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GUIDELINE ON DATA REQUIREMENTS FOR THE REPLACEMENT OF ESTABLISHED MASTER SEEDS (MS) ALREADY USED IN AUTHORISED IMMUNOLOGICAL VETERINARY MEDICINAL PRODUCTS (IVMPs)

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GUIDELINE ON DATA REQUIREMENTS FOR THE REPLACEMENT OF ESTABLISHED MASTER SEEDS (MS) ALREADY USED IN AUTHORISED IMMUNOLOGICAL VETERINARY MEDICINAL PRODUCTS (IVMPs)

1. INTRODUCTION (background)

The production of vaccines is usually based on seed lots. For this purpose, a seed lot system is established at the manufacturers. When necessary, a WS is derived from the Master Seed (MS) and is used as starting micro-organism/cell to produce the final vaccine. In certain circumstances, the MS must be replaced, usually because either the seed material is depleted or because of new regulatory requirements. Normally, the introduction of a new MS requires a new Marketing Authorisation application. A number of Marketing Authorisation Holders (MAHs) have in such cases withdrawn the product from the market, rather than make new applications.

2. SCOPE

This guideline applies to the replacement of an antigen (e.g. virus, bacteria, fungus) master seed by a master seed of the same origin. It applies also to the replacement of the master cell seed used to produce a vaccine organism by a master cell seed of the same origin.

The replacement of MS traces back to the original isolates of antigens and/or the original passage of a cell line. Starting from the Master seed, replacement in the context of this NfG is defined as the step backward approach or the step forward approach respectively.

This guideline does not cover the replacement of MS by MS from other origin than described above.

3. LEGAL BASIS

MS are starting materials as defined in Directive 2001/82/EC as amended, Annex I, Title II. Changes to starting materials are subject to variations as described in Commission Regulations 1084/2003/EEC and 1085/2003/EEC as amended.

This guideline provides advice on the scientific data to be presented whenever a variation on MS will be applied.

It is indicated in Annex I, Title II of Directive 2001/82/EC as amended that whenever possible, vaccine production shall be based on a seed lot system and on established cell banks.

The origin and history of starting materials shall be described and documented. Seed materials, including cell banks shall be tested for identity and adventitious agents.

Information shall be provided on all substances of biological origin used at any stage in the manufacturing procedure (source of the materials, details of any processing, purification and inactivation applied, details of any tests for contamination carried out on each batch of the substance).

When cell banks are used, the cell characteristics shall be shown to have remained unchanged up to the highest passage level used for the production.

For live attenuated vaccines, proof of the stability of the attenuation characteristics of the seed has to be given.

This guideline has to be read in conjunction with the introduction and general principles (4) and Title 2 of the Annex I to Directive 2001/82/EC as amended.

4. Virus Master Seed (MSV)

4.1 General remarks

Some scientific statements on Master Seed Antigen (MSA) are made in the various legal provisions. These statements are mainly focused on viruses as the cultivation of bacteria sometimes follows different principles.

The Ph. Eur. monograph 62 “Vaccines for veterinary use” indicates that the production of vaccine is not normally undertaken using virus more than 5 passages from the master seed lot. The master seed lot is checked for identification, bacterial and fungal contamination (Ph. Eur. 2.6.1.), mycoplasmas (Ph. Eur.2.6.7.), and absence of extraneous viruses.

4.2 Replacement by a master seed obtained from a pre-master seed passage

It is expected that not more than two passages before the MS are accepted to be used as new basis for a replaced MS.

Quality

All characteristics as required by Directive 2001/82/EC as amended for starting materials have to be provided. The new master seed should be tested according to the requirements of the Ph. Eur. 62 monograph and the results should be provided. The results of the control of the finished product should be provided for one batch of vaccine produced with the new master seed.

Safety

The relevance of the already existing data on safety as provided by testing of the “old” MSV should be justified. For live attenuated vaccines, proof of the stability of the attenuation characteristics of the seed has to be given.

Efficacy

The relevance of the already existing data on efficacy as provided by testing of the “old” MSV should be justified and confirmed by experimental data.

The efficacy of the vaccine obtained with the new master seed should be demonstrated. Whenver a Ph. Eur. monograph is applicable; the efficacy test should be performed with a vaccine batch produced with the new master seed. The performance of the efficacy test could be reduced to one category and one age of animals.

Wherever possible, the basic efficacy test as described in Ph.Eur. should be used.

For IVMPs where no Ph.Eur. monographs exist;, the same approach should be made.

Results of batch potency test could be used, if justified.

Whenever the batch potency test is used instead, the applicant has to justify the approach.

Wherever justified and with respect to the nature of the antigen in question, challenges may be replaced by serological data or established batch potency tests.

4.3

4.3 Replacement by a master seed obtained from a post-master seed passage

4.3.1. Post-master seed obtained from old MSV+1 to MSV+4 and vaccine still below old MSV+5

Quality

As usually the applicant has performed some tests on the intermediate passages, he should complete the testing to be in compliance with the requirements of the Ph. Eur. 62 monograph and the results should be provided.

Safety and efficacy

No supplementary data are requested.

