional step may be introduced. Article 82 of Directive 2001/82/EC, as amended by Directive 2004/28/EC, of the European Parliament and the Council allows, for reasons of human or animal health, a Member State to request samples of each batch of a given IVMP to be submitted to a Competent Authority (CA) for official testing by an Official Medicine Control laboratory (OMCL) before it is placed on the market and establishes the conditions under which a restricted test list can be applied. This is referred to as 'Official Control Authority Batch Release'. OCABR performed by any given Member State must be mutually recognised by all other member states requiring OCABR for that product.

Article 81 of Directive 2001/82/EC allows a Member State, where appropriate, to ask a MA holder to provide documentation to a control authority or an OMCL proving that control tests were carried out in accordance with the methods laid down in the MA dossier. This is referred to as an 'Official Batch Protocol Review'. A goodwill agreement has been adopted by the Veterinary Batch Release Network (VBRN) to mutually recognise Official Batch Protocol Review (OBPR) certificates between Member States provided the procedure and rules codified by the network are followed. This legislation concerns EU/EEA Member States and is also applied by any state having signed a formal agreement, which includes recognition of OCABR, with the EU. Currently, Switzerland has done so via a Mutual Recognition Agreement (MRA) (source EDQM).

2.5. The role of the European Pharmacopoeia

The Convention on the elaboration of a European Pharmacopoeia (or international treaty) adopted at the Council of Europe in 1964, laid the groundwork for the European Pharmacopoeia as a guarantee of the quality of medicines produced in Europe.

The European Pharmacopoeia Convention has now been signed by 37 Member States¹ and the EU; moreover 27 European and non-European countries², and the World Health Organisation (WHO) have observer status. Close relations are maintained with the regulatory authorities of the European

1 Austria, Belgium, Bosnia and Herzegovina, Bulgaria, Croatia, Cyprus, Czech Republic, Denmark, Estonia, Finland, Former Yugoslav Republic of Macedonia, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, Montenegro, Netherlands, Norway, Poland, Portugal, Romania, Serbia, Slovakia, Slovenia, Spain, Sweden, Switzerland, Turkey, Ukraine, United Kingdom and the European Union. Member States must apply the standards of the European Pharmacopoeia.

2 Albania, Algeria, Argentina, Armenia, Australia, Azerbaijan, Belarus, Brazil, Canada, China (People's Rep. of), Chinese Taipei (Food and Drug Administration), Georgia, Guinea, Israel, Kazakhstan, Korea (Rep. of), Madagascar, Malaysia, Moldova, Morocco, Russian Federation, Senegal, Singapore, South Africa, Syria, Tunisia, United States of America and the World Health Organization. Observer States do not have to apply the European Pharmacopoeia standards. Some of them apply the standards on a voluntary basis.

Economic Area, where integration is developing through contact with the EMA and the implementation of common directives and guidelines on medicines for human and veterinary use.

The European Pharmacopoeia consists of monographs describing individual quality standards (set of control tests applicable to one ingredient) and general quality standards applicable to families of ingredients or to dosage forms, as well as general methods of analysis. It defines the minimum acceptable standards for products to be authorised within the European Union because compliance with monographs is a mandatory requirement within Directive 2001/82/EC. This requires that products must comply with the relevant specific monograph where one exists or with the general monographs where one does not.

The European Directorate for the Quality of Medicines & Health Care (EDQM) is the administrative entity in the Council of Europe that provides the secretariat services for the European Pharmacopoeia. EDQM creates, maintains and distributes the international standard reagents referred to in monographs of the European Pharmacopoeia, including standards for veterinary biologicals.

In 1990, the European Pharmacopoeia co-founded, with the Japanese Pharmacopoeia and the United States (US) Pharmacopoeia, the Pharmacopoeial Discussion Group (PDG); this group is working assiduously for harmonisation at the global level.

The European Pharmacopoeia Commission adopted several harmonised texts for veterinary vaccines. The safety tests and the tests for increased virulence performed during development of the vaccines were harmonised in the framework of harmonisation with VICH (International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Products; see below) Guidelines 41 and 44, and to ensure consistency with European regulations.

