European Medicines Agency
Veterinary Medicines and Inspections

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OVERVIEW OF COMMENTS RECEIVED ON DRAFT GUIDELINE ON THE REQUIREMENTS FOR THE REPLACEMENT OF ESTABLISHED MASTER SEEDS (MS) ALREADY USED IN AUTHORISED IMMUNOLOGICAL VETERINARY MEDICINAL PRODUCTS

Interested party (Organisations or individuals) that commented on the draft Guideline as released for consultation

Stakeholder No.	Name of Organisation or individual
1	IFAH Europe

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1. GENERAL COMMENTS – OVERVIEW:

Stakeholder No. *(see coverpage)*	General Comment (if any)	Outcome (if applicable)
1	**Introduction** IFAH-Europe welcomes the "*Guideline on data requirements for the replacement of established master seeds (MS) already used in authorized immunological veterinary medicinal products (IVMPs)*", and likes to express appreciation for the opportunity to comment on the previous Concept Paper and on the current Guideline. We are pleased with the steps undertaken by the CVMP to facilitate the regulation process of vaccines from Marketing Authorisation Holders, avoiding withdrawals of products from the market that would otherwise need a new application. **Key points** 1. As indicated in the Concept Paper on the preparation of the above referred GL, this document should provide for the possibility of retaining more IVMPs on the EU market and avoid that a number of vaccines disappear from the market when there is need for replacing the MS. Although this draft GL proposes a variation instead of a new application, it does not offer a significant reduction of the requirements. IFAH-Europe is concerned that if a clear reduction of requirements is not considered, the need for MS replacement remains a big stumbling block for continuing the availability of a specific product. 2. The present proposal prescribes a lot of analytical, safety and efficacy testing to be repeated ("unless…"). In fact, this guideline, for which the scope is restricted to replacement by master seed of the same origin, prescribes more extensive retesting than is indicated in the Note for Guidance EMEA/CVMP/116/96 on "Harmonisation of requirements for equine influenza vaccines specific requirements for substitution of a strain", where (a)	

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	completely new virus strain(s) is (are) introduced. This apparent imbalance is not justified. In our view, a better and well justified approach for the GL on replacement of MS, in particular for the product's safety and efficacy aspects, would follow the principle that showing equality of FPC results, including those of the batch safety and batch potency test between the product manufactured with the old seed and product manufactured with the new seed suffices. An exception would occur in specific, identified cases where (partial) repeat of analytical, safety and/or efficacy studies is necessary. A specific distinction between live and inactivated vaccine products would also be appropriate here. In the specific comments below this is further elaborated. 3. To support the approach described above, a role could be added for intensified Pharmacovigilance. 4. The guideline can be simplified by leaving out sections that seem non-relevant (see a) and c) below). It is unlikely that a MAH would apply for a variation to replace a master seed in the following situations: a) new master seed derived from post old-master seed level, with finished product still within the already approved passage levels (situations as described in sections 4.3.1., 5.3 and 6.3); b) new master seed derived from post old-master seed level not exceeding the maximum allowed number of passages, with finished product at a level beyond the maximum allowed number of passages (note: guidance would be useful here, but this is not covered by the draft guideline); c) new master seed derived from a level past the maximum passage level allowed (situations described in section 4.3.2 and as second option of sections 5.2 and 6.2.); In the first situation (a), manufacture of finished product within approved passage levels is supported with still available (working)	The presentation of the requirements has been simplified. The requirements are consistent for the different situations (MSV and MSB) and cover all the situations that can be faced for the replacement of a MS.

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	seed materials. In the latter two situations (b and c), showing the acceptability of finished product manufactured at a level beyond the maximum number of passages is essential and a new MS is not necessary. An additional GL for these situations in which a new MS is not necessary (b and c), would be also helpful and highly appreciated. 5. Necessary correction: although the Ph. Eur. indicates normal maximum passage levels for virus and cell seeds, higher passage levels may be allowed if justified by experimental evidence. Marketing authorisations exist, where higher maximum passage levels are authorised. Hence in this guideline, passage levels "+5" for viruses and "+20" for cells should be replaced with "maximum passage level allowed in MA" Conclusion: 6. The table on Section 7 has been adapted to summarise and include the proposed changes. As the requirements for new viral and for new bacterial master seeds are very comparable these have been combined in the table to one set covering "Vaccine organism Master Seeds". This combination may also be possible for the texts of the separate sections (currently 4 and 6).	

