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4 Guideline on requirements for the production and control 5 of immunological veterinary medicinal products

6 Draft

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8 The guideline was revised to include a new annex (annex 2) entitled “The approach to demonstrate
9 freedom from extraneous agents as part of the production and control of immunological veterinary
10 medicinal products for mammalian species and finfish”, and replace the table of extraneous agents to
11 be tested for in relation to the general and species-specific guidelines on production and control of
12 mammalian veterinary vaccines (7BIm10a).

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Guideline on requirements for the production and control of immunological veterinary medicinal products

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Executive summary

This document provides information on items to be considered for the production and control of all immunological veterinary medicinal products (IVMPs).

The guideline outlines important items related to the quality, safety and efficacy parts of the marketing authorisation dossier that are not sufficiently defined in the requirements of Annex I of Directive 2001/82/EC and the European Pharmacopoeia (Ph. Eur.). Therefore compliance with this guideline (and the above mentioned regulatory documents) provides an assurance that the IVMP will be considered satisfactory by all the Member States.

I. Introduction

The guideline is intended to supplement Directive 2001/82/EC, the European Pharmacopoeia, in particular Ph. Eur. 0062 Vaccines for veterinary use, and relevant VICH guidelines. This guideline intends to clarify the requirements that are not covered by these. Principles of GMP are covered by specific guidance and by Directive 91/412/EC and are out of the scope of this guideline but they should be kept in mind in order to understand the rationale behind the requirements of this guideline.

All IVMPs shall normally comply with this guideline.

Compliance with the guidelines provides an assurance that the research and development work undertaken will be considered valid by all Member States. Nevertheless, in order not to place undue constraints on scientific research, an alternative approach to the one described in a guideline may be used, if it can be shown that this is justified.

Reductions in the requirements that may be acceptable are provided in a specific guideline "Guideline on data requirements for immunological veterinary medicinal products intended for minor use or minor species/limited markets".

Specific requirements for the production and control of immunosera and colostrum substitutes are attached as Annex 1 to this guideline.

The approach to demonstrate freedom from extraneous agents as part of the production and control of IVMPs for mammalian species and finfish is attached as Annex 2 to this guideline.

Guidance on safety and efficacy requirements in the application for marketing authorisation for fish vaccines is outlined in "Guideline on the design of studies to evaluate the safety and efficacy of fish vaccines".

II. Quality

1. Devices

1.1. Definition

Annex I of Directive 2001/82/EC, Title II, Part 2.A, 1. Qualitative particulars states that:

"These particulars shall be supplemented …, together with details of devices with which the IVMP will be used or administered and which will be delivered with the medicinal product. If the device is

not delivered together with the IVMP, relevant information about the device shall be provided, where necessary for the assessment of the product."

For the purpose of this guideline, devices are defined as equipment used for the proper administration of IVMPs and which may influence the safety and efficacy of the product (e.g. devices for spray, intranasal, eye drop, intracutaneous, intrafollicular, *in ovo* administration).

1.2. Data requirements

As the use of a device can have an impact on the safety and efficacy of the IVMP, all the necessary data should be provided:

- A precise description of the device including an analysis of the possible influence on safety and efficacy of the IVMP.
- A detailed description of the sterilisation or disinfection of the device.
- A detailed description of the handling of the device.
- A clear statement of whether the device is delivered together with the IVMP or not
- A clear indication of the sources accessible in each Member State if the device is not delivered with the IVMP.

To avoid the use of inappropriate devices not evaluated in the safety and efficacy trials, the product information should indicate the type of device that should be used when administering the IVMP, and describe the physical and biological prerequisites and specifications of the device (e.g. volume of the delivered dose, pattern of distribution in skin, location of administration (intracutaneous, subcutaneous, and intradermal), pressure of the device, droplet size, etc.).

2. Starting materials and control during the manufacturing process

2.1. Absence of extraneous agents

When the Directive 2001/82/EC and the Ph. Eur. refer to the testing of potential contaminants, Annex 2 (The approach to demonstrate freedom from extraneous agents as part of the production and control of immunological veterinary medicinal products for mammalian species and finfish) to this guideline should be taken into account.

