International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products

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Final

Concept Paper for two VICH Guidelines: (1) general principles for detection of extraneous viruses in veterinary vaccines and defining the testing of seeds and materials of animal origin (2) a list of extraneous viruses that need to be covered

1. Introduction and background

Freedom from extraneous agents (EA) is a high priority for any medicinal product, which is reflected by the requirement, across VICH regions, to test immunological veterinary medicinal products (IVMP) for infectious contaminants before they are placed on the market. For example, in the EU, these requirements are specified in Directive 2001/82/EC and in the European Pharmacopoeia (Ph. Eur.).

At its 10th meeting (Tokyo, October 2015) the VICH Biological Quality Monitoring Expert Working Group (BQM-EWG) discussed a revised approach towards EA testing, recently developed in the EU. This revised approach moves away from prescribing specific tests and towards describing a general approach, starting with a lists of agents to consider, then continues with risk assessment to define which agents can be excluded for testing before starting actual testing, including the demonstration of suitability of tests applied to show freedom of the relevant substrate from specified EA.

The stepwise approach was widely supported by the BQM-EWG group, which subsequently proposed development of 2 guidelines to VICH Steering Committee (SC) – one that would describe the general principles for EA testing and another that would provide a list of EA that should be considered.

The SC, at its 32nd meeting (Tokyo, October 2015), supported the proposal to develop two further guidelines on EA testing of veterinary vaccines in principle but requested the development of a concept paper for the proposed guidelines. This document responds to that request.

2. Problem Statement

In ensuring the safety of veterinary vaccines demonstration of freedom from EA is one of high importance.

Regulations and guidelines on EA testing of veterinary vaccines are available in the EU (from the CVMP and the Ph. Eur.), the US (USDA Code of Federal Regulations, Title 9 - CFR and Veterinary Services Memoranda) and also in Japan (Minimum Requirements for Veterinary Biological Products in the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, and Cosmetics in Japan). A very brief description of the systems in place is provided in the annex. However, requirements for detection of EA in veterinary vaccines vary between the VICH regions.

International harmonisation of the general approach and the requirements to demonstrate freedom from EA from veterinary vaccines is of high importance for global licensing purposes to avoid performance of additional tests or the need for justification of different methods used.

The issue of EA has been discussed by the VICH BQM-EWG and VICH SC many times over the last twenty years with draft guidance developed but, due to regional regulatory changes, not finalised.

At its 32nd meeting the VICH SC, following discussions at the 10th meeting of the BQM-EWG, agreed that the time was right to move forward with the development of VICH guidance on EA. The BQM-EWG was given a mandate to work further on the existing draft guideline on cell-based test methods to be used for master seed viruses, master cell seeds and other starting materials of animal origin for mammalian veterinary virus vaccines but restricting the scope of the guideline to the description of the use of cell cultures for the detection of extraneous viruses. While this guideline will provide valuable technical information relevant specifically to the use of cell cultures for the detection of extraneous viruses, harmonisation across VICH regions would be greatly aided by the provision of higher level guidance describing the general principles and requirements for EA testing (i.e. the overall approach) as well as specific information on the EA that need to be addressed.

3. Discussion

IVMPs and materials of biological origin used in their production should be demonstrated to be free from contamination with EA. Therefore prevention of potential contamination through EA testing embraces the entire production process of veterinary vaccines, from raw materials to all components of animal origin (cell substrates, virus seeds, substances of animal origin), in-process materials and the finished product. This includes reliable sourcing and testing of raw materials; standardised, controlled production processes using Good Manufacturing Practices (GMP) in order to assure consistent production; and, tests confirming the quality of starting and in-process materials as well as the final product.

Historically, the approach taken (at least in the EU and Japan) for testing of vaccines for freedom from EA has been to specify the materials that need to be tested at the various stages of production (e.g. substrates, in process materials, final products) and to specify the agents from which freedom needs to be shown. Tests for EA are divided into 'general' tests (which test for some "unknown" agents) and 'specific' tests (which test for "known" agents) and details of how the tests should be performed are given.

However, it is no longer considered sufficient to assume that a 'general' test (testing for "unknown" agents in cell cultures and/or in animals, and/or in embryonated eggs) will detect all agents indicated as being picked up by such a test as it is known that detection may in fact vary depending on the viruses and cell lines used. Under such conditions, a negative result cannot be interpreted as indicating the absolute absence of EA. Therefore, to ensure that the relevant substrate is free from known EA, the viruses of particular importance need to be specified and the possibility of their presence addressed.

At its 10th meeting the VICH BQM-EWG discussed a revised approach towards EA testing, recently developed in the EU, and described in the CVMP guidance document entitled 'The approach to demonstrate freedom from extraneous agents as part of the production and control IVMPs for mammalian species and finfish'. For this stepwise approach the following needs to be considered:

- Substances, substrates, starting materials, intermediate and final products for which testing are required.