2. SPECIFIC COMMENTS ON TEXT

Line No. or location	Stakeholder No.	Comment and Rationale; proposed changes	Outcome
title	1	**Comments:** The title should reflect the limitations of the Guideline as defined in the scope. **Proposed change:** Guideline on data requirements for the replacement of established master seeds (MS) already used in authorized immunological veterinary medicinal products (IVMPs) by new MS of same origin.	Accepted
Section **2** **1st Paragraph**	1	**Comments:** The use of the term *"antigen"* in the context of antigen master seed is unusual; the same paragraph has a more suitable wording in its last sentence: "*vaccine organism*". **Proposed change:** *This guideline applies to the replacement of ~~an antigen~~ vaccine organism (e.g. virus, bacteria, fungus) master seed by a master…*	Accepted
Section **4.2** **1st Paragraph**	1	**Comments:** *"It is expected that not more than two passages before the MS are accepted to be used as new basis for a replaced MS."* If the replacing MS is obtained by normal passage methods, i.e. not involving cloning steps or rDNA techniques, the restriction to two passages before the old MS as starting point for the generation of a new MS is not justified. **Proposed change:** IFAH-Europe suggests replacing the sentence: *~~It is expected that not more than two passages before the MS are~~*	

Line No. or location	Stakeholder No.	Comment and Rationale; proposed changes	Outcome
		~~*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.*	Accepted
Section **4.2** ***Quality***	1	**Comments:** The section should be clarified. It is understood that the original master is re-established from a pre-master seed whereas table at section "*7 Summary of data requested"* mentions *pre-master seed* only. Additionally, when the new master seed is re-established from the pre- master it is not justified to re-perform the whole purity testing since compliant raw materials will be used and GMP standards applied. Therefore reduced testing should be sufficient. More specifically: sterility and mycoplasma testing should suffice. Particularly when method of culture and raw materials remain unchanged and compliant. Further, Ph. Eur. 62, paragraph 2.1.3.2.1 states that "*In the tests on the master seed lot described below, the organisms used are normally not more than 5 passages from the master seed lot at the start of the tests, unless otherwise indicated*". Hence, no new testing would be needed for the new seed (if within 5 passages from original master material). **Proposed change:** IFAH-Europe suggests adding the following sentences: *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. Reduced purity testing should be acceptable for the new master seed when method of culture and raw materials remain unchanged and compliant. Data already existing on the quality*	Partly accepted (see section 4.3 and 5.3 of the revised guideline)

Line No. or location	Stakeholder No.	Comment and Rationale; proposed changes	Outcome
		testing of the "old" master seed may be used when their relevance is justified.	
Section **4.2** ***Safety***	1	**Comments:** *"The relevance of the already existing data on safety as provided by testing of the "old" MSV should be justified."* Further detail about an acceptable "justification" would be useful to avoid unnecessary repetition of safety studies. Nevertheless, for this category of new Master Seed, satisfactory FPC results obtained with the finished product should suffice (Key point 2). When finished product from new master seed is at or beyond level of that for which safety was demonstrated, new safety testing is not justified. **Proposed change:** We suggest rephrasing the following sentence: ~~*The relevance of the a*~~*Already existing data on safety as provided by testing of the "old" MSV* ~~*should be*~~ *may be used when their relevance is justified.*	Accepted (see section 4.3 and 5.3 of the revised guideline)
Section **4.2** ***Safety***	1	**Comments:** *"For live attenuated vaccines, proof of the stability of the attenuation characteristics of the seed has to be given."* One can consider repetition of the reversion to virulence study. However, if it can be proven that the passage from pre-MS to MS has been carried out in the same way (classical techniques as cell-culture or eggs) with old and new MS, there is no reason that this new MS would behave differently, i.e. there is no change in the attenuation. For live vaccines, when the new master seed is re-established at the same or higher passage level as the old seed, and by conventional methods (see remark to be introduced at	

Line No. or location	Stakeholder No.	Comment and Rationale; proposed changes	Outcome
		introduction of 4.2), the additional proof of stability of the strain attenuation does not seem justified. **Proposed change:** *For live attenuated vaccines, when new master seed re-established at the same or higher passage level as the old seed and by conventional methods ~~proof of the stability of the attenuation characteristics of the seed has to be given~~, satisfactory batch safety results obtained with the finished product suffice.*	Not accepted When the vaccine is outside old MSV+5 or if the maximum subcultures are exceeded for the vaccine, the proof of stability of the attenuation is needed. It is considered that the increase of the number of passages could potentially affect the characteristics of the vaccine strain.
Section **4.2** ***Efficacy***	1	**Comments:** *"The relevance of the already existing data on efficacy as provided by testing of the "old" MSV should ...* *... where no Ph.Eur. monographs exist, the same approach should be made."* When the new master seed is re-established at the same passage level as the old one, or when maximum passage level for finished product remains unchanged, new efficacy testing is not justified. For this category of new Master Seed, satisfactory FPC results obtained with the finished product should suffice (see also Key Point 2). **Proposed change:** IFAH-Europe would appreciate the following changes: *~~The relevance of the a~~Already existing data on efficacy as provided by testing of the "old" MSV ~~should be~~ may be used when their relevance is justified. ~~and confirmed by experimental data.~~* *~~The efficacy of the vaccine obtained with the new master seed should be demonstrated. Whenever a Ph. Eur. monograph is applicable; the efficacy test should be performed with a vaccine~~*	Accepted. Nevertheless, if no correlation between the batch potency test and the efficacy is shown, an immunogenicity test is needed.

