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OIE standards for vaccines and future trends

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Summary
The World Organisation for Animal Health (OIE), sets out international standards for vaccines in the *Manual of Diagnostic Tests and Vaccines for Terrestrial Animals (mammals, birds and bees)*. The texts are drafted by experts then sent for scientific peer review and for comment by all OIE Member Countries, thus achieving a consensus at the point of adoption. Introductory chapters in the *Terrestrial Manual* provide general principles of laboratory management and vaccine production, and disease-specific chapters provide detailed standards for vaccines for the OIE listed diseases. Issues that the OIE Biological Standards Commission are currently addressing or will address in the near future include the matching of vaccine strains to currently circulating infectious agents, the use of companion diagnostic tests to differentiate infected from vaccinated animals, the development of vaccine banks, and the application of DNA technology to vaccine design and production.

Keywords
Biotechnology – Differentiating infected from vaccinated animals (DIVA) strategy – International standard – Quality control – Safety – Vaccine – Vaccine bank.

Introduction

The World Organisation for Animal Health (OIE) is an intergovernmental organisation of 169 Member Countries. The Organisation is mandated under the Sanitary and Phytosanitary Agreement of the World Trade Organization to set standards that safeguard international trade in animals and animal products. It has six primary objectives, which include the promotion of international solidarity in the control of animal diseases, the publication of animal health standards, and provision of a better guarantee of safety in food of animal origin.

One of the OIE's principal standard texts is the *Manual of Diagnostic Tests and Vaccines for Terrestrial Animals (mammals, birds and bees)* (hereafter referred to as the *Terrestrial Manual*) (13), currently in its 5th edition. This article will explain the process by which the *Terrestrial Manual* chapters are developed and approved, will outline the vaccine-related contents of the *Terrestrial Manual*, and will seek to put these in the context of other national and supra-national regulatory frameworks. The *Terrestrial Manual* covers all the OIE listed diseases of terrestrial animals together with a number of other diseases of animal or public health concern. It has become widely adopted as a key reference book for veterinary laboratories around the world. Much of it is devoted to laboratory diagnostic tests, but this article will focus on the vaccine elements. There is a series of generic introductory chapters which give general guidelines, including six with specific relevance to vaccines. The rest of the *Terrestrial Manual* consists of disease-specific chapters that provide general background to:

a) the disease, its diagnosis and control

b) approved diagnostic techniques

c) requirements for vaccines and diagnostic biologicals.

A new updated edition of the *Terrestrial Manual* is published approximately every four years, but it has been agreed by the International Committee of the OIE that urgent updates, once approved by the Committee, may be incorporated in the online edition on the OIE website (www.oie.int) without waiting for the next full printed edition.

The OIE *Terrestrial Animal Health Code* (14) also makes reference to use (or non-use) of vaccines, particularly in regard to the certification of animals or animal products for international trade, or to the surveillance and declaration of freedom from diseases or infections in specified populations. In such cases any vaccines should comply with the standards published in the *Terrestrial Manual*.

Development and approval of vaccine standards

The OIE *Terrestrial Manual* is produced under the *aegis* of the Biological Standards Commission, supported by an editorial team. The Commission appoints authors for each chapter who are recognised as international scientific experts on the particular disease or topic, and who produce a draft text, or modify and update an existing text. This is then submitted to scientific peer reviewers, and to the delegates of all OIE Member Countries, for comment. Comments are collated, incorporated into the chapter if straightforward, or where necessary referred back to the Commission for a decision. Finally, texts are presented by the President of the Commission to the OIE International Committee for approval and adoption. Thus, the OIE can rightly claim that the texts have consensus approval and support from its Member Countries, and that they therefore represent valid international standards.

Chapters often make reference to new technologies under development, usually at the stage of ongoing research, but it should be clear that these are included for information and are not yet adopted as formal standards. Conversely, in some cases older vaccine technologies may still have a place in certain circumstances but may not be acceptable for use in all Member Countries.