3. In the United States of America

3.1. Introduction

In the United States of America (USA), veterinary biologics or veterinary biological products are defined as all viruses, sera, toxins (excluding substances that are selectively toxic to microorganisms, e.g. antibiotics), or analogous products at any stage of production, shipment, distribution, or sale, that are intended for use in the treatment (prevention, diagnosis, management, or cure) of diseases of animals and that act primarily through the direct stimulation, supplementation, enhancement, or modulation of the immune system or immune response. The term biological products includes, but is not limited to, vaccines, bacterins, allergens, antibodies, antitoxins, toxoids, immunostimulants, certain cytokines, antigenic or immunising components of live organisms, and diagnostic components that are of natural or synthetic origin or that are derived from synthesising or altering various substances or components of substances such as microorganisms, genes or genetic sequences, carbohydrates, proteins, antigens, allergens, or antibodies.

3.2. Legal basis

The Virus/Serum/Toxin Act of 1913 (the 'VST Act'), as amended, 21 U.S.C. Sections 151 to 159, provides the legal authority for the regulation of immunologicals and biologicals for animal use in the USA. The regulatory programme implementing the requirements of the VST Act is administered by the Center for Veterinary Biologics (CVB), Animal and Plant Health Inspection Service (APHIS) of the United States Department of Agriculture (USDA). Administrative regulations, duly promulgated and with effect of law, are published in Title 9, Code of Federal Regulations, Parts 101 to 118 (2006). In addition, APHIS has issued programme guidance in CVB Notices, Veterinary Services Memoranda, Veterinary Biologics General Licensing Considerations, and the Veterinary Biologics Program Manual. These may be accessed on the CVB web site at www.aphis.usda.gov/vs/cvb.

The VST Act requires that products governed by the Act that enter channels of commerce be 'not worthless, contaminated, dangerous or harmful'. The regulatory scheme implementing these standards is structured to require manufacturers of these products to apply for licences prior to marketing, and to place certain evidentiary responsibilities on those applicants, i.e. manufacturers are required to demonstrate through the submission of certain information, research data, and test results that their

products are 'pure, safe, potent and efficacious'. The APHIS programme for immunologicals and biologicals for animal use regulates the manufacture and release of products on to the market through a system of licensing, inspection, testing and post-marketing surveillance that ensures that the statutory and regulatory standards are met.

3.3. Licensing and initial inspection

Any person or firm seeking to manufacture in the USA an immunological or biological for animal use must obtain from APHIS both a licence to manufacture at a specified facility (Establishment Licence), and a licence for every particular product to be manufactured (Product Licence). These licence requirements apply whether the product is to be released on to the US market or is to be exported to markets abroad. Typically, an applicant will request a facility licence at the same time as the licence for the first product. Once the facility licence and one product licence have been obtained, a firm that seeks to manufacture and market new products needs only to apply for additional product licences. A person or firm located overseas that seeks to market its product in the USA must also apply for marketing authorisation. In the case of an imported product, however, the authorisation is termed a 'permit' rather than a 'licence'.

To obtain a facility licence, the applicant must submit for approval the blueprint (that is, the architect's plan of the buildings) and blueprint legends for the facility. APHIS reviews these blueprints and legends to ensure that the facility will operate in a manner consistent with GMP. If the applicant subsequently makes any physical or operational changes to the facility, revised blueprints and legends must be submitted immediately.

To obtain a product licence, the applicant must establish the purity and identity of all master seeds and master cell stocks that will be used in the manufacture of the product, and must submit for approval a detailed outline of production. The outline of production includes not only the details of the method of product manufacture, but also a description of the procedures for collecting and submitting samples and for releasing batches. The applicant must also provide information regarding the professional and technical credentials of company personnel, and must identify a qualified individual (termed under US regulations as the 'government liaison') who acts as the official contact with CVB during the licensing process, and who is subsequently responsible for the submission of the firm's test reports in conjunction with the release of the product on to the market. The applicant is required to submit test data that demonstrate that the product produced in accordance with the outline is pure, safe, potent and efficacious. The applicant must submit to CVB laboratories samples of three consecutive batches of the product so that the results of the applicant's tests of the product can be confirmed.

