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4 Table of extraneous agents to be tested for in relation 5 to the Guideline on requirements for the production and 6 control of immunological veterinary medicinal products

7 Draft

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Comments should be provided using this template. The completed comments form should be sent to vet-guidelines@ema.europa.eu

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Table of extraneous agents to be tested for in relation to the Guideline on requirements for the production and control of immunological veterinary medicinal products

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1. Explanatory note

In Directive 2001/82/EC, and in the European Pharmacopoeia (Ph. Eur.) (0062, 0030, 5.2.4, 5.2.5) there is a requirement to test immunological veterinary medicinal products for potential contaminants. Based on those, the Guideline on the *Requirements for the Production and Control of Immunological Veterinary Medicinal Products* (EMA/CVMP/IWP/206555/2010) requires that a table of extraneous agents should be taken into account.

The testing refers to all components of animal origin (cell substrates, virus seeds, substances of animal origin), and the final product, as specified in the respective legislation, Ph. Eur. and relevant guidelines. Different requirements may apply: for master seed lots “no living organisms of any kind other than the species and strain stated” are permitted (0062). Batches of substances of animal origin, if found contaminated, are “either discarded or reprocessed and shown to be satisfactory” (5.2.5).

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 the permissivity of cells to other agents than those from the species of origin of the raw material and those from the target species.

The following table contains a list of agents which must be taken into account when considering what testing for extraneous agents is appropriate. The list is not exhaustive. Other agents in addition to those listed in the table might have to be considered, if scientifically justified, by the competent authority. On the contrary, the presence of an agent on the list does not mean that a test for that agent must be carried out. However, for not carrying out a test for an agent, the applicant must provide justification based on a risk assessment.

The following procedure should be followed:

Step 1: Justification that an agent can be excluded from testing.

The types of justification that can be given include:

a) Disease/agent does not occur in country of origin and material could not have been contaminated by this agent subsequently (e.g. traceability). Convincing supporting official documented evidence should be provided (e.g. current OIE status).

b) Disease/agent does not occur in herd of origin (i.e. specific pathogen free status, SPF). 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 “Immunosera for veterinary use” (Ph. Eur. 0030).

c) Substance in question cannot be contaminated with this agent, e.g. agent does not cross placenta or does not produce viraemia. Strong justification must be provided, as for example, it is easier to prove that an agent regularly crosses the placenta but it is not easy to prove that it may not exceptionally do it.

d) Where applicable (e.g. for substances of animal origin), the agent can be inactivated using a validated method. Alternatively, a demonstration that the contaminant is removed by the

production process may be acceptable as well, including an adequate justification and risk-benefit analysis.

Step 2: Testing

The extraneous agents to be tested are viruses and selected bacteria.

All test methods should be validated. The parameters to be validated in each case should be chosen in agreement with the purpose of the assay. Alternatively, test methods described in dossiers for which marketing authorizations were granted within the EU might be suitable without any further validations.

For the detection of viruses, appropriate methods for virus isolation and identification can be used (cell cultures, embryonated eggs, animal inoculation) 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.

Selected bacteria include those not detectable by the sterility test (Ph. Eur. 2.6.1). Specific tests include mycobacteria (2.6.2) and mycoplasmas (2.6.7). Specific tests should also be used for the detection of obligatory intracellular bacteria (e.g. *Chlamydophila*, *Coxiella*).

Antigen and genome detection methods (e.g. PCR) can also be used, under the same requirements as above. Their specificity should be known (e.g. group or type specific). However, these methods do not usually differentiate between live and inactivated agents. When the purpose is to detect live contaminating agents, 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 (e.g. application in detecting of specified extraneous agents in SPF herds).

2. Table of extraneous agents

The table is 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.

Extraneous agents for Avian Vaccines are dealt in the specific chapter of the Ph. Eur. For Transmissible Spongiform Encephalopathies (TSEs) the specific TSE Note for Guidance applies.

BOVINE

Viral agents

Akabane virus

Alcelaphine herpesvirus

Bluetongue virus

Borna disease virus

Bovine adenovirus

Bovine coronavirus

Bovine enterovirus

Bovine ephemeral fever virus

Bovine herpesvirus

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

Swine herpesvirus 1

Tick-borne encephalitis virus

Vesicular stomatitis virus

Wesselsbron virus

Bacterial agents

***Brucella* spp**

***Chlamydophila* spp.**

Coxiella burnetii

***Leptospira* spp.**

Mycobacterium paratuberculosis

***Mycobacterium* spp.**

***Mycoplasma* spp.**

OVINE/CAPRINE

Viral 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

Peste-des-petits ruminants virus

Rabies virus

Rift Valley Fever virus

Sheeppox / goatpox virus

Swine herpesvirus 1

Tick-borne encephalitis virus

Wesselsbron virus

Bacterial agents

***Brucella* spp**

***Chlamydophila* spp.**

Coxiella burnetii

***Leptospira* spp.**

Mycobacterium paratuberculosis

***Mycobacterium* spp**

***Mycoplasma* spp.**

PORCINE

Viral 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

Porcine enterovirus

Porcine parvovirus

Porcine reproductive respiratory syndrome virus

Porcine retrovirus

Porcine rotavirus

Rabies virus

Swine herpesvirus

Swinepox virus

Vesicular stomatitis virus

Bacterial agents

***Brucella* spp**

***Leptospira* spp.**

***Mycoplasma* spp.**

EQUINE

Viral 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

Equine infectious anemia virus

Equine influenza virus

Equine rotavirus

Hendra virus

Japanese encephalitis virus

Rabies virus

Vesicular stomatitis virus

West Nile virus

Bacterial agents

Burkholderia mallei

Burkholderia pseudomallei

CANINE

Viral agents

Canid herpesvirus

Canine adenovirus

Canine coronavirus

Canine distemper virus

Canine oral papilloma virus

Canine Parainfluenza 2 virus

Canine parvovirus

Endogenous retrovirus (replication competent)

Rabies virus

Swine herpesvirus 1

Bacterial agents

Brucella canis

***Leptospira* spp.**

FELINE

Viral 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

Bacterial agents

Chlamydophila felis

RABBIT[1]

Viral agents

Arenavirus (Lymphocytic choriomeningitis virus)

Encephalomyocarditis virus

Endogenous retrovirus (replication competent)

Herpes simplex-like virus

Leporid herpesvirus 2

Myxoma fibroma virus

Pleural effusion disease virus

Rabbit enteric adenovirus

Rabbit enteric coronavirus

Rabbit hemorrhagic disease virus

Rabbit kidney vacuolating virus

Rabbit parvovirus

Rabbit pox virus

Rabies virus

Rotavirus type 1

Swine herpesvirus 1

Bacterial agents

Francisella tularensis

RODENT (MOUSE, RAT, HAMSTER) [2]

MOUSE

Viral agents

Ectromelia virus

Endogenous retrovirus (replication competent)

Hantaan virus

Kilham rat virus

Lactic dehydrogenase elevating virus

Lymphocytic chorio-meningitis virus

[1] Agents tested for rabbit SPF colonies by commercial and institutional laboratories are included.
[2] Note for Guidance on quality of biotechnological products: Viral safety evaluation of biotechnology products derived from cell lines of human or animal origin (CPMP/ICH/295/95).

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

Bacterial agents

Cilia associated respiratory bacillus

Helicobacter

Mycoplasma pulmonis

HAMSTER

Viral agents

Endogenous retrovirus (replication competent)

Lymphocytic chorio-meningitis virus

Pneumonia virus of mice

Reovirus type 3

Sendai virus

Simian vacuolating virus type 5

Bacterial agents

Cilia associated respiratory bacillus

Helicobacter

Mycoplasma pulmonis

RAT

Viral agents

Endogenous retrovirus (replication competent)

Hantaan virus

Kilham rat virus

Mouse encephalomyelitis virus

Pneumonia virus of mice

Rat coronavirus

Reovirus type 3

Sendai virus

Sialoacryoadenitis virus

Toolan virus

Bacterial agents

Cilia associated respiratory bacillus

Helicobacter

Mycoplasma pulmonis

PRIMATES (e.g. VERO CELLS)

Viral agents

Bovine viral diarrhoea virus

Endogenous retrovirus (replication competent)

Herpesvirus

Reovirus

Simian vacuolating virus 40

Simian vacuolating virus 5

Bacterial agents

***Mycobacterium* spp.**

***Mycoplasma* spp.**

FINFISH

Viral agents

Betanodavirus

Channel catfish virus

Epizootic haematopoietic necrosis virus

Infectious haematopoietic necrosis virus

Infectious pancreatic necrosis virus

Infectious salmon anaemia virus

Koi herpes virus

Oncorhynchous masou virus

Perch rhabdovirus

Red sea bream iridovirus

Salmon alphaviruses

Spring viraemia of carp virus

Viral haemorrhagic septicaemia virus

Bacterial agents

Aeromonas salmonicida

Edwardsiella ictaluri

Fish-pathogenic *Francisella* spp.

Flavobacterium psychrophilum

Piscirickettsia salmonis

Renibacterium salmoninarum,

Vibrio anguillarum