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

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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 or 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 of the same source requires a variation, whilst the introduction of cells of different source requires an extension to an existing marketing authorisation. A number of MAHs have in such cases withdrawn the product from the market, rather than generate the data needed to make the change.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 line 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 contains complementary/additional information to the already existing guideline on 'Data requirements for the replacement of established master seeds (MS) already used in authorised IVMPs by new MS of the same origin' (EMEA/CVMP/IWP/105504/2007). The reflection paper is therefore applicable in situations where it is not possible to replace the MCS by a pre-MCS or a post-MCS but needs to be replaced by a cell seed of the same defined cell line obtained from a different supplier or laboratory or by a cell seed of a different defined cell line.

4. Legal basis

Master Cell Seeds are starting materials as defined in Directive 2001/82/EC, Annex I, Title II. Changes to starting materials are subject to variations as described in Commission Regulation (EC) No 1234/2008.

It is indicated in Annex I, Title II of Directive 2001/82/EC 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, and the relevant provisions of Ph.Eur.

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

The replacement of a MCS by another MCS of the same defined 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 cell seed does not change the finished product.

The replacement of a MCS by another MCS of the same defined 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, to ensure that the MCS complies with the current provisions on quality (e.g. laboratories run under GMP/GLP conditions or equivalent).
- the number of passages performed since the defined cell line was obtained in the production of each MCS should be as close as possible.
- the equipment and conditions of propagation of both MCSs should be similar. Larger differences (e.g. monolayer versus suspension culture) require further justification.
- the media/solutions used for propagation of both MCSs should be similar, concerning composition and purity unless otherwise justified, e.g. a change in media/solutions composition could sometimes be useful to clear extraneous agents, such as RD114. In this case, and depending on the changes, new relevant safety and efficacy trials to support the changes may be needed.

- the treatments that both MCSs may 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) needs 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 should be kept to the minimum and, if any change is needed, it needs to be described and justified.

The *in process* controls should remain unchanged or additional controls may be added. Removal of controls may be justified if the reason for control has been removed by the change in MCS.

Any differences between the two production processes have to be identified and assessed so that the impact on the finished product and its specifications 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 equivalence between the two MCS is sufficiently demonstrated, the stability results of three batches produced with the new MCS are sufficient to grant the same shelf life to the finished product. These data may be from pilot scale size batches. 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 the 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/or efficacy tests as required in Title II of Annex I to Directive 2001/82/EC should be taken into consideration. With sufficient justification, a selected set of well-designed safety and efficacy trials may be sufficient to

confirm target animal safety and efficacy. For example, a GLP safety study in the most sensitive subcategory of animal species and an onset of immunity challenge study against the concerned antigen(s) (i.e. the antigen impacted by the change of defined cell line) may be sufficient to address the safety and efficacy in the target species.

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/or efficacy of the vaccine produced on the MCS of defined 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 affected by the change required in Directive 2001/82/EC, annex I, 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) needs 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 three batches produced with the new MCS are sufficient to grant the same shelf life to the finished product. These data may be from pilot scale size batches. 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 the three batches confirming the full shelf life of the vaccine are requested as a commitment. If the specifications of the finished product are different, additional real-time stability data may be needed at submission of the application.

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. It should be justified that the benefit-risk-ratio of the finished product remains unchanged.

Laboratory safety and efficacy tests as required in Directive 2001/82/EC, annex I, Title II should be considered. With sufficient justification, a selected set of well-designed safety and efficacy trials may be sufficient to confirm target animal safety and efficacy. For example, a GLP safety study in the most

sensitive subcategory of animal species and an onset of immunity study against the concerned antigen(s) (i.e. the antigen impacted by the change of defined cell line) may be sufficient to address the safety and efficacy in the target species. 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.