Finally, before the facility or product licences are issued, the applicant's premises are subject to a comprehensive inspection by APHIS examiners. The inspection ensures that the facility is operating in a manner consistent with GMP by confirming that the establishment is configured in the manner set out in the approved blueprints and legends, that the production line is set up and operating in accordance with the approved outline of production, and that records are adequately kept and maintained for each step in production. The inspection also confirms that the applicant follows procedures consistent with GLPs, that the in-process and final product testing programme is conducted properly and appropriately documented, that the sampling is conducted properly, and that adequate procedures for determining and documenting the release of the product on to the market are in place.

3.4. Post-licensing inspection

Once a firm has been issued facility and product licences, APHIS will routinely conduct thorough follow-up inspections of the facility to ensure that the licensee continues to operate the establishment in accordance with the programme regulations and in the manner represented at the time of licensing. Post-licensing inspections are conducted unannounced periodically. If the licensee proposes any significant changes to the facility or to the method of production of a licensed product, APHIS retains the right to conduct a special inspection prior to approving the changes.

3.5. Testing

Each licensee is responsible for thoroughly testing all of its production processes and each serial (or lot) of every product prior to release on to the market. The type and amount of testing required

depends on the particular product, but is determined and approved by the regulatory authority prior to the issuing of the product licence. A qualified individual employed by the licensee ('government liaison') is responsible for selecting the samples to be tested, for monitoring the licensee's testing programme, and for certifying the test results to the regulatory authority.

At the same time that the firm selects its samples for its own in-house testing, it also selects samples to be submitted to the CVB laboratories. The CVB retains the right to conduct confirmatory testing. CVB then selects a percentage of the samples submitted for confirmatory testing to verify the accuracy and proficiency of the manufacturer's tests. The testing is conducted prior to marketing authorisation for each serial. By regulation, CVB policy stipulates that it is required to put its selected samples on test within 14 days of the date on which the samples are received; ordinarily, samples are put on test sooner than the 14-day limit so that the testing of production by the firm and the CVB proficiency testing programme are effectively being conducted at the same time.

When the firm receives the results of its own tests, the government liaison submits those results to the regulatory authority along with a batch release form, initiating the release procedure. If the batch has not been selected as part of the proficiency testing programme, or if it has been selected but the CVB tests confirm the company's test results, the release form is counter-signed by the regulatory authority completing the release procedure. If either the company tests or the proficiency tests indicate that the batch may be unsatisfactory, the batch is not eligible for release.

If the licensee makes a proposal to modify its facility or its operation in any way that could affect the purity, safety, potency or efficacy of the product, the regulatory authority may require the licensee to provide data demonstrating the purity, safety, potency and efficacy of the product as well as to submit samples of the product to CVB's laboratories for confirmatory testing.

3.6. Post-marketing surveillance

CVB operates a post-marketing surveillance programme to monitor the performance of products on the market. Under this programme, CVB typically learns of any problems relating to product quality through consumer reports or complaints, although the programme regulations also place an obligation on the licensee to inform CVB of any problem that comes to its attention regarding the purity, safety or potency of the product. CVB has the legal authority to intervene in the marketplace where there are serious concerns with respect to the purity, safety, potency or efficacy of the product.

B. COMPARISON OF EUROPEAN UNION AND UNITED STATES REGULATIONS

Veterinary biologicals must meet certain basic criteria, regardless of the Regulatory Agency overseeing their production. These criteria include:

- Safety: the product must be safe in the target species and, if live, in species exposed to shed organisms;
- Efficacy: the product should be effective according to claims indicated on the label;
- Quality: includes purity, potency and consistency;
- Purity: the product must be free from contaminating agents;
- Potency: each batch of product should be formulated, and tested, to ensure effectiveness and reproducibility of activity as demonstrated in the registration data.

Although, on a global basis, agencies and regulations differ, all strive to ensure that products offered to the end-consumer conform to these basic standards.

