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4 Reflection paper on the replacement of cell lines used for 5 the production of immunological veterinary medicinal 6 products (IVMPs)

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Reflection paper on the replacement of cell lines used for the production of immunological veterinary medicinal products (IVMPs)

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Executive summary

This reflection paper outlines the data requirements to be submitted by the marketing authorisation holder (MAH) to replace the cell line as host system for production of immunological veterinary medicinal products (IVMPs) without significant changes to the production process and maintaining finished product specifications.

1. Introduction (background)

A large number of IVMPs are produced on permanent cell lines. For this purpose, master cell seeds (MCS) are established by the vaccine manufacturer. In certain circumstances, these MCSs must be replaced, usually because the seed material is depleted or needs to be changed for other reasons, such as contamination with extraneous agent(s). The introduction of a new cell seed requires a variation or extension to an existing Marketing Authorisation. A number of Marketing Authorisation Holders (MAHs) have in such cases withdrawn the product from the market, rather than generate the data needed to make the change. To allow the MAHs to evaluate the feasibility of the replacement of the MCS, the scientific requirements need to be clarified.

2. General Remarks

The following definitions should be taken into account when reading this reflection paper, which are used for the purpose of this paper:

A **defined cell line** (source) is a type of cell population with defined characteristics that originates by serial subculture of a primary cell population that can be banked.

A **master cell seed** is a quantity of well-characterized cells derived from a cell seed at a specific passage level and stored frozen under defined conditions in aliquots of uniform composition. It is prepared from a single homogeneously mixed pool of cells.

Master cell seeds derived from the same defined cell line are considered to be of the same source, even if they may be obtained from different commercial suppliers or laboratories.

Different cell lines are considered not to be of the same source.

3. Scope

This reflection paper applies to the replacement of a defined master cell seed (MCS) used to produce a vaccine by a MCS of the same cell line and to the replacement of a MCS by a MCS of different cell line.

4. Legal basis

Master Cell Seeds 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 1234/2008/EC as amended.

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.

This reflection paper has to be read in conjunction with the introduction and general principles of Title II of the Annex I to Directive 2001/82/EC as amended, and the relevant provisions of Ph.Eur.

5. Data requirements for the replacement of a MCS by a MCS of the same cell line

The replacement of a defined MCS by another MCS of the same cell line may have an impact on the finished product. A prerequisite for the acceptance for this change is therefore confirmation that the change of the seed does not change the finished product.

The replacement of a MCS by another MCS of the same cell line requires sufficient proof of the equivalence between the two MCSs, especially when they are obtained from different commercial suppliers or laboratories.

5.1 Quality

5.1.1 Equivalence of the MCSs

The equivalence of the two MCSs needs to be proven. For this purpose the following data have to be provided:

The history and performance of the two MCSs should be documented and compared in detail, and the biography of the two MCSs should be as close as possible.

The following items need to be carefully considered:

- the site(s) where each MCS was maintained / established. Wherever possible, the sites should be of comparable quality, e.g. laboratories run under GMP/GLP conditions or equivalent.
- the number of passages performed in the production of each MCS should be as close as possible.
- the equipment and conditions of propagation should be similar. Larger differences (e.g. monolayer versus suspension culture) require further justification.
- the media/solutions used for propagation should be similar, concerning composition and purity.
- the treatments that both MCSs have undergone (e.g. cloning,) need to be described as precisely as possible and should not be too different
- the storage conditions should be similar.
- the data on the characterisation of both MCSs as required according to Ph.Eur. Chapter 5.2.4. karyotype and morphology should not differ.

Any differences between the two MCSs have to be identified and assessed so that the impact on the finished product is reduced to an acceptable level.

5.1.2 Control of the new MCS

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". In addition freedom of extraneous agents (including RD114 or other extraneous agents which might have led to the change of the cell line) according to the table included in the CVMP guideline 'Requirements for the production and control of immunological veterinary medicinal products' (EMA/CVMP/IWP/206555/2010) need to be confirmed.

5.1.3 Production

The performance of both MCSs when used for vaccine production should be compared. Key parameters include the growing capacity of the cells and the quality of harvest and antigen. Changes in the manufacturing process, if any, need to be described and justified.

The *in process* controls should remain unchanged or additional controls may be added.

Any differences between the two production processes have to be identified and assessed so that the impact on the finished product is reduced to an acceptable level.

5.1.4 Finished product

To confirm consistency of production the results obtained for the control of three finished product batches derived from each MCS need to be compared. For the new MCS two pilot batches and one full scale batch are acceptable.

If the change of the MCS is performed due to viral contamination of the former MCS, these three batches should additionally be tested for freedom of the specific extraneous agent(s) either *in process* or on the finished product.

If the equivalence between the two MCS is sufficiently demonstrated, the stability results of two pilot batches and one full scale batch produced with the new MCS are sufficient to grant the same shelf life to the finished product. Testing results at release and after three months storage including potency test results should be sufficient for the immediate acceptance of the application. The necessary additional real time data on three batches confirming the full shelf life of the vaccine are requested as a commitment.

5.2 Safety and efficacy

If the results of the control of the finished product provided for three batches of vaccine produced with the new MCS are satisfactory, the specifications of the finished product remain unchanged and there is minimal change to the manufacturing process, it is likely that the safety and the efficacy profile of the product will remain unchanged and no additional safety or efficacy testing is necessary.

If the equivalence between the two MCS is not demonstrated, laboratory safety and efficacy tests as required in Dir. 2009/9/EU, annex 1, Title II should be provided. Field trials should be performed in exceptional cases only, when the laboratory tests cannot confirm the safety and efficacy of the vaccine produced on the MCS of same cell line.

6. Data requirements for the replacement of a MCS by a MCS of a different cell line

6.1 Quality

The use of a different cell line for vaccine production requires detailed confirmation that the finished product remains unchanged with respect to quality. Changes to starting materials, in process and finished product controls should be restricted as much as possible to ensure that the finished product remains unchanged.

All of the Part 2 data required in Directive 2001/82/EC, annex 1, Title II should be provided.

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”. In addition freedom of extraneous agents (including RD114 or other extraneous agents which might have led to the change of the cell line) according to the table included in the CVMP guideline ‘Requirements for the production and control of immunological veterinary medicinal products’ (EMA/CVMP/IWP/206555/2010) need to be confirmed.

To confirm that the finished product remains unchanged, the results of the controls of three finished product batches derived from each MCS need to be compared. For the new MCS two pilot batches and one full scale batch are acceptable.

If specifications of the finished product are the same for the products obtained from both MCSs, the stability results of two pilot batches and one full scale batch produced with the new MCS are sufficient to grant the same shelf life to the finished product. Testing results at release and after three months storage including potency test results should be sufficient for the immediate acceptance of the application. The necessary additional real time data on three batches confirming the full shelf life of the vaccine are requested as a commitment.

6.2 Safety and efficacy

The use of a different cell line for vaccine production requires detailed confirmation that the finished product remains unchanged with respect to safety and efficacy.

Laboratory safety and efficacy tests as required in Directive 2001/82/EC, annex 1, Title II should be provided. To reduce animal trials and for animal welfare reasons, challenge trials can be replaced by valid alternative methods, whenever possible, by comparing results obtained with finished product batches derived from the original and the new MCS.

Field trials should be performed in exceptional cases only, when the laboratory tests cannot confirm the safety and efficacy of the vaccine produced on the MCS of different cell line.