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SCIENCE MEDICINES HEALTH

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Committee for Medicinal Products for Veterinary Use (CVMP)

Questions and Answers on management of extraneous agents in immunological veterinary medicinal products (IVMPs)

Background

Freedom from extraneous agents (EAs) is a high priority for any medicinal product. For any IVMP placed on the market in the EU, freedom from EAs (bacteria, mycoplasma, fungi and viruses) shall be demonstrated according to the requirements of the European Pharmacopoeia (Ph. Eur.).

Prevention of potential contamination encompasses the entire production process, from raw (starting) materials to the final product. This includes reliable sourcing of raw materials; standardised, controlled production processes using Good Manufacturing Practices (GMP) in order to assure consistent production; and, testing to confirm the quality of starting and in-process materials as well as the final product. Therefore, the management of potential contamination also comprises all components of animal origin such as seed materials, substrates for production (e.g. cell substrates, embryonated eggs, animals), ingredients in culture media, other substances, in-process materials and the final product, as specified in the Ph. Eur. and relevant EMA guidelines.

The revised Ph. Eur. approach for management of EAs which is elaborated in monographs and general chapters has changed from a prescriptive approach, mainly relying on extensive laboratory testing, to a scientifically sound and targeted risk-based approach. It is restricted to living replicative EAs and includes a reference to risk management including risk assessment and risk control.

Regulatory challenges/concerns regarding the implementation of this risk management approach to potential contamination by EAs have been identified during public consultation of the Ph. Eur. texts. According to industry, the described approach would introduce uncertainty into the development cycle of both new vaccines using new seed materials and new vaccines using existing seeds that have been previously approved; unpredictability and the risk that EAs status of existing seeds may be brought into doubt could have an impact on the availability of IVMPs in future. These aspects are considered to be outside the scope of Ph. Eur. texts, in particular where matters for authorisation are concerned.

The aim of this question and answer document is to address the aforementioned comments and concerns on the revised risk management approach to the potential for EA contamination on areas concerning the authorisation of IVMPs and to provide clarification on these aspects.

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Question 1:

What is required with respect to re-testing of existing cell banks and master seeds? - Applicability of revised/new requirements to seeds as starting materials for existing products or for new products where the seed is already in use for existing products.

Answer:

The new/revised Ph. Eur. requirements apply to new products, cell banks and master seeds but also to existing products and existing cell banks and master seeds used for the production of new products.

For existing cell banks and master seeds currently used in approved products in the EU no re-testing is required.

If an existing cell bank/master seed (currently used in approved products) is to be used in a new product, a thorough risk assessment as outlined in the Ph. Eur. texts should be provided. Tests performed already for the existing cell banks/master seeds are in most cases found acceptable. Re-validation of these test methods is not required (see Question 2). All documentation for originally performed tests should however be provided in the dossier. Justification should be provided for all EAs for which testing is not provided with regard to the list of EAs included in Annex I of Ph. Eur. 5.2.5. Examples of types of justification for not performing a test for a specific EA (or disease) in cell seeds/master seeds are given in answer to question 4. If new EAs have been identified since the original tests were performed, testing will be required if the presence of this EA cannot be excluded by a risk assessment. Justification provided for specific EAs not tested for should be supported by reliable independent sources and scientific evidence. Additionally, new developments in science or methodologies of detection should be taken in consideration.

For new products with new master cell banks/master seeds, the new/revised requirements need to be fulfilled. Furthermore, the new/revised Ph. Eur. requirements need to be fulfilled when introducing a new master cell bank/master seed to an existing product.

Question 2:

Previous requirements and detailed testing methods as mentioned in the previous versions of Ph. Eur. (before 10.2 supplement): can they still be used?

Answer:

Detailed descriptions of the test methods for EAs in materials which are used during the manufacture of IVMPs previously referred to in Monograph 0062, chapter 5.2.4, chapter 2.6.24 and chapter 2.6.25 were deleted. The new approach on managing EAs is now described in Ph. Eur. chapter 5.2.5 and chapter 2.6.37.

The test methods for EAs described in previous versions of Ph. Eur. (up until July 2020) performed originally for existing cell seeds/master seeds (both used in approved and in new products) are in most cases found acceptable. They were used by applicants for decades and accepted by regulatory authorities to grant marketing authorisations for IVMPs. These detailed test methods can still be used with the new approach if they have been shown to be fit for purpose. No further validation or re-validation will be requested if the methods are compliant with previous Ph. Eur. requirements and if valid controls are included in each test run (appropriate positive run controls with specified content of a

representative agent and negative run controls, in order to validate the results and evaluate test performance).

Detailed protocols for these methods deleted from the current Ph. Eur. edition, can be referenced in the Ph. Eur. archives (https://pheur.edqm.eu/app/arch/search/).

Question 3:

Validation of new test techniques – What is the expectation with regard to validation and documentation in the dossier?

Answer:

IVMPs, including components of biological origin used in their production, must be free from contaminating EAs. Careful consideration should be given to the suitability of test methods used to detect an extraneous agent and should be considered as an essential prerequisite.

In principle, the concepts presented in VICH GL1 (Validation: definition) and VICH GL2 (Validation: methodology) are applicable to the analytical methods used for the detection of EAs as the objective of validation of an analytical procedure is to demonstrate that it is suitable for its intended purpose and that the test results obtained are of relevance. Nevertheless, due to their complex nature, analytical procedures for biological products may be approached slightly differently and not all validation characteristics mentioned in the guidelines may be necessary. Omission of certain validation characteristics as specified in the guidelines should be justified accordingly.