2.2. Antibiotics

Antibiotics used during the production of an IVMP should be used under the restrictions of the Ph. Eur. 0062 Vaccines for veterinary use.

Antibiotics used in the production of IVMPs may be present in the finished product. It is therefore recommended that for IVMPs intended for food producing species, antibiotics for which maximum residue limits (MRLs) have been established in the relevant species should be used (i.e. the antibiotics should be listed in table 1 of the annex to Commission Regulation (EU) 37/2010 for the relevant species). If an antibiotic not listed in table 1 of the annex to Commission Regulation (EU) 37/2010 is used, then the applicant should address the consumer safety implications arising from its potential presence in the finished product. Applicants should note that residues of antibiotics not included in table 1 of Commission Regulation (EU) 37/2010, found at residue control, would be considered as violative residue findings.

The number of antibiotics used has to be justified. The maximum concentration level of antibiotics used during the production should be defined. The level of remaining antibiotic content in the finished product should be indicated in the dossier and can be based on calculation.

2.3. Preservatives

In selecting a preservative system the applicant should consider

- the effectiveness against potential microbial contaminants;
- possible interaction with the formulation or container (for example, thiomersal is ineffective in sera, and can bind to sulphydryl (SH) groups and polymeric material);
- the potential pharmacological and toxicological effects on the target animal species, at the dose rates appropriate to the veterinary medicinal product;
- any MRLs which have been fixed for the preservative substance(s), if appropriate;
- possible effects on testing of the immunological veterinary medicinal product, for example tests on cell cultures or mammalian species.

Long term experience with the use of the preservative in numerous similar products (e.g. thiomersal, formaldehyde) can be regarded as sufficient justification. The test procedures and microorganisms employed for demonstrating preservative efficacy should be as outlined in the Ph. Eur. 5.1.3. Efficacy of antimicrobial preservation. The range of microorganisms chosen for the testing should reflect the potential risk. As the Ph. Eur. allows some flexibility in the experimental conditions and range of microorganisms, the materials and methods for testing, if different from the ones listed in Ph. Eur. 5.1.3., should be described in appropriate detail by the applicant who must also validate the method to “ensure that any residual antimicrobial activity of the product is eliminated by dilution, filtration or by the use of a specific inactivator” in the recovery operation. The maintenance of the quantity of preservative (or the preservative efficacy, if justified) throughout the period of the IVMP shelf life should be demonstrated.

2.4. Diluents

2.4.1. Definition

Annex I of Directive 2001/82/EC, Title II, Part 1.A states that: “Information on diluents needed for making the final vaccine preparation shall be included in the dossier. An immunological veterinary medicinal product is regarded as one product even when more than one diluent is required so that different preparations of the final product can be prepared, which may be for administration by different routes or methods of administration.” The diluent does not contain any active substance.

2.4.2. Data requirements

The data for production and control should follow the principles for IVMPs (Annex I, Title 2), where applicable. The dossier should provide the relevant data especially for:

- Qualitative and quantitative particulars
- Description of the manufacturing method
- Production and control of starting materials

- Control tests during the manufacturing process
- Control of the finished product
- Sterility
- Virucidal/bactericidal effect on the active substance by using the diluent to solve the active substance prior to titration
- Stability tests
- Starting materials used for the production of IVMPs for food producing species should comply with the current MRL legislation.

The IVMP for which the diluent is intended for should be fully tested for safety and efficacy. Provided the relevant studies are performed with the final product solved in the diluent, no separate studies on the diluent concerning safety and efficacy are required.

2.5. Purity of antigen harvest for inactivated vaccines produced on eggs (bioburden)

For viruses grown in eggs, each batch of clarified virus harvest shall be tested for the amount of bacteria present and the value obtained shall be included on the batch test protocol. In general, it is stated that the production (harvest) process should ensure that the bioburden is as low as possible. Reduction of the bioburden and the validation of the inactivation procedures shall be considered not only for the vaccine antigen but also for the amount of bioburden present in the bulk prior to inactivation.

The maximum bioburden should be defined by the applicant, based on data from validation of inactivation and safety studies and it should be controlled in each harvest or bulk as an in process control.