The EU uses a complete system that is a combination of GMP, including validated processes and specifications of materials, together with production methods that ensure the quality of the final product. In-process and batch controls (tests) constitute additional guarantees of the quality of IVMPs. The safety tests are conducted under GLP and the field efficacy tests under GCP. The USA defines acceptable manufacturing processes in the outline of production and detailed facility description (blueprints and blueprint legends), and relies on inspection and confirmatory testing to achieve the same goal. Although different, both systems are designed to allow only pure, safe, potent, and effective biologicals to be released to the consumer.

In addition to the data provided by the applicant, expert reports have to be included in the EU marketing authorisation application file (dossier). Each main section of the EU dossier, including analytical, safety and efficacy, must be reviewed by an independent expert. The assessment of the expert is included in the marketing authorisation file. No such system of third-party review exists under the USDA registration system with the exception of certain biotechnologically derived products.

There are many procedural differences between the EU and the USA. Harmonisation between the two systems should be established where possible, on the recognition of equivalence for tests and procedures that are performed to assess a vaccine and that ensure quality, safety and efficacy of the product. Mutual recognition agreements (MRAs) covering veterinary biologicals have been signed between the EU and Australia and between the EU and New Zealand. These MRAs are now at an operational stage. Progress on MRAs between the EU and the USA, regarding veterinary biologicals, is likely to take longer to achieve.

C. THE ROLE OF INTERNATIONAL ORGANISATIONS

Most nations have a range of official acts that regulate the sale and use of veterinary biologicals. Almost all of these acts stipulate 'minimum requirements' for quality, safety and efficacy of veterinary biologicals (mostly vaccines), to be tested at independent laboratories, usually under State supervision. These acts and tests may differ from one country to another, and they involve costs and restrictions for producers, users and testers.

Many of the vaccines described in this *Terrestrial Manual* are produced and/or used in countries that do not currently apply regimens of authorisation and testing as stringent as those described in this chapter. Nevertheless, it is useful to be aware of the regulations operating in different regions and, therefore, the testing and inspection that is likely to have been carried out there on a veterinary biological.

The idea of harmonising this testing to simplify and reduce costs on a regional, or even world scale, is not new, and much has been accomplished during the past 20 years. The purpose of this section is to review the current situation by describing the role of international organisations in the regulation of veterinary vaccines.

In this section the term 'international organisation' refers to those concerned with animal health on a world-wide scale (WOAH, the Food and Agriculture Organization of the United Nations [FAO] and the WHO).

1. The role of WOA (World Organisation for Animal Health)

WOAH was founded, as OIE, in Paris in 1924 as the world organisation for animal health, and comprised 182 Member Countries in the year 2018. The principal aims of WOA are: to ensure transparency in the global animal disease and zoonosis situation, to collect, analyse and disseminate scientific veterinary information, to provide expertise and encourage international solidarity in the control of animal diseases, within its mandate under the Agreement on Sanitary and Phytosanitary Measures (SPS Agreement) of the World Trade Organization (WTO), to safeguard world trade by publishing health standards for international trade in animals and animal products, to improve the legal framework and resources of national Veterinary Services and to provide a better guarantee of the safety of food of animal origin and to promote animal welfare through a science-based approach (Truszczyński & Blancou, 1992).

Within WOA there are four Specialist Commissions: the Terrestrial Animal Health Standards Commission, which deals with the *Terrestrial Animal Health Code*, the Biological Standards Commission, the Scientific Commission for Animal Diseases and the Aquatic Animal Health Standards Commission (including diseases of molluscs and crustaceans). In addition, there is one Working Group: the Working Group on Wildlife.

Among the Specialist Commissions, the one most closely connected with standardisation is the Biological Standards Commission. This Commission establishes standards for diagnostic methods (including diagnostic preparations) and for vaccines. Its terms of reference reflect the Commission's obligation to participate in the standardisation of biological products, including vaccines used for prophylactic purposes. The Biological Standards Commission is responsible for the preparation of the WOA *Manual of Diagnostic Tests and Vaccines for Terrestrial Animals*, and the organisation of Reference Laboratories for many of the diseases on the WOA List.