Generic chapters with relevance for vaccine development

Tests for sterility and freedom from contamination

It is essential to show that all vaccines are free from adventitious agents that may be accidentally introduced during various stages of the production process. This is a particular hazard with vaccines containing live attenuated organisms where a number of contaminants are recognised as high risk, notably mycoplasmas and non-cytopathogenic viruses (particularly pestiviruses) in cell cultures used for viral vaccine production. The chapter provides methodologies for detection of these and other contaminants.

Seed lots used for production of the vaccine must be shown to be pure and free from contaminating strains. In addition, inactivated vaccines need to be shown to be fully inactivated. Again, appropriate methodologies are provided.

Safety in the veterinary microbiology laboratory

Laboratories (including vaccine manufacturing plants) are intrinsically hazardous environments. The chapter sets out the principles of safe working practices taking into account physical and chemical hazards as well as the need to protect staff from pathogenic micro-organisms. Although many vaccines are derived from attenuated strains, this is not always the case and comprehensive risk assessments are essential before any work is started. The standards complement, and do not replace, those established by the World Health Organization or national authorities. In addition, veterinary laboratories and vaccine manufacturers need to avoid accidental release of animal pathogens, even where there is minimal risk to humans. An appendix to the chapter sets out the principles of such biocontainment specifying four containment levels, with the highest (level 4) applying to highly contagious organisms such as foot and mouth disease (FMD) virus.

Principles of veterinary vaccine production

The regulatory framework for vaccine production is complex and varies between countries and regions. Specific reference is made in the chapter to European Union Directive 2001/82/EC (as amended) (2), the European Pharmacopoeia (3), and the Code of Federal Regulations in the United States of America (USA) (9). The OIE is not a regulatory body, but sets out general principles that should be applied to any situation to ensure that authorised products are pure, safe, potent and effective. This provides a secure basis for the successful operation of control programmes for many animal diseases.

The chapter deals with questions of nomenclature, types of vaccine, the requirements for a production plant, quality management, vaccine ingredients (including master seeds and other components), and the range of tests required to demonstrate safety, efficacy and stability, both during manufacture and in field use. Special reference is made to the use of vaccines derived from recombinant DNA technology, where guidelines are still at the stage of active development, and this is considered in more detail in the chapter on biotechnology (see below).

International standards for vaccine banks

This new guideline, adopted in 2005 and available online from the OIE website, recognises the importance for

Member Countries of having rapid access to vaccines to deal with outbreaks of epizootic diseases. The manner in which such emergency vaccination is applied will vary with the disease, the epidemiological situation, and the disease control policies of the country concerned. Vaccine banks are designed to maintain stocks of vaccine or vaccine antigen for emergency use, often in countries where vaccination for the disease is not normally practised. The banks may be national or held on behalf of multi-country consortia. In the latter case clear legal agreements are required concerning access by individual countries. Arrangements need to take account of regulatory controls as well as lead time for reconstitution and filling to final product. The vaccine bank and its management should be an integral part of a country's contingency plan for control of exotic diseases. Key decisions need to be made concerning the number of doses to be stored and the strains of organism to be included in the bank – particularly for antigenically variable pathogens such as FMD virus, where the constituents of the bank may need to be regularly reviewed and updated to match currently circulating field strains. Although there may be special regulatory provisions for the use of emergency vaccination in Member Countries, the vaccine bank is not exempt from the general principles underlying safety and efficacy, and the facility must still comply with the quality principles of Good Manufacturing Practice.

Biotechnology in vaccine development

A number of biotechnological approaches are now well established in vaccinology and authorised products are already in use for disease control in the field. Good examples are the deletion of genes from bacteria or viruses to reduce the virulence (e.g. *Aro* mutants of *Salmonella* spp. [4]), in contrast to traditional methods of attenuation through multiple passage in culture. The chapter provides several examples where such gene-deleted vaccines can be used in conjunction with a companion diagnostic test to differentiate infected from vaccinated animals (the DIVA strategy), e.g. Aujeszky's disease (10) and infectious bovine rhinotracheitis. Other technologies, which also offer the opportunity for DIVA strategies, include subunit viral vaccines, based on individual immunogenic proteins expressed in heterologous systems such as baculovirus or poxvirus (e.g. E2 protein of classical swine fever virus [14]). The DIVA approach allows the eradication of a disease in the presence of a vaccination strategy for disease control (11).