2.6. Inactivation

Annex I of Directive 2001/82/EC states under Title II, Part 2.D Control tests during the manufacturing process: “For inactivated or detoxified vaccines, inactivation or detoxification shall be tested during each production run as soon as possible after the end of the inactivation or detoxification process and after neutralisation if this occurs, but before the next step of production.” Under Title II, Part 2.E Control tests on the finished product, it is mentioned that a test to verify inactivation shall be carried out on the product in the final container unless it has been conducted at a late stage in-process.

It is considered that a single test to confirm complete inactivation carried out at the stage after inactivation when detection of any residual live antigen is most likely should give sufficient assurance of complete inactivation and compliance with the pharmacopoeial standard.

Validation of the inactivation process of IVMPs is subjected to the provision of data showing complete inactivation of the micro-organism. To this aim, according to Ph. Eur. 0062, Vaccines for veterinary use, data on inactivation kinetics should be obtained using the selected method of inactivation. However a clear indication is only given concerning the time required for inactivation which, normally, should not exceed 67% of the duration of the inactivation process. It is considered that extrapolation of inactivation kinetics results (during a 1-step process) to higher pre-inactivation titres than those used in the corresponding validation studies is not permitted. The maximum titre of the micro-

organism capable to be inactivated by the selected method of inactivation should be then established based on the actual data obtained from inactivation kinetics studies.

2.7. Samples

Representative samples of all seed materials (e.g. subsequent passages), reagents, in-process materials and finished product shall be supplied to the competent authorities, on request.

3. Control on the finished product

The control tests on the finished product mentioned in the Annex I of Directive 2001/82/EC under Title II, Part 2.E shall normally be performed on each batch or sub-batch of IVMP produced. In the case of sub-batches which differ only due to their processing after bulk blending, for example in their filling session or vial size, some tests may be carried out on the final bulk or on one of the sub-batches, if justified.

It should be demonstrated that the subsequent procedure does not result in differences in test results and the results obtained from tests on the bulk can be reproduced on the sub-batch(es) of the finished product. For example, it may be expected that tests of potency of inactivated IVMPs could be done on the final bulk. On the other hand, tests for sterility must be carried out on each sub-batch.

3.1. Batch titre or potency

For a live IVMP, the titration of the active substance shall be validated according to the principles of the VICH GL1 "*Guideline on validation of analytical procedures: definition and terminology*" and VICH GL 2 "*Validation of analytical procedures: methodology*". An inactivated IVMP shall be shown to be of satisfactory potency using validated methods.

3.2. Preservatives – Identification and assay of excipients components

Tests for the concentrations of preservatives shall be carried out to show that these are in conformity with the limits set for the product. The concentration of preservative at release can be higher than at the end of the shelf life if the efficacy of the preservative has been demonstrated with the lower concentration. The composition of the product shall indicate the lower concentration of the preservative.

3.3. Safety tests

The Directive 2001/82/EC requests that an overdose safety test is performed on the finished product. As the Ph. Eur. 0062 Vaccines for veterinary use does not request this test anymore, it is considered that the batch safety test is not mandatory as a control of the finished product.

3.4. Batch protocols

The batch protocols should be based on the templates issued by the European Commission and the European Directorate for the Quality of Medicines (EDQM) at the time the batch was produced.

4. Stability tests

Stability testing shall be carried out as specified in the Directive 2001/82/EC and in the Ph. Eur. 0062 Vaccines for veterinary use on not fewer than three representative consecutive batches. The

three consecutive production runs may be carried out on a pilot scale, providing this mimics the full-scale production described in the application. The sterility of the IVMPs has to be proven at the end of the shelf life. This can be achieved by sterility testing or alternatives (e.g. test for container/closure integrity). Where bulk material is to be stored before formulation and final manufacturing, stability data should be provided.