- Criteria according to which the requirement to demonstrate freedom of a material from particular EA may be waived (these criteria may include source and nature of material, species and country of origin, target species for the product, treatment applied, etc.).
- Implementation of tests for agents that cannot be waived.
- Demonstrating suitability of tests applied to show freedom of the relevant substrate from specified EA based on defined performance criteria (sensitivity, specificity).
- Lists of agents per species for which testing is required or for which the absence of testing must be justified.

This stepwise approach was widely supported by the BMQ-EWG.

4. Recommendation

With a view to encouraging harmonisation of EA testing across and beyond VICH regions, and to allow justification for not carrying out a test for a specific agent as well as the use of any suitable methods for EA testing the development of two new guidelines is recommended:

1. a guideline on the general principles for detection of extraneous viruses and defining the testing of seeds and materials of animal origin
2. a guideline that provides a list of extraneous viruses that need to be considered

The expertise required for this work is not expected to be different to that required for the ongoing work on the development of guidance on the use of cell cultures for the detection of extraneous viruses and so is already present within the BMQ-EWG.

The EU is willing to be the topic leader for the development of these guidelines.

5. Timetable

The BQM-EWG should work mainly by written procedure (email exchanges) and may meet in the margins of the next EWG meeting to discuss the draft, subject to progress made until then.

6. Milestones

First draft GLs to be circulated by 31 January 2017.

BQM-EWG comments by 30 April 2017.

Sign-off draft GL at step 2 by BQW-EWG: to be determined.

References

1. Directive 2001/82/EC - Directive 2001/82/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to veterinary medicinal products (Official Journal L 311, 28/11/2001 p. 1 - 66). (consolidated version : 18/7/2009) Directive 2001/82/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to veterinary medicinal products.

2. European Pharmacopoeia Monographs 0062 and 0030, general chapters 5.2.4 and 5.2.5, Extraneous agents for avian vaccines are dealt with in the Ph. Eur. general chapters (2.6.24,

2.6.25. and 5.2.2.). For Transmissible Spongiform Encephalopathies (TSEs), Ph. Eur. general chapter 5.2.8 and the most recent version of the TSE Note for Guidance apply (Note for guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products - EMA/410/01) are applicable. Selected bacteria in the list include those not detectable by the sterility test (Ph. Eur. 2.6.1). Vaccines must be free of mycoplasmas and mycobacteria. The tests for mycoplasmas (Ph. Eur. 2.6.7) and mycobacteria (Ph. Eur. 2.6.2) are considered suitable and sufficient to show absence of mycoplasmas and mycobacteria.

3. The table of extraneous agents to be tested in relation to general and species specific guidelines on production and control of mammalian veterinary vaccines (7BIm10a).

4. CVMP guideline on the requirements for the production and control of immunological veterinary medicinal products (EMA/CVMP/IWP/206555/2010-Rev.1).

5. Code of Federal Regulations title 9 (9CFR). Animals and animal products, Part 113 standard requirements.

   113.31 Detection of avian lymphoid leucosis
   113.34 Detection of haemagglutinating viruses
   113.36 Detection of pathogens by the chicken inoculation test
   113.37 Detection of pathogens by the chicken embryo inoculation test
   113.42 Detection of lymphocytic choriomeningitis contamination
   113.43 Detection of chlamydial agents
   113.46 Detection of cytopathic and/or haemadsorbing agents
   113.47 Detection of extraneous viruses by fluorescent antibody technique
   113.51 Requirements for primary cells used for production of biologics
   113.52 Requirements for cell lines used for production of biologics
   113.53 Requirements for ingredients of animal origin used for production of biologics
   113.55 Detection of extraneous agents in Master Seed Virus
   113.64(a) General requirements for live bacterial vaccines
   113.100(a)(2) General requirements for inactivated bacterial products
   113.200(c)(4) General requirements for killed virus vaccines
   113.300(a) General requirements for live virus vaccines.

   Veterinary Services Memoranda 800.88 (Testing for Reticuloendotheliosis Virus Contamination) and 800.89 (Chicken Anemia Virus)

6. Minimum Requirements for Veterinary Biological Products in the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics in Japan

ANNEX – Brief description of extraneous agents testing approaches currently used in EU, USA and Japan

EU

Historically, the approach taken (at least in the EU) for testing of vaccines for freedom from EA (2 & 3) has been to specify the materials that need to be tested at the various stages of production (e.g. substrates, in process materials, final products) and to specify the agents from which freedom needs to be shown. Tests for EA are divided into 'general' tests (which test for some "unknown" agents) and 'specific' tests (which test for "known" agents) and details of how the tests should be performed are given.

For testing of "unknown" agents, samples are inoculated into suitable cell cultures of the donor species of the organism and the target species of the product.

Testing for specific "known" agents as listed in the relevant tables should be undertaken according to a protocol specific for each organism (tests may involve embryonated eggs, tissue cultures, nucleic acid amplifications techniques, etc).