Vaccines have also been developed in which a live virus vector is used to express an immunologically relevant protein of the pathogenic organism, giving the advantages of live virus vaccines (replication in the host leading to better immune responses) without the risk of reversion to virulence. A classic example is the vaccinia-vectored rabies vaccine that has been used successfully for disease control in wildlife (7). More recently, a number of vaccines based on avian pox viruses have been developed (8). When used in mammalian hosts these express the foreign vectored gene and stimulate protective immunity without replicating to produce progeny virus.

Finally, the role of DNA vaccines is considered. Although not as yet a fully developed technology it shows considerable potential (6) and the current state of scientific development is described in the chapter.

The role of official bodies in vaccine regulation

This chapter (online version updated in 2005) outlines in some detail the regulatory procedures in the three regions that have made most progress in this field, namely Japan, the European Union, and the USA. In addition, the role of the appropriate pharmacopoeias is discussed, particularly the European Pharmacopoeia (3) (which has 35 signatory member states, as well as a further 17 with observer status). The procedural differences are described between the American and European systems, together with efforts being made to harmonise these with each other, and with regulations of other countries and regions. The International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products (abbreviated to VICH) is a trilateral programme of the EU, Japan and the USA which has an ongoing commitment to develop harmonised technical standards for vaccine production. Unfortunately progress to date has been rather slow.

Disease-specific chapters

Vaccination as a disease control method is not applicable in all cases, but where there are useful vaccines available each disease-specific chapter provides a basic standard for their manufacture and usage. The standards follow a consistent format of:

- seed management
- method of manufacture
- in-process control
- batch control
- tests on the final product.

Where there is more than one vaccine type available, an introductory account is given to enable users to make informed choices on the preferred approach. It is not

possible in this short article to go into detail for all the listed diseases, for which reference should be made to the *Terrestrial Manual*. We shall briefly examine two specific aspects of particular interest, namely, vaccine matching tests for FMD and DIVA strategies.

Foot and mouth disease: vaccine matching tests

Vaccinal immunity to FMD virus is serotype-specific, but even within serotypes complete cross-protection between different isolates may not occur. A new text, adopted in May 2006 by the OIE International Committee, presents for the first time a detailed explanation of how to select circulating field viruses, and how to evaluate these using antisera specific to different vaccine strains for the best fit for cross-protection. Tests used may be based on complement fixation, enzyme-linked immunosorbent assay, or virus neutralisation technologies.

Strategies for differentiating infected from vaccinated animals

There are a number of diseases for which a DIVA approach may be used, allowing continued vaccination while still being able to detect infected animals through serological responses to proteins that are absent from the vaccine. So far this has been limited to certain virus infections, but the principle could be applied more widely. The details of the DIVA approach vary with the disease. Thus, for FMD, the vaccines used are conventional inactivated viral vaccines, but highly purified during manufacture so that they lack immunologically significant levels of non-structural proteins (NSP) (5). Animals naturally infected with FMD virus do develop antibodies to NSP, even if already vaccinated, so an NSP-specific antibody test can be used in a DIVA strategy. This has the additional advantage of not being serotype-specific.

In the case of avian influenza, use can be made of naturally occurring strains for vaccine manufacture where the neuraminidase type is different from the circulating field virus, taking advantage of the fact that the main protective immune response is to the haemagglutinin protein. Thus, neuraminidase inhibition serological tests provide a means of detecting field infection in birds that have been vaccinated against a haemagglutinin type homologous to the field virus (1).

Other examples of DIVA applications, as mentioned above include the use of gene-deleted vaccines for herpesviruses (Aujeszky's disease, infectious bovine rhinotracheitis), and recombinant vaccines expressing a single immunogenic viral protein (classical swine fever E2 glycoprotein).