III. Safety and efficacy tests

Animal welfare concerns should be taken into consideration in compliance with Directive 2010/63/EC when designing studies to test the safety and efficacy of IVMPs. Aspects to be considered include:

- Personnel conducting the studies should be appropriately trained to detect signs of illness as well as behavioral changes in the test animals.
- The method used to identify vaccinated and controls animals should involve the least harmful technique for the animals in the study.
- The number of animals in the vaccinated and control groups should be sufficient to obtain statistically significant and clinically reliable results. However, for vaccination-challenge studies, the possibility of reducing the number of control non-vaccinated animals should be investigated as these animals will suffer disease and associated distress.
- Mortality as an evaluation parameter in vaccination-challenge studies should be questioned whenever possible; humane endpoints are preferable. Moribund animals should be humanely killed.

1. Safety tests

Safety testing shall be carried out as specified in the Ph. Eur. 5.2.6 Evaluation of safety of veterinary vaccines and immunosera, and in Directive 2001/82/EC. The IVMPs to be tested shall be diluted in the recommended diluent, if appropriate.

2. Field trials

Safety and efficacy must be studied in field trials performed on a sufficient number of target species distributed in more than one premises.

Annex 1 - Additional items, specific requirements for the production and control of immunosera and colostrum substitutes

This annex is intended to provide additional guidance on the type of data which should be included in applications for marketing authorisations for immunosera and colostrum substitutes. It is intended to supplement Directive 2001/82/EC and the general guideline.

The annex has not been prepared to give guidance for applications for products containing monoclonal antibodies and may not be applicable to such products.

DEFINITIONS

The definitions in the Ph. Eur. 0030 Immunosera for veterinary use apply together with the following additional definition:

Immunoserum – a veterinary medicinal product containing for example, polyclonal antibodies, or immunoglobulin fractions, or antibodies produced in eggs and used to provide passive immunity, through its immunoglobulin content.

Colostrum Substitute – a veterinary medicinal product for administration by the oral route to new-born animals to provide passive immunity, through its immunoglobulin content. It contains, for example, polyclonal antibodies, or immunoglobulin fractions, or antibodies produced in eggs.

Donor Animal – an animal which is kept for the production of immunoserum or colostrum or antibodies produced in eggs.

The donor animals may or may not have been actively immunised to boost the concentration of immunoglobulins to one or more specific antigens.

1. Starting materials

Preparation of the material containing the active ingredient

1.1 Donor animals

Donor animals should comply with the Ph. Eur. 0030 Immunosera for veterinary use 01/2008/0030.

Detailed information must be provided of the testing regime used to monitor the health status of the animals and this must include information on the test methods used and their validation.

1.2 Immunising antigen

Immunising antigen should comply with the Ph. Eur. 0030 Immunosera for veterinary use 01/2008/0030.

Wherever possible, the immunising antigen used should be a product with a marketing authorisation granted in the relevant Member State, in accordance with the requirements of Directive 2001/82/EC.

When an authorised product is used, it will be sufficient, in the dossier provided in support of the application for a marketing authorisation for the immunoserum or colostrum substitute, to provide

brief details of the immunising antigen (e.g. name, licence number, holder of the marketing authorisation, manufacturer(s) and the SPC).

Where the immunising antigen is not an authorised product the principles and the format of Directive 2001/82/EC and this guideline can be used as a guide for this.

For live organisms, for inoculation into a donor animal, information should also be provided on the safety of the organisms for the donor animal and it may be necessary to provide information on the rate of clearance of the organism from the material to be collected from the donor (e.g. where there may be a long lasting infection or a short time from immunisation to collection of material).

2. Finished product – batch testing for sterility

The product shall be shown to meet the requirements of the Ph. Eur. 2.6.1. Sterility and 2.6.7.Mycoplasmas unless it is a colostrum substitute to be administered orally, in which case it may contain not more than one saprophytic organism per dose.

Annex 2 - The approach to demonstrate freedom from extraneous agents as part of the production and control of immunological veterinary medicinal products for mammalian species and finfish

1. Explanatory note

Freedom from extraneous agents is a high priority for any medicinal product. For any IVMP placed on the market in the EU, the requirement to test IVMPs for potential infectious contaminants is specified in Directive 2001/82/EC and in the European Pharmacopoeia (Ph. Eur.) (Monographs 0062 and 0030, general chapters 5.2.4 and 5.2.5).

Prevention of potential contamination through extraneous agent 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) in order to assure consistent production; and, tests confirming the quality of starting and in-process materials as well as the final product.

