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Viral safety and extraneous agents testing for veterinary vaccines

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Immunisation of animals with high quality vaccines is the primary means of control for many animal diseases. Considerable progress in the production of vaccines for animal use has been made over the past few decades with the increasing use of continuous cell lines as a substrate and the adoption of fermentation technology for antigen production. However, the use of material of animal or human origin in the production of medicinal products includes the risk of contamination due to extraneous agents. Regulations and guidelines have been developed to assure the viral safety of human and animal medicinal products. These guidelines, however, are based on our knowledge regarding extraneous agents, the available testing technologies and experience, all of which are constantly evolving. In the past few decades, several factors including changes in the regulatory approach, advances in molecular biology and increased globalization of veterinary vaccine production have culminated in the need for a review of the progress and requirements in this area.

To provide a forum for discussion and moving forward, the International Association for Biologicals (IABS) in partnership with the International Federation for Animal Health Europe (IFAH-Europe) organized an international workshop on "*Viral Safety and Extraneous Agents Testing for Veterinary Vaccines*," 25–27 October 2009, in Annecy, France. Scientists, vaccine manufacturers, regulators and suppliers gathered together to review and evaluate the current procedures and purity standards ensuring the safety of veterinary vaccines, and consider potential modifications in regulatory policies, in light of the experience accumulated over the past few decades, new changes in production standards and the development of more sensitive testing methods.

This summary reviews the main issues discussed at the workshop and presents the recommendations produced by the participants. The first session of the workshop, chaired by Jacques Léchenet (Merial, France), set the scene, with a broad overview of past vaccine contamination incidents and a review of the current challenges in viral safety. In the second session, chaired by Philippe Vannier (The French Food Safety Agency (AFSSA), France) and Paul-Pierre Pastoret (The World Organization for Animal Health (OIE)), the rationale and limitations of the current requirements and the sources of potential contamination were described. A third session, chaired by David Mackay (The European Medicines Agency (EMEA)), addressed decontamination and inactivation treatments. The fourth session, chaired by Wim Hesselink (Intervet/Schering Plough Animal Health, The Netherlands), included presentations on specific viral contaminants and new tests. Final sessions, chaired by Carmen Jungbäck (Paul-Ehrlich-Institut, Germany), Lukas Bruckner (Institute of Virology and Immunoprophylaxis, Switzerland) and Jacques Léchenet, included a round table on risk-benefit assessment, followed by conclusions and recommendations.

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1. Key issues and constraints regarding viral safety of veterinary vaccines

Viral safety is a key issue for veterinary vaccines. In the past, contamination of human and veterinary vaccines has resulted in a few spectacular incidents, leading industry to change certain practices and regulatory authorities to develop more stringent and detailed requirements [see article by Paul-Pierre Pastoret, p. 332–334].

The three main concerns of viral safety of immunological veterinary medicinal products are (1) the presence of extraneous agents, (2) the residual pathogenicity of live viruses used as active ingredients in live viral vaccines and (3) the inadequate inactivation of viruses used as active ingredients in inactivated viral vaccines. While this meeting focused on extraneous agents, topics and discussions also concerned the latter two points. Contamination by extraneous agents can result from the use of contaminated source materials or contamination during production. Viral purification is an expensive procedure: the quality and safety of veterinary vaccines is consequently based on the basic principle of building quality into vaccines.

Assuring the viral safety of a veterinary medicinal product thus involves the selection and testing of the raw materials, cell lines and seed materials used; assessing the extent to which manufacturing processes clear infectious viruses; and testing at appropriate steps throughout the process and at the level of the final product [see article by David Mackay p. 335–337].

2. Definition of viral safety: a challenge to manufacturers and regulators

Defining viral safety poses a real challenge to manufacturers and regulators. It is increasingly understood that the ideal of viral safety – absolute freedom from extraneous agents or residual pathogenicity – is neither possible nor realistic. This is in part due to the process of testing starting materials or final product for extraneous agents which is, by definition, based on probability since only a portion is tested. There are also technical limits to testing and inactivation techniques, and neither can confer a full guarantee of freedom from extraneous agents. The nature of the extraneous agents and our level of knowledge about them are also important when it comes to assuring viral safety. Generally speaking, there are three types of extraneous agents: 'known known' agents that are both known and suspected in a sample and should be tested for; the 'known unknowns' or agents that are known and can be tested for, but are not necessarily suspected in a sample; and the 'unknown unknowns' meaning agents that are recognized but cannot currently be tested for, or agents that are as yet unknown. The last group is the most difficult, in terms of detection and determining an appropriate response, although unknown agents may be detected by molecular techniques. Considering the above limitations, David Mackay proposed a realistic definition of viral safety as the maximum possible assurance of a sufficiently low risk of harm arising from any virus present in a veterinary medicinal product.