However, full standardisation of vaccine testing can be achieved only when the necessary standards have been devised. It is hoped to reach the goal of standardisation and wide availability of standards through the participation of WOAHP Reference Laboratories. In 2018, the WOAHP has 182 Member Countries with a global network of 246 Reference Laboratories covering 105 diseases or topics in 35 countries, and 55 Collaborating Centres covering 49 topics in 28 countries. The functions and responsibilities of experts at the WOAHP Reference Laboratories include the provision of a centre of excellence in a designated activity; standardisation of methods; preparation, storage and distribution of standard antisera, antigens and other reagents.

Among the WOAHP Collaborating Centres, seven may be involved at some stage in veterinary vaccine control or harmonisation: the Collaborating Centre for Veterinary Medicinal Products in Fougères (France), the Collaborating Centre for ELISA (enzyme-linked immunosorbent assay) and Molecular Techniques in Animal Disease Diagnosis in Vienna (Austria), Collaborating Centre for Diagnosis and Control of Animal Diseases and Related Veterinary Product Assessment in Asia in Tokyo (Japan), the Collaborating Centre for the Diagnosis of Animal Diseases and Vaccine Evaluation in the Americas in Ames (USA), the Collaborating Centre for Development and Production of Vaccines, Pharmaceutical Products and Veterinary Diagnostic Systems using Biotechnology, Centro de Ingeniería Genética y Biotecnología, Havana (Cuba), the Collaborating Centre for Quality Control of Veterinary Vaccines, Pan-African Veterinary Vaccine Centre (Ethiopia) and the Collaborating Centre for Validation, Quality Assessment and Quality Control of Diagnostic Assays and Vaccine for Vesicular Diseases in Europe, Centre d'Etudes et de Recherches Vétérinaires et Agrochimiques de Ukkel (Belgium).

In 1994, following discussions with the International Technical Consultation on Veterinary Drug Registration (ITCVDR), WOAHP set up an *ad hoc* Group on the Harmonisation of Veterinary Medicines, which was the first step towards the creation of the VICH (International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Products) (see Section C.4 below).

In May 2003, the WOAHP International Committee (now World Assembly) adopted a resolution entitled WOAHP Procedure for Validation and Certification of Diagnostic Assays (Test Methods) for Infectious Animal Diseases. This resolution required the WOAHP Director General to establish a WOAHP registry for assays with levels of validation specified. Fitness for purpose is used as a criterion for validation.

2. The role of the Food and Agriculture Organization of the United Nations

FAO, established in 1945, is responsible for agricultural development and food production. The Animal Production and Health Division ('AGA') within the Agriculture Department is concerned with livestock development, and it includes the Animal Health Service ('AGAH'), the main role of which is to assist Member Countries in the control of animal diseases, with the aim of improving livestock production as an integral component of general social, economic and agricultural development. FAO's involvement in testing veterinary biologicals is primarily through its technical assistance system to Member Countries to set up and even execute independent quality control of vaccines and other biologicals. One example is FAO's assistance to the AU (African Union) in setting up a system for continental testing of veterinary vaccines, by the Pan African Veterinary Vaccine Center (PANVAC). FAO also commissions, at the request of Member Countries, initiatives for either quality assurance of vaccines and other biologicals or expert consultations on this subject, or publication of manuals on the production and quality control of vaccines. Furthermore, two auxiliary services can be asked to intervene on matters concerning these products, namely Codex Alimentarius and the Division of Nuclear Techniques in Food and Agriculture. The latter is operated jointly by FAO and the International Atomic Energy Agency (IAEA) based in Vienna (Austria). It has an Animal Production and Health Section, which assists veterinary services and research institutes in developing countries to establish radio-immunoassay (RIA) and ELISA techniques. Linked to this activity is a quality assurance scheme under which laboratories in receipt of FAO/IAEA ELISA kits are required to routinely monitor internal quality controls and to periodically (once or twice a year) test a batch of unknown samples, and to forward the results to IAEA. The overall aim is to provide assurance to all concerned that the results being generated through the use of such internationally standardised and validated kits can be relied upon as correct.