Therefore the testing refers to all components of animal origin (cell substrates, virus seeds, substances of animal origin), in-process materials and the finished product, as specified in the respective legislation, Ph. Eur. and relevant guidelines. Different requirements may apply. For master seed virus lots no living organisms of any kind other than the species and strain stated is the rule (Ph. Eur. 0062). Cell seeds must not be contaminated by viruses (Ph. Eur. 5.2.4). Batches of substances of animal origin if found contaminated are either discarded or reprocessed and shown to be satisfactory (Ph. Eur. 5.2.5).

This annex is applicable to IVMPs for mammalian species and finfish. 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.

As indicated in the Ph. Eur., consideration has to be given to the species of origin of the test material and the target species for the product. In addition, the applicant must also take into account:

1. the disease situation in the country of origin, including emerging or re-emerging diseases - in this context, this annex should be read in conjunction with the Clarification note on the requirements for the starting materials of biological origin (EMEA/CVMP/439633/2007),
2. the nature of the material, and
3. for cell cultures, their permissivity to extraneous agents from other species than the species of origin of the cells and the target species of the vaccine, if the cells have been maintained in the presence of substances of animal origin of other species, unless these substances were subjected to appropriate virus inactivation procedures.

The list of extraneous agents as provided in section 2 of this document, 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 according to the steps mentioned below.

For appropriate testing for extraneous agents, the following steps should be accomplished:

Step 1: Justification for not carrying out a test for a specific agent

The types of justification that can be given include:

a) Disease/agent did not occur in country/geographical area of origin at the time of isolation/recovery of the material supported by convincing official data (e.g. OIE's status in the applicable time period, literature information); continuous traceability to support the absence of contamination by this agent during subsequent processing of the material (e.g. preparation, culture, etc.).

b) Disease/agent does not occur in herd of origin (i.e. specific pathogen free (SPF) status). Supporting documentary evidence must be provided for monitoring with serological and/or agent detection methods, accompanied by strict biosecurity measures. For an example refer to "Donor animals" in Ph. Eur. 0030 Immunosera for veterinary use.

c) Substance in question cannot be contaminated with this agent, e.g. agent does not cross placenta or does not produce viraemia. Adequate justification must be provided.

d) The need for testing might not be relevant when an extraneous agent cannot grow in some systems or under some specific conditions, e.g. the extraneous agent does not grow in cell culture, or does not grow in the absence of trypsin.

e) Where applicable, the agent can be inactivated using a validated method. Alternatively, a demonstration that the extraneous agent is removed by the production process may be acceptable as well, including an adequate justification.

f) For active substances derived by recombinant DNA techniques, the presence of extraneous agents from the species of origin or the target species can often be excluded because of the implemented biotechnological processes. Testing for extraneous agents may therefore not be necessary. In cases of partial or complete omission of testing, a risk assessment must be made, including the materials of animal origin that were/are used to produce the rDNA-derived active substance, and a thorough justification must be provided.

Step 2: Implementation of tests for the detection of extraneous agents

The extraneous agents to be tested are those which could not be excluded after implementation of step 1.

The suitability of test methods used to detect extraneous agents is an essential prerequisite. The following aspects are identified as key criteria for test suitability: defined method, sensitivity, specificity, robustness of the method and need for positive and negative controls.

The parameters used to show suitability should be chosen based on the purpose of the assay. Proven testing and production experience are good tools to justify the suitability of test methods. The use of positive controls is of major importance, e.g. for general tests on cell cultures. Whenever one cell culture is used to detect several agents, the use of one agent as positive control is sufficient to demonstrate the suitable growth characteristics of the cell culture.

Alternatively, test methods described in the document "CVMP reflection paper on methods found suitable within the EU for demonstrating freedom from extraneous agents of the seeds used for the production of immunological veterinary medicinal products for mammalian species and finfish" (EMA/CVMP/IWP/251741/2015) can be considered when implemented by qualified laboratories.

For the detection of viruses, appropriate methods for virus isolation and identification can be used and criteria established, e.g. cytopathic effect, haemadsorption, immunostaining, etc (Ph. Eur. 0062, 5.2.4, 5.2.5). Their sensitivity for specified agents should be known not only for laboratory adapted strains, but also for field (wild) strains.