4.3.2 Post-master seed obtained from old MSV+5 or more

Quality

The new master seed should be tested according to the requirements of the Ph. Eur. 62 monograph and the results should be provided. The results of the control of the finished product should be provided for one batch of vaccine produced with the new master seed.

Safety

The relevance of the already existing data on safety as provided by testing of the "old" MSV should be justified.

For live attenuated vaccines, proof of the stability of the attenuation characteristics of the seed has to be given.

Efficacy

The relevance of the already existing data on efficacy as provided by testing of the "old" MSV should be justified.

For IVMPs where no Ph.Eur. monographs exist; a comparable test should be performed.

The efficacy of the vaccine obtained with the new master seed should be demonstrated. If a Ph. Eur. monograph is applicable, the efficacy test should be performed with a vaccine batch produced with the new master seed. The performance of the efficacy test could be reduced to one category and one age of animals.

The requirements as indicated in section 4.2. apply accordingly.

5. Master cell seed (MCS)

5.1 General remarks

The Ph. Eur. 5.2.4. "Cell culture for the production of veterinary vaccines" mentions that the production of vaccine is not normally undertaken on cells more than 20 passages from the master cell seed. If cells beyond twenty passage levels are to be used for production, it shall be demonstrated by validation or further testing, that the production cell cultures are essentially similar to the master cell seed with regard to their biological characteristics and purity and that the use of such cells has no deleterious effect on vaccine production.

The following tests are performed on the master cell seed: general microscopy, identification of the species, bacterial and fungal contamination (Ph. Eur. 2.6.1.), mycoplasmas (Ph. Eur. 2.6.7.), absence of contaminating viruses (cytopathic viruses, haemadsorbent viruses, specified viruses), karyotype, tumorigenicity.

5.2. Replacement by a master seed obtained from a pre-master seed passage or

from a post-master seed obtained from old MCS+21 or more

Quality

The new master cell seed should be tested according to the requirements of the Ph. Eur. 5.2.4. “Cell culture for the production of veterinary vaccines” and the results should be provided.

Safety and efficacy

The results of the control of the finished product should be provided for one batch of vaccine produced with the new master cell seed in order to demonstrate the safety and efficacy of the final product produced on the new MCS.

5.3. Replacement by a master seed obtained from a post-master seed obtained from old MCS+1 to MCS+20 and vaccine still produced with cells not more than old MCS+20

Quality

As usually the applicant has performed some tests on the intermediate passages, he should complete the testing to be in compliance with the requirements of the Ph. Eur. 5.2.4. “Cell culture for the production of veterinary vaccines” and the results should be provided.

Safety and efficacy

The results of the control of the finished product should be provided for one batch of vaccine produced with the new master cell seed in order to demonstrate the safety and efficacy of the final product produced on the new MCS.

6. Bacterial Master Seed (MSB)

6.1 General

The Ph. Eur. monograph “Vaccines for veterinary use” states that the minimum and maximum numbers of subcultures of each master seed lot prior to the production stage are specified. It shall be demonstrated that the characteristics of the seed material are not changed by these subcultures. The identity and the purity of the MSL are demonstrated.

6.2 Replacement by a master seed obtained from a pre-master seed passage or

from a post-master seed exceeding the maximum numbers of subcultures

Quality

All characteristics as required by Directive 2001/82/EC as amended for starting materials have to be provided. Details of passage history, propagation, manufacturing, container identification and storage should be documented. The new master seed should be tested according to the requirements of the dossier of the product, which should comply with Ph.Eur. and the results should be provided.

Safety

The relevance of the already existing data on safety as provided by testing of the "old" Master seed should be justified. For live attenuated vaccines, proof of the stability of the attenuation characteristics of the seed has to be given.

Efficacy

The relevance of the existing data on efficacy as provided by final vaccine batches derived from the "old" MS should be justified.

The efficacy of the vaccine obtained with the new master seed should be demonstrated. If a Ph. Eur. monograph is applicable, the efficacy test should be performed with a vaccine batch produced with the new master seed. The performance of the efficacy test could be reduced to one category and one age of animals, whenever the test is performed in the target species.

The requirements as indicated in section 4.2. apply accordingly.

6.3 Replacement by a master seed obtained from a post-master seed passage not exceeding the maximum number of subcultures

Quality

As usually the applicant has performed some tests on the intermediate passages, he should complete the testing to be in compliance with the requirements of dossier of the product, which should comply with Ph.Eur and the results should be provided.

Safety and efficacy

No supplementary data are requested.

7. Summary of data requested

	Data requested		
Replacement with	**Analytical**	**Safety**	**Efficacy/Potency**
Virus Master Seed			
Pre-master seed	+	+	+
Post-master seed obtained from MSV+1 to MSV+4	+	-	-
Post-master seed obtained from MSV+5 or more	+	+	+
Bacterial Master Seed			
Pre-master seed or post-master exceeding the maximum number of subcultures	+	+	+

Post-master seed not exceeding the maximum number of subcultures	+	-	-
Master Cell Seed			
Pre-master seed or post-master seed from MCS+21 or more	+	+	+
Post-master seed obtained from MCS+1 to MCS+20	+	-	-