3. The role of the World Health Organization

Currently WHO is not directly involved in preparing international reference preparations (i.e. antigens or antibodies) for purely veterinary use, but has developed and still retains in the National Institute for Biological Standards and Control, Potter's Bar (UK) some materials related to purely veterinary diseases (e.g. Newcastle disease live vaccine, classical swine fever serum). WHO wishes to retain a role in this area in instances where the veterinary reference preparations and guidance documents have a direct relevance to human health (Joint

FAO/WHO Expert Committee on Brucellosis, 1986; Meslin *et al.*, 1996; WHO Expert Committee on Biological Standardisation, 1992; WHO Expert Committee on Rabies, 1992). This involves zoonotic and potentially zoonotic agents and other infectious agents of animal origin that are potential contaminants of biological products, whether these are vaccines produced in cell cultures or organs for xenotransplantation. At the meeting of the Expert Committee on Biological Standardization in October 1998, a review of currently retained international standards and reference preparations for veterinary medicine was carried out and a list of candidates for discontinuation, replacement and revision was suggested (Joint FAO/WHO Expert Committee on Brucellosis, 1986). The Expert Committee however decided to defer taking action on preparation of veterinary reference materials pending an evaluation by WHO with its partners in the veterinary field of the need for these various biological products. In addition, the present day topicality of certain preparations, especially veterinary vaccines against known zoonoses (e.g. anthrax, brucellosis) adopted and/or revised in the 1960s and 1970s, also needs to be evaluated.

The format of the list of Requirements for Biological Substances published as an Appendix to each report of the Expert Committee on Biological Standardization was revised in 1998 and should facilitate the retrieval of information and achieve the aim of improved transparency.

4. The role of VICH

4.1. What is VICH?

4.1.1. Short description of VICH

The International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products (VICH) is an international programme aimed at providing guidance on the technical requirements for registration of veterinary medicinal products. VICH was established in 1996 as a means of collaboration, primarily between the regulatory authorities and the animal health industry of the EU, Japan and the USA. The regulatory authorities and animal health industry of Australia, New Zealand, Canada and South Africa also participate actively as VICH observer members. WOAHA participates as an associate member in the VICH process with the goal of supporting and disseminating the outcomes at the global level.

4.1.2. Background and history

The initiative to begin the harmonisation process came in 1983 when the first International Technical Consultation on Veterinary Drug Registration (ITCVDR) was held. Since then a series of government and industry initiatives have been developed, culminating in the formation of the VICH.

The Codex Alimentarius formed a Committee on Residues of Veterinary Drugs in Foods in 1985. Standard requirements for veterinary product registration were adopted in Europe in 1981.

The US Food and Drug Administration and the European Commission have held regular bilateral meetings for the last decade to discuss common areas of interest. This has involved mutual exchange of guidelines for consultation.

The first International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) was held in Brussels in November 1991. The meeting brought together regulators and industry representatives from the USA, the EU and Japan to address quality, safety and efficacy requirements in the three regions.

Meetings on harmonisation of veterinary biologicals were held in Ploufragan, France, in January 1992, in Arlington, USA, in 1994 and in Singapore in 1995.

In January 1993 the GHOST (Global harmonisation of standards) discussion document was published by FEDESA³. It set out a programme for the international harmonisation of registration requirements for veterinary pharmaceuticals and biologicals.

Following discussions at ITCVDR and WOAHA conferences, WOAHA set up an *ad hoc* Group on harmonisation of veterinary medicinal products in 1994.

4.1.3. The creation and scope of VICH

Preparatory work for the establishment of VICH was carried out by this WOAHA *ad hoc* Group. During 1994 and 1995, two meetings were held at which the scope of veterinary harmonisation was discussed and the membership and objectives of the VICH proposed.

On the subject of food safety standards, it was decided that the VICH should complement the work of Codex and JECFA⁴. Issues related to GLP and GMP that are already the subject of mutual agreements will not normally come within the remit of the VICH. Issues related to biologicals were considered appropriate to fall within the scope of VICH.

Fundamental to the selection of priority topics for consideration by the VICH was the discussion document prepared by COMISA for the Steering Committee. This report:

- assesses those ICH guidelines which could be adapted to the VICH programme;
- defines in detail areas of non-harmonisation between the EU, the US and Japan and provides a series of 'concept papers' on key topics; and
- puts forward preliminary suggestions for priority topics.

With all the ground-breaking work completed, the Steering Committee of the VICH held its first meeting in April 1996, at which the membership and the working procedures were agreed and a work programme established.

