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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) BY NEW MASTER SEED OF THE SAME ORIGIN

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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) BY NEW MS OF THE SAME ORIGIN

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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 A number of Marketing Authorisation Holders (MAHs) have in such cases withdrawn the product from the market, rather than make new applications.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 a vaccine organism (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 (MS-2) are accepted to be used as new basis for a replaced MS. The replacing MS is obtained by normal passage methods, i.e. not involving cloning steps or rDNA techniques. Plaque purification of seeds might be acceptable on a case by case basis.

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 and efficacy

The results of the control of the finished product is considered to be sufficient to demonstrate the safety and the efficacy of the new MSV as the production of vaccine is not normally undertaken using virus more than 5 passages from the new master seed lot (old MS+3).

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

4.3.1. New master seed derived from old MSV(MSV+1 to MSV+5) and vaccine produced within the maximum allowed number of passages (i.e. vaccine still within old MSV+5)

Quality

The demonstration of the compliance with the requirements of the Ph. Eur. 62 monograph has to be shown 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.

Data already existing on the quality testing of the "old" master seed (and possibly the working seed) may be used when their relevance is justified.

Safety and efficacy

No supplementary data are requested.

4.3.2 New master seed derived from old MSV (MSV+1 to MSV+5) and vaccine produced outside the maximum allowed number of passages (i.e. vaccine beyond old MSV+5)

Quality

The demonstration of the compliance with the requirements of the Ph. Eur. 62 monograph has to be shown 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.

Data already existing on the quality testing of the "old" master seed (and possibly the working seed) may be used when their relevance is justified.

Safety

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

For inactivated vaccines, the batch safety test is considered sufficient to demonstrate the safety of the new MSV.

Efficacy

The efficacy of the vaccine obtained with the new master seed should be demonstrated. If the applicant has demonstrated a clear correlation between the batch potency test performed on the finished product (live or inactivated vaccines) and the efficacy of the vaccine, the results obtained for the batch potency test will be considered sufficient to support the efficacy.

If this correlation is not demonstrated, the efficacy of the vaccine has to be shown with an immunogenicity test compliant with the requirements of the Ph. Eur. monograph if applicable or with the same protocol as the efficacy study provided in the original file. The requested immunogenicity test could be reduced to one category of animals.

4.3.3 New master seed higher than old MSV+5

Quality

The demonstration of the compliance with the requirements of the Ph. Eur. 62 monograph has to be shown 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

For live attenuated vaccines, proof of the stability of the attenuation characteristics of the seed has to be given. For inactivated vaccines, the batch safety test is considered sufficient to demonstrate to safety of the new MSV.

Efficacy

The efficacy of the vaccine obtained with the new master seed should be demonstrated. If the applicant has demonstrated a clear correlation between the batch potency test performed on the finished product (live or inactivated vaccines) and the efficacy of the vaccine, the results obtained for the batch potency test will be considered sufficient to support the efficacy.

If this correlation is not demonstrated, the efficacy of the vaccine has to be shown with an immunogenicity test compliant with the requirements of the Ph. Eur. monograph if applicable or with the same protocol as the efficacy study provided in the original file. The requested immunogenicity test could be reduced to one category of animals.

5. Bacterial Master Seed (MSB)

5.1 General remarks

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 master seed are demonstrated.

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

It is expected that not more than two passages before the MSB (MSB –2) 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 and efficacy

The results of the control of the finished product is considered to be sufficient to demonstrate the safety and the efficacy of the new MSB if the maximum number of subcultures authorised for the vaccine in the marketing authorisation is not exceeded.

If the maximum number of subcultures authorised for the vaccine in the marketing authorisation is exceeded, the safety and the efficacy of the vaccine obtained with the new master seed should be demonstrated. For live attenuated vaccines, proof of the stability of the attenuation characteristics of the seed has to be given. For inactivated vaccines, the batch safety test is considered sufficient to demonstrate the safety of the new MSV.

If the applicant has demonstrated a clear correlation between the batch potency test performed on the finished product (live or inactivated vaccines) and the efficacy of the vaccine, the results obtained for the batch potency test will be considered sufficient to support the efficacy.

If this correlation is not demonstrated, the efficacy of the vaccine has to be shown with an immunogenicity test compliant with the requirements of the Ph. Eur. monograph if applicable or with the same protocol as the efficacy study provided in the original file. The requested immunogenicity test could be reduced to one category of animals.

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

5.3.1 New master seed obtained from a post-master seed passage not exceeding the maximum number of subcultures

Quality

The demonstration of the compliance with the requirements of the Ph. Eur. 62 monograph has to be shown 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.

Data already existing on the quality testing of the "old" master seed (and possibly the working seed) may be used when their relevance is justified.

Safety and efficacy

No supplementary data are requested if the maximum number of subcultures authorised for the vaccine in the marketing authorisation is not exceeded.

If the maximum number of subcultures authorised for the vaccine in the marketing authorisation is exceeded, the safety and the efficacy of the vaccine obtained with the new master seed should be demonstrated. For live attenuated vaccines, proof of the stability of the attenuation characteristics of the seed has to be given. For inactivated vaccines, the batch safety test is considered sufficient to demonstrate the safety of the new master seed.