Jean-Claude Rouby (AFSSA-ANMV, France) stressed the difficulty of detecting 'low level' contaminants and even of defining what can be considered as a 'low level.' The level of risk linked to the potential presence of extraneous agents was discussed, and more specifically, how the situation is handled in practice [article p. 354–357].

3. Current regulations

Guidelines and regulations have been established in Europe and in the USA to ensure viral safety of veterinary vaccines. In the European Union (EU), extraneous agents testing is addressed by different regulations of the European Pharmacopoeia (Ph. Eur.) and guidelines issued by the Committee for Medicinal Products for Veterinary Use (CVMP) under the European Medicines Evaluation Agency (EMEA). Lukas Bruckner explained how the Ph. Eur. approach to the prevention of contamination through extraneous agents testing embraces the entire production process, from raw materials to the final product. This includes reliable sourcing and testing of raw materials; standardized, controlled production processes using good manufacturing practices (GMP); and tests confirming the quality of the final product. The general monograph *Vaccines for Veterinary Use* and texts such as Chapter 5.2.5 *Substances of Animal Origin for the Production of Immunological Veterinary Medicinal Products* address requirements for the purity of raw materials; the details regarding which tests should be used for specific products are specified in monographs [see article p. 338,339].

Requirements in the USA were described by Donna Gatewood (US Department of Agriculture, Animal and Plant Health Inspection Service, Veterinary Services, USA); they are based on the Virus-Serum-Toxin Act (VSTA) of 1913 as amended in 1985 and Code of Federal Regulations Title 9 (9CFR), Part 113. The Center for Veterinary Biologics (CVB) is responsible for promulgating regulations and enforcing the provisions of the VSTA. The 'master seed' and 'master cell' concepts are used (as in the EU), requiring extensive testing of these materials by the manufacturer; the tests are then confirmed by the CVB. All cells and viruses must be tested for bacteria, mycoplasma, and cytopathic and haemagglutinating agents. They must also be tested for bovine virus diarrhoea virus, reovirus and rabies virus by fluorescent antibody. Each seed is also tested for other specific contaminating agents based on the origin of the seed, its passage history and its intended use.

4. Attempts at harmonization

With the increased globalization of veterinary vaccine production, registration and marketing, there is also a consequent need for globally harmonized standards. The International Cooperation on Harmonization of Technical Requirements for Registration of Veterinary Medicinal Products (VICH) was launched in 1996 with the aim of harmonising technical requirements for veterinary product registration in three regions: the EU, the USA and Japan (Australia, New Zealand and Canada are observer countries in the group). The first guideline of the Expert Working Group on the harmonization of the guidelines for extraneous agents testing was meant to be on tests for mammalian live viral vaccines. Wim Hesselink explained that following the last meeting in 2003, it was decided to adjourn until Japan has introduced the seed lot system, as used in Europe and the USA. Japan accomplished this in 2008, however, the next VICH meeting is not scheduled until 2010. Understandably, many consider that the negotiation process is too slow. Improving the processes at the international level so that negotiations for harmonization can move forward is a challenge facing this area.

Currently, the differences in requirements between Europe and the USA are such that no one test may satisfy both sets of regulations, as pointed out by Sarah Sheridan (BioReliance, Scotland – see article p. 340–345). In order to comply with both, it may be necessary to perform additional tests and/or justify methods chosen from one set of regulations over another. Interestingly, no direct comparison of the accuracy of the two approaches, with respect to which one is better at assuring freedom from extraneous agents, has ever been done.

The EU adopted GMP in order to assure more consistent production, validation of production processes and testing. The situation in the USA, however, is different, since there is no official GMP requirement for the production and control for veterinary