Future trends/concluding remarks

The need for new and improved vaccines will continue in the future because the demand for livestock and livestock products is expected to grow enormously in the next fifty years, particularly in developing countries. This will lead to more disease problems and emerging diseases. The demand for cheap, reliable vaccines will increase and general guidelines are essential, especially for the developing countries.

There is a pressing need to encourage efforts towards international harmonisation, including technical procedures related to quality control, the evaluation of safety and efficacy of vaccines, and the regulatory protocols used to authorise products in different countries. In this respect the VICH initiative is to be welcomed. Meanwhile, the continual improvement of the chapters in the OIE *Terrestrial Manual* will provide internationally recognised standards that are of particular value to those countries which do not as yet have fully formed regulatory processes.

Vaccine banks are expensive to set up and maintain, but this must be set against the enormous potential costs of non-vaccination strategies in the face of increasing global spread of diseases. Agreed standards for the maintenance and exploitation of such banks are therefore essential.

Advances in biotechnology, immunology and proteomics will continue to generate novel approaches to vaccine design. It is essential that robust standards are in place and are applied to ensure that new products are adequately evaluated both for their safety and efficacy for the animal and the consumer, and for any environmental impacts that may ensue.

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Normes de l'OIE relatives aux vaccins et tendances pour l'avenir

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Résumé

Les normes internationales prescrites par l'Organisation mondiale de la santé animale (OIE) en matière de vaccins sont décrites dans le *Manuel des tests de diagnostic et des vaccins pour les animaux terrestres (mammifères, oiseaux et abeilles)*. Ces normes sont préparées par des experts, soumises à une évaluation collégiale puis diffusées auprès des Pays Membres de l'OIE afin de recueillir leurs commentaires ; au moment d'être adoptées, elles sont donc le fruit d'un large consensus. Les premiers chapitres du *Manuel terrestre* exposent les principes généraux régissant la gestion des laboratoires et la production de vaccins, tandis que les chapitres sur les maladies décrivent en détail les normes relatives aux vaccins pour chaque maladie figurant sur la liste de l'OIE. Plusieurs questions d'intérêt immédiat ou futur sont actuellement examinées par la Commission des normes biologiques de l'OIE : l'adéquation des souches vaccinales avec les souches pathogènes en circulation ; le recours à des tests diagnostiques compagnons, permettant de distinguer les animaux infectés des animaux vaccinés ; la création de banques de vaccins et les technologies de l'ADN applicables au développement et à la production de vaccins.

Mots-clés

Banque de vaccins – Biotechnologie – Contrôle de qualité – Norme internationale – Sécurité – Stratégie pour différencier les animaux infectés des animaux vaccinés (DIVA) – Vaccin.

Normas de la OIE sobre vacunas y tendencias de cara al futuro

S. Edwards

Resumen

La Organización Internacional de Sanidad Animal (OIE) fija normas internacionales sobre vacunas en su *Manual de pruebas de diagnóstico y vacunas para los animales terrestres (mamíferos, aves y abejas)*. Tras una primera fase de redacción, a cargo de especialistas, los textos se someten al examen de otros expertos de igual nivel y a las observaciones que puedan formular todos los Países Miembros de la OIE, proceso que culmina con un consenso en el momento de la aprobación. Los capítulos introductorios del *Manual terrestre* sientan principios generales sobre procedimientos de laboratorio y fabricación de vacunas, mientras que en los capítulos siguientes, dedicado cada uno a una patología, se fijan normas detalladas sobre las vacunas contra las enfermedades inscritas en la lista de la OIE. Entre los temas de los que se ocupa o va a ocuparse la Comisión de Normas Biológicas de la OIE figuran la adecuación de las cepas vacunales a los agentes infecciosos actualmente en circulación, el uso de pruebas de diagnóstico complementarias para distinguir entre animales infectados y vacunados, la creación de bancos de vacunas o la aplicación de la tecnología del ADN a la concepción y fabricación de vacunas.

Palabras clave

Banco de vacunas – Biotecnología – Control de calidad – Estrategia de discriminación entre animales infectados y vacunados (DIVA) – Norma internacional – Seguridad – Vacuna.

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