EU experts considered that it is no longer sufficient to assume that a general test will detect all agents indicated as being picked up by such a test as it is known that detection may in fact vary depending on the strain of virus and cell line used to perform the test. Furthermore, the tests described rely on detection of virus in cell culture whereas substantial progress has been made in detection of virus by molecular techniques such as PCR and deep sequencing. It is clear that these techniques will become even more widely used in future and it is therefore important that any new guidance takes into account these important scientific advances.

In the revised EU approach, guidance moves away from prescribing the test methodology that must be used for a particular agent or substrate and moves towards describing the general approach that applicants need to take in order to demonstrate the suitability of the tests applied to show freedom of the relevant substrate from specified EA.

Guidance (4) describes the performance characteristics that need to be demonstrated to enable a decision to be taken on the suitability of the method. Key criteria for test suitability: defined method, sensitivity, specificity, robustness of the method and need for positive and negative controls. This approach allows the applicant more flexibility when deciding the tests to be used for demonstrating freedom from EA, provided that the specified requirements are met and to use any suitable methods for EA testing, provided the performance characteristics, as defined in the guidance, demonstrate its suitability. The list of extraneous agents included in the guidance is taken as reference list which must be taken into account when considering which testing for extraneous agents is appropriate. The current list was established in accordance with the existing knowledge at the time of writing this guideline. If scientifically justified, the list may be updated in the future. The presence of an agent on the list does not mean that a test for this agent must be carried out. However, for not carrying out a test for a specific agent, the applicant must provide justification. A stepwise approach is proposed. The extraneous agents to be tested are those which could not be excluded after justification for not carrying out a test for a specific agent.

USA

In the United States of America (USA) veterinary vaccines are regulated by the Center for Veterinary Biologics (CVB), Animal and Plant Health Inspection Service (APHIS), US Department of Agriculture (USDA) where regulations for safety testing of raw materials (primary cells, cell lines, ingredients of animal origin, master seed virus) used in the production of veterinary vaccines are laid out in title 9, Code of Federal Regulations; Animals and Animal Products (9 CFR), with additional guidance provided in Veterinary Services Memoranda (VSM).

Master cell seeds (MCS) and working cell seeds (WCS) as well as master seed viruses and bacterial seeds used in the production of veterinary vaccines must be tested to exclude extraneous agents (9 CFR 113.55, 113.64(a), 113.100(a)(2), 113.200(c)(4), and 113.300(a)). Furthermore, substances of animal origin used during the manufacture of veterinary vaccines (e.g. serum and trypsin used in the cultivation of cell seeds) must be tested for freedom from extraneous agents (9 CFR 113.53).

For the detection of extraneous agents, *in vivo* and *in vitro* assays are recommended using cell cultures, eggs and animals.

Depending on the test material, cell lines will include some or all of the following (9 CFR 113.52): primary cells and/or cells of the source species; cells sensitive to viruses pathogenic for the species for which the vaccine is intended; cells of the species of the cell line in which the vaccine is produced; cells of bovine origin and VERO cells. In the 9 CFR, lists of viruses that should be tested for by specific means only are included. Cultures are maintained for a minimum specified period with regular subculture and observation for cytopathic effects (CPE) and morphological changes. Primary cells are tested for general extraneous agents as well as those specific for the species of the cells (9 CFR 113.51)

During and/or following the culture period, endpoint tests for viral contaminants are performed on the cells. These include general methods for the use of cell cultures such as cytological staining and haemadsorption assay (HA; 9 CFR 113.46) in addition to specific tests such as immunofluorescence assay (IFA; 9 CFR 113.47). Where in *vitro tests* are not considered to be sensitive enough for the virus of concern, alternative detection methods may be used such as nucleic acid tests (VSM 800.88 and 800.89), *in vivo* tests (9 CFR 113.36) and tests in embryonated eggs (9 CFR 113.37).

Japan

Test on the presence of extraneous viruses is regulated under the Minimum Requirements for Veterinary Biological Products in the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, and Cosmetics in Japan.

Master seed viruses, master cell seeds, and raw materials (such as primary cells and bovine sera) used for the production of live vaccines must be tested for freedom from extraneous agents. For live vaccines not manufactured under the seed-lot system defined in the Minimum Requirements for Veterinary Biological Products, final products need to be tested for freedom from extraneous agents.

Tests for freedom of extraneous agents consist of a general test for the detection of non-specific extraneous agents including unknown agents, and a specific test for the detection of specific agents.

For general tests, samples are inoculated into suitable cell cultures and/or embryonated eggs, and presence of extraneous agents is detected by observation for cytopathic effects, morphological changes and hemagglutinate activity of the culture.

For specific tests, samples are inoculated into susceptible cells and/or animals, and specific viruses are detected by the prescribed protocol (FA test, detection of antibodies, clinical signs, etc.) according to the Minimum Requirements for Veterinary Biological Products.

Cells used for general tests and specific tests are selected by taking into account the animal origin of materials and target animals of products. A list of extraneous agents that should be tested for master seed viruses and master cell seeds is published by the National Veterinary Assay Laboratory.