Line No. or location	Stakeholder No.	Comment and Rationale; proposed changes	Outcome
		~~*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.*~~	
Section **4.2** ***Efficacy***	1	**Comments:** *"Results of batch potency test could be used, if justified.* *…replaced by serological data or established batch potency tests."* IFAH-Europe supports this approach, taking it as a first way of justification. If the batch potency test was validated correctly and the efficacy test was also performed using the reference batch of old MS, compliance of the new pre-MS batch with the unchanged finished product specification (including the validated potency test) can prove validity of the "already existing data on efficacy" quoted in the 1st sentence of this section.	
Section **4.3**	1	**Comments:** *"4.3 Replacement by a master seed obtained from a post-master seed passage"* It is not likely that a MAH would apply for a new master seed in these cases: • With sufficient working seed available for production at maximum allowed passage level (option described in paragraph 4.3.1), there is no need for a new master seed. • With production starting within, but extending beyond the maximum allowed passage level (option not mention in draft GL), only extension of this passage level is	

Line No. or location	Stakeholder No.	Comment and Rationale; proposed changes	Outcome
		required, with additional efficacy data for live vaccines. With respect to finished product this option fits with the situation described in 4.3.2. If production beyond the maximum allowed level (option described in paragraph 4.3.2) would solve the problem, there is no need for a new master seed. Extension of the maximum allowed passage level would be sufficient. **Proposed change:** Preferably, remove section 4.3 completely (see Key Point 4 at General Comments).	The different strategies of replacement and requirements are presented taking into account all the possibilities. Then, the MAH can choose the appropriate strategy to replace the MSV.
Sections **5** and **6**	1	**Comments:** These sections should be swapped to maintain the order "antigen (virus, bacteria, fungus) master seed" and "master cell seed" **Proposed change:** IFAH-Europe would like to suggest changes to the numbering of the sections: *5. Bacterial Master Seed (MSB)* *6. Master cell seed (MCS)*	Accepted
Section **5.2** (Second option)	1	**Comments:** *"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**."* It is not likely that a MAH would apply for a new master seed in case of the second option described in the title of this section. If	

Line No. or location	Stakeholder No.	Comment and Rationale; proposed changes	Outcome
		production beyond the maximum allowed level would solve the problem, there is no need for a new master seed. Extension of the maximum allowed passage level would be sufficient. In any case, the situations included in the title of this section have to be dealt with differently. **Proposed change:** We would appreciate (see Key Point 4) removal of the second option in the title of section 5.2.: *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.~~*	The requirements are modified and simplified.
Section **5.2** ***Quality***	1	**Comments:** See comments on Section 4.2 *Quality*. **Proposed change:** IFAH-Europe suggests adding the following sentence: *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.*	Accepted
Section **5.3**	1	**Comments:** *"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"* It is not likely that a MAH would apply for a new master seed in such a case. With sufficient working seed available for production within the maximum allowed passage level there is no need for a new master seed.	

Line No. or location	Stakeholder No.	Comment and Rationale; proposed changes	Outcome
		With production starting within, but extending beyond the maximum allowed passage level (option not mentioned in draft GL), only extension of this passage level will trigger evaluating the biological characteristics, purity and absence of deleterious effect on vaccine production. **Proposed change:** IFAH-Europe would appreciate complete removal of section 5.3 (see also Key Point 4).	The requirements are modified and simplified.
Section **6.2** (Second option)	1	**Comments:** *"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**"* It is not likely that a MAH would apply for a new master seed in case of the second option described in the title of this section. If production beyond the maximum allowed number of subcultures would solve the problem, there is no need for a new master seed. Extension of the maximum allowed number of subcultures would be sufficient. In any case, the situations included in the title of this section have to be dealt with differently. **Proposed change:** We would appreciate removal of the second option in the title of section 6.2 (see Key Point 4): *6.2 Replacement by a master seed obtained from a pre-master seed passage ~~or from a post-master seed exceeding the maximum number of subcultures.~~*	The different strategies of replacement and requirements are presented taking into account all the possibilities. Then, the MAH can choose the appropriate strategy to replace the MSV.
Section **6.2** ***Quality***	1	**Comments:** See comments on Section 4.2 *Quality*.	

Line No. or location	Stakeholder No.	Comment and Rationale; proposed changes	Outcome
		Proposed change: IFAH-Europe suggests adding the following sentence: *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. Data already existing on the quality testing of the "old" master seed may be used when their relevance is justified.*	Accepted. See 4.3 and 5.3
Section **6.2** ***Safety***	1	**Comments:** *"The relevance of the already existing data on safety as provided by testing of the "old" Master seed should be justified."* See comments on Section 4.2 *Safety*. **Proposed change:** We would like to