In November 2011, the VICH Outreach Forum was created to provide a basis for wider international harmonisation of registration requirements beyond the VICH member and observer regions and countries. The Forum aims to improve information exchange and raise awareness of VICH and understanding of VICH guidelines, thereby facilitating their wider adoption. The VICH Outreach Forum currently includes representatives from the regulatory authorities of many countries and three regional organisations for Africa, Asia and Americas.

4.1.4. The objectives of VICH

The objectives of the VICH are along the same lines as those of the ICH.

- i) Establish and implement harmonised regulatory requirements for veterinary medicinal products in the VICH regions, which meet high quality, safety and efficacy standards and minimise the use of test animals and costs of product development.
- ii) Provide a basis for wider international harmonisation of registration requirements.
- iii) Monitor and maintain existing VICH guidelines, taking particular note of the International Conference on Harmonisation of Technical Requirements for the Registration of Pharmaceuticals for Human Use (ICH) work programme and, where necessary, update these VICH Guidelines.
- iv) Ensure efficient processes for maintaining and monitoring consistent interpretation of data requirements following the implementation of VICH guidelines.

3 FEDESA: Fédération Européenne de la Santé Animale. In 2002, FEDESA became the International Federation for Animal Health (IFAH) and later HealthforAnimals. Now fulfils the role of VICH Secretariat.

4 JECFA: Joint FAO/WHO Expert Committee on Food Additives.

- v) By means of a constructive dialogue between regulatory authorities and industry provide technical guidance enabling response to significant emerging global issues and science that impact on regulatory requirements within the VICH regions.

4.1.5. Progress toward achieving the VICH objectives

- i) For veterinary immunologicals there is an ongoing programme of harmonisation in a number of areas including target animal safety studies, reversion to virulence and tests for the presence of *Mycoplasma*. To date only a relatively small number of VICH guidelines have been developed for veterinary biologicals and it is worth emphasising the difficulties in reaching agreement on veterinary biologicals between the three regions.
- ii) The first two VICH Guidelines for veterinary biologicals were adopted in May 2003; one concerned the testing of residual formaldehyde and the other the testing of residual moisture. Several other Guidelines that apply to veterinary biologicals and all other veterinary medicinal products have also been adopted.
 - a) In 2013 and 2015 two new Guidelines were adopted: one concerning the harmonisation of criteria to waive target animal batch safety testing (TABST) for inactivated vaccines for veterinary biologicals (GL50), and one on the harmonisation of criteria to waive TABST for live vaccines (GL55).
 - b) In 2016, the Steering Committee (SC) adopted a Concept Paper on the development of further guidance on testing of veterinary vaccines for freedom from extraneous viruses, and a list of viruses. These two future VICH guidelines will be developed by taking into account the new relevant revised WOAHP Chapter 1.1.9 *Tests for sterility and freedom from contamination of biological materials intended for veterinary use*.

Following the “VICH5” conference, held in Tokyo, Japan in 2015, the VICH Priorities Phase 4 document was published providing a vision for 2016–2020. To foster the already close collaboration with WOAHP and in view of implementing the wider objective of international harmonisation, VICH supports the strategic activities of WOAHP that are targeted at good governance of veterinary medicinal product in WOAHP Member Countries.

More information is available at: <https://vichsec.org/en/>.

CONCLUSION

There is a clear intention to achieve greater international harmonisation of regulatory requirements for veterinary biologicals (Vannier *et al.*, 1997). Progress has already been achieved through international organisations to allow fair competition in the marketing of veterinary products. Although past efforts by international organisations have not resulted in a level of harmonisation sufficient to facilitate international trade, they have laid the groundwork for current efforts. National authorities recognise the advantages of harmonisation and are now committed to working toward this goal.

The efforts of international organisations have made the goal of harmonisation possible and have resulted in an organisation and process for proceeding toward this goal. Success in achieving this goal will depend on the willingness of participating national authorities to work together and accept the compromises that will be necessary to resolve the difficult scientific and policy issues.

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NB: FIRST ADOPTED IN 2000. MOST RECENT UPDATES ADOPTED IN 2018.