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

Quality

The demonstration of the compliance with the requirements of the Ph. Eur. 62 monograph has to be shown 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 and efficacy

As the maximum number of subcultures authorised for the vaccine in the marketing authorisation is exceeded, the safety and the efficacy of the vaccine obtained with the new master seed should be demonstrated. For live attenuated vaccines, proof of the stability of the attenuation characteristics of the seed has to be given. For inactivated vaccines, the batch safety test is considered sufficient to demonstrate the safety of the new MSV.

If the applicant has demonstrated a clear correlation between the batch potency test performed on the finished product (live or inactivated vaccines) and the efficacy of the vaccine, the results obtained for the batch potency test will be considered sufficient to support the efficacy.

If this correlation is not demonstrated, the efficacy of the vaccine has to be shown with an immunogenicity test compliant with the requirements of the Ph. Eur. monograph if applicable or with the same protocol as the efficacy study provided in the original file. The requested immunogenicity test could be reduced to one category of animals.

6. Master cell seed (MCS)

6.1 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.

6.2 Replacement of the master cell seed

6.2.1 Quality requirements

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. Data already existing on the quality testing of the "old" master seed may be used when their relevance is justified. The results of the control of the finished product should be provided for one batch of vaccine produced with the new master seed.

6.2.2 Safety and efficacy requirements

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

7. Summary of data requested

	Data requested for the new MS			
Master seed (MS) replaced	**Replaced by**	**Analytical**	**Safety**	**Efficacy/Potency**
Virus Master Seed	Pre-master seed (old MSV-2 maximum)	Compliance with Ph. Eur. monograph 62 Results of the batch release of one batch of finished product	No data requested (covered by the results of one batch of finished product)	No data requested (covered by the results of one batch of finished product)
	Post-master seed obtained from old MSV+1 to MSV+5 and vaccine still within old MSV+5	Compliance with Ph. Eur. monograph 62 Existing data of old MSV accepted if relevant. Results of the batch release of one batch of finished product	No data requested (covered by the results of one batch of finished product)	No data requested (covered by the results of one batch of finished product)
	Post-master seed obtained from old MSV+1 to MSV+5 and vaccine outside old MSV+5	Compliance with Ph. Eur. monograph 62 Existing data of old MSV accepted if relevant. Results of the batch release of one batch of finished product	No data requested except for live vaccine: proof of stability of the attenuation needed.	Efficacy demonstrated for one category of animals (species and age) using an immunogenicity test or the batch potency test if a correlation with the efficacy is demonstrated.
	Post-master seed higher than old MSV+5	Compliance with Ph. Eur. monograph 62 Results of the batch release of one batch of finished product	No data requested except for live vaccine: proof of stability of the attenuation needed.	Efficacy demonstrated for one category of animals (species and age) using an immunogenicity test or the batch potency test if a correlation with the efficacy is demonstrated

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	Data requested for the new MS			
Master seed (MS) replaced	**Replaced by**	**Analytical**	**Safety**	**Efficacy/Potency**
Bacterial Master Seed	Pre-master seed (old MSV-2 maximum)	Compliance with Ph. Eur. monograph 62 Results of the batch release of one batch of finished product	If maximum subcultures not exceeded: No data requested (covered by the results of one batch of finished product) If maximum subcultures exceeded: for live vaccine, proof of stability of the attenuation needed. Inactivated vaccine: covered by the result of the batch safety test	If maximum subcultures not exceeded: No data requested (covered by the results of one batch of finished product) If maximum subcultures exceeded: Efficacy demonstrated for one category of animals (species and age) using an immunogenicity test or the batch potency test if a correlation with the efficacy is demonstrated.

	Data requested for the new MS			
Master seed (MS) replaced	**Replaced by**	**Analytical**	**Safety**	**Efficacy/Potency**
	Post-master seed not exceeding the maximum number of subcultures authorised	Compliance with Ph. Eur. monograph 62 Existing data of old MSB accepted if relevant. Results of the batch release of one batch of finished product	If maximum subcultures not exceeded for the vaccine: No data requested (covered by the results of one batch of finished product) If maximum subcultures exceeded for the vaccine: Live vaccine: Proof of stability of the attenuation needed. Inactivated vaccine: covered by the result of the batch safety test .	If maximum subcultures not exceeded for the vaccine: No data requested (covered by the results of one batch of finished product) If maximum subcultures exceeded for the vaccine: Efficacy demonstrated for one category of animals (species and age) using an immunogenicity test or the batch potency test if a correlation with the efficacy is demonstrated.
	Post-master seed exceeding the maximum number of subcultures authorised	Compliance with Ph. Eur. monograph 62 Results of the batch release of one batch of finished product	Live vaccine: proof of stability of the attenuation needed.	Efficacy demonstrated for one category of animals (species and age) using an immunogenicity test or the batch potency test if a correlation with the efficacy is demonstrated.
Master Cell Seed	Pre-master seed, post-master seed below or beyond maximum passages allowed	Compliance with Ph. Eur. monograph 62 Existing data of old MCS accepted if relevant. Results of the batch release of one batch of finished product	No data requested (covered by the results of one batch of finished product)	No data requested (covered by the results of one batch of finished product)