The use of primary cells of the species of origin of the seed is mandatory by Ph. Eur. 0062 and Ph. Eur. 5.2.4. Hence, suitable primary cells must be part of the cell types selected for the detection of extraneous viruses not excluded by step 1.

Selected bacteria in the list below 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 in IVMPs. These tests should be implemented on a case-by-case basis, whenever relevant. A thorough justification must be provided for the complete or partial omission of these testing.

Antigen and genome detection methods (e.g. PCR) can also be used. Their sensitivity and specificity for specified agents should be known for laboratory adapted strains and field (wild) strains. These methods do not usually differentiate between live and inactivated agents. In case of a positive finding an appropriate method for differentiation should be implemented.

Detection of an agent may also be based on detection of corresponding antibodies. In this case, appropriate serological methods should be used.

2. List of extraneous agents

Extraneous agents are listed below, divided into sections by animal species.

International Committee on Taxonomy of Viruses (ICTV) virus nomenclature is followed. Viruses are listed as family, genus or species. All relevant types should be considered.

BOVINE	
Viral agents	***Bacterial agents***
Akabane virus	Brucella spp.
Alcelaphine herpesvirus	Chlamydia spp.
Bluetongue virus	Coxiella burnetii
Borna disease virus	Leptospira spp.
Bovine adenovirus	
Bovine coronavirus	
Bovine enterovirus	
Bovine ephemeral fever virus	
Bovine herpesvirus BoHV-1 (IBR)	
Bovine leukaemia virus	
Bovine papilloma virus	
Bovine papular stomatitis virus	
Bovine parainfluenza virus 3	
Bovine parvovirus	

Bovine polyoma virus Bovine respiratory syncytial virus Bovine rhinovirus Bovine viral diarrhoea virus Cache Valley virus Cowpox virus Endogenous retrovirus (replication competent) Epizootic haemorrhagic disease virus Foot-and-mouth disease virus Jena virus (Norwalk-like) Lumpy skin disease virus Ovine herpesvirus 2 (malignant catarrhal fever virus, European type) Pseudocowpox virus Rabies virus Reovirus Rift Valley fever virus Rinderpest virus Rotavirus Schmallenberg virus Swine herpesvirus 1 Tick-borne encephalitis virus Vesicular stomatitis virus Wesselsbron virus	

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OVINE/CAPRINE	
Viral agents	***Bacterial agents***
Akabane virus Bluetongue virus Border disease virus Borna disease virus Bovine viral diarrhoea virus Cache Valley virus Caprine herpesvirus Endogenous retrovirus (replication competent) Epizootic haemorrhagic disease virus Foot-and-mouth disease virus Maedi-Visna / Caprine arthritis encephalitis virus Nairobi sheep disease virus Orf virus Ovine herpesvirus 2 (malignant catarrhal fever virus, European type) Ovine papilloma virus Ovine pulmonary adenocarcinoma virus (jaagziekte) Ovine respiratory syncytial virus Ovine/caprine adenovirus	Brucella melitensis Brucella ovis Chlamydia spp. Coxiella burnetii Leptospira spp.

Peste-des-petits-ruminants virus Rabies virus Rift Valley Fever virus Sheeppox / goatpox virus Schmallenberg virus Swine herpesvirus 1 Tick-borne encephalitis virus Wesselsbron virus	

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PORCINE	
Viral agents	***Bacterial agents***
African swine fever virus Bovine viral diarrhoea virus Classical swine fever virus Encephalomyocarditis virus Endogenous retrovirus (replication competent) Foot-and-mouth disease virus Hepatitis E virus Influenza virus Japanese encephalitis virus Nipah virus Porcine adenovirus Porcine circovirus Porcine coronavirus (TGEV, PRCoV, PEDV) Porcine enterovirus Porcine parvovirus Porcine reproductive respiratory syndrome virus Porcine rotavirus Rabies virus Swine herpesvirus Swinepox virus Vesicular stomatitis virus	Brucella suis Leptospira spp.

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EQUINE	
Viral agents	***Bacterial agents***
African horse sickness virus Borna disease virus Endogenous retrovirus (replication competent) Equine adenovirus Equine arteritis virus Equine encephalomyelitis alphavirus Equine encephalosis virus Equine herpesvirus (EHV-1, EHV-4) Equine infectious anaemia virus Equine influenza virus Equine rotavirus	Burkholderia mallei Burkholderia pseudomallei

Hendra virus Japanese encephalitis virus Rabies virus Vesicular stomatitis virus West Nile virus	

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CANINE	
Viral agents	***Bacterial agents***
Canid herpesvirus Canine adenovirus Canine coronavirus Canine distemper virus Canine oral papilloma virus Canine Parainfluenza 2 virus Canine parvovirus Rabies virus Swine herpesvirus 1	Brucella canis Leptospira spp.

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FELINE	
Viral agents	***Bacterial agents***
Cowpox virus Endogenous retrovirus (replication competent) Feline calicivirus Feline coronavirus Feline foamy virus (feline syncytia forming virus) Feline herpesvirus 1 Feline immunodeficiency virus Feline leukemia virus Feline panleucopenia virus Feline sarcoma virus Rabies virus Swine herpesvirus 1	Chlamydia felis

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RABBIT	
Viral agents	***Bacterial agents***
Arenavirus (Lymphocytic choriomeningitis virus) Encephalomyocarditis virus Endogenous retrovirus (replication competent) Herpes simplex-like virus Leporid herpesvirus 2 Myxoma fibroma virus Rabbit enteric coronavirus Rabbit haemorrhagic disease virus	Francisella tularensis

Rabbit parvovirus Rabbit pox virus Rabies virus Rotavirus Swine herpesvirus 1	

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RODENT (MOUSE)	
Viral agents	***Bacterial agents***
Ectromelia virus Endogenous retrovirus (replication competent) Hantaan virus Kilham rat virus Lactic dehydrogenase elevating virus Lymphocytic chorio-meningitis virus Minute virus of mice Mouse adenovirus Mouse cytomegalovirus Mouse encephalomyelitis virus Mouse hepatitis virus Mouse rotavirus Pneumonia virus of mice Polyoma virus Reovirus type 3 Sendai virus Thymic virus	Cilia associated respiratory bacillus Helicobacter spp.

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RODENT (HAMSTER)	
Viral agents	***Bacterial agents***
Endogenous retrovirus (replication competent) Lymphocytic chorio-meningitis virus Pneumonia virus of mice Reovirus type 3 Sendai virus Simian virus type 5	Cilia associated respiratory bacillus Helicobacter spp.

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RODENT (RAT)	
Viral agents	***Bacterial agents***
Endogenous retrovirus (replication competent) Hantaan virus Kilham rat virus Mouse encephalomyelitis virus Pneumonia virus of mice Rat coronavirus/Sialoacryoadenitis virus Reovirus type 3 Sendai virus	Cilia associated respiratory bacillus Helicobacter spp.

Toolan viru	

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PRIMATES (VERO CELL)	
Viral agents	***Bacterial agents***
Bovine viral diarrhoea virus Endogenous retrovirus (replication competent) Herpesvirus Reovirus Simian virus 40 Simian virus 5	

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FINFISH	
Viral agents	***Bacterial agents***
Betanodavirus Channel catfish virus Epizootic haematopoietic necrosis virus (EHNV) Infectious haematopoietic necrosis virus (IHNV) Infectious pancreatic necrosis virus (IPNV) Infectious salmon anaemia virus (ISAV) Koi herpes virus Oncorhynchous masou virus Perch rhabdovirus Red sea bream iridovirus Salmon alphaviruses Spring viraemia of carp virus (SVCV) Viral haemorrhagic septicaemia virus (VHSV)	Aeromonas salmonicida (Ph.Eur 2.6.1 may be used provided the suitability of the Ph. Eur. 2.6.1 method to detect this agent is demonstrated). Edwardsiella ictaluri Fish-pathogenic Francisella spp. Flavobacterium psychrophilum Piscirickettsia salmonis Renibacterium salmoninarum, Vibrio anguillarum

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