As outlined in EMA/CVMP/IWP/206555/2010[1], the following aspects are identified as key parameters for test suitability: defined method, sensitivity, specificity, repeatability of the method and need for positive and negative controls. If available, the controls used may be provided by reference laboratories (as such nominated by OIE, WHO, EU or other competent authorities).

With regard to the methods used to detect EAs, among all the validation characteristics that are necessary, the following criteria will be considered with special attention:

- Specificity of the assay, which is the ability to distinguish unequivocally an EA in the presence of components that may be expected to be present and interfere with the targeted EA. Specificity is defined as the ability of the test to correctly identify the true negative rate.
- Sensitivity of the assay, is the ability to detect the presence of the EA enabling as accurate as possible a measurement. Sensitivity is defined as the ability of a test to correctly identify the true positive rate. The limit of detection (LOD) is a measure of the analytical sensitivity of the method. It corresponds to the lowest amount of EA in a sample that can be detected but not necessarily quantitated as an exact value.
- The method sensitivity and specificity for EAs should be known for laboratory adapted and field (wild) strains, as well as their suitability for the detection of field (wild) strains.

The results obtained for these parameters should allow for demonstration that the method used should be "fit for purpose", i.e. able to detect satisfactorily EAs.

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

The method is considered specific if it is able to differentiate an EA from similar organisms or other interference from components of the sample other than the analyte of interest that could have a positive or negative effect on the assay value.

The validation assay should be adapted to the method of detection on a case by case basis. For example, if the method is an ELISA assay, the specificity should be demonstrated by testing other relevant microorganisms and showing that there is no cross-reaction. In the case of a PCR assay it must be able to detect all (known, relevant) strains/serotypes. The details of the primers and probes should be provided and their specificity to detect relevant EAs should be investigated by comparing the chosen sequences with sequences in published data banks. There should be no major homology found with sequences unrelated to the EA. Independent of method, the use of quality control samples (positive controls (including positive controls around the cut off to confirm test performance)/negative/internal controls) is necessary in each run to validate the results and evaluate test performance.

Since specificity and sensitivity are relative parameters, it is necessary to maintain a balance between specificity and sensitivity with respect to the potential contamination by the agent under investigation. Therefore, the applicant should justify the proposed parameters of the methodology with regard to the EA to be tested. Test controls should always be included. For NAT methods, there should always be external controls (positive and negative controls) for each sample included.

For the LOD, the same approach applies and no acceptable cut-off can be defined a priori. A justification of the cut-off limits should be described with relevancy to the test method used for the particular agent being tested (in a relevant matrix) and the target species (literature references could be used to support this and/or the minimum infectious dose if available from known challenge studies). The relevance of the results obtained in the validation assay should be assessed with regard to the risk of contamination by living replicative EAs.

Development of new techniques of detection of EAs is encouraged. Collaboration and dialogue between industry and regulatory authorities are necessary to facilitate the development, standardisation and regulatory acceptance of new techniques for the detection of EAs in veterinary medicinal products.

Question 4:

Uncertainty regarding assessment based on a risk management approach – What kind of justification is required for not carrying out a test for a specific agent? Is reference to bibliographic data acceptable?

Answer:

No single measure or combination of measures can ensure the safety of use of materials of animal and human origin, but they can reduce the risks associated with such use. The risk of contamination of the materials and the resulting IVMP with EAs must always be managed.

Updated reference lists of EAs, which may be present in the material of animal origin are provided in Ph. Eur. chapter 5.2.5, Annex I should be considered as part of the risk assessment. The lists provided in Annex I do not preclude additional agents from being considered, if necessary.

The presence of an agent on the lists 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.

Examples for types of justification for not performing a test for a specific agent are given below. Justification should be supported by reliable independent sources and scientific evidence.

- Disease/agent did not occur in country/geographical area of origin at the time of isolation/recovery of the material and the time supported by convincing official data (e.g. OIE's status in the applicable time period, official websites, literature information); continuous traceability to support the absence of contamination by this agent during subsequent processing of the material (e.g. preparation, culture, etc.).
- Disease/agent does not occur in herd of origin (i.e. specific pathogen free (SPF) status). If animals from a flock free from specified pathogens are used, supporting documentary evidence must be provided for the SPF status of the herd. SPF certificates indicating the methods of control used and showing that the herd is free of the respective EA must be provided. If animals from conventional healthy herds are used, the herd management practices, the sanitary status, the routine testing performed should be described and should guarantee that the risks of contamination by specified EAs is under control.
- Substance in question/type of material cannot be contaminated with this agent, e.g. agent does not cross placenta, does not transmit vertically via eggs or does not produce viraemia. Adequate justification must be provided, e.g. by literature.
- The likely infectivity in the source organ or tissue and results of any test for EAs already available can be taken into consideration.
- The need for testing might not be relevant when an EA cannot grow in some systems or under some specific conditions, e.g. the EA does not grow in cell culture, or does not grow in the absence of trypsin. The capacity of the production process to amplify an EA should be considered. Bibliographical references/literature can be used to confirm that the contaminating EA present in a starting material cannot replicate in the substrate used for the production.
- Where applicable, the agent can be removed (e.g. by purification), sterilised or inactivated using a validated method. The effectiveness of any specific treatment applied to materials, which depends on the resistance of the potential EAs to this treatment and the extent of contamination should be shown. Alternatively, a demonstration that the EA is removed by the production process may be acceptable as well, including an adequate justification. Bibliographical references if relevant to the specific case are suitable, too.
- For active substances derived by recombinant DNA techniques, the presence of EAs from the species of origin or the target species can often be excluded because of the implemented biotechnological processes. Testing for EAs in these regards may therefore not be necessary. In any case, 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.

The EAs to be tested are those which could not be excluded by justification. For detection of EAs in IVMPs highly sensitive methods should be used. In vitro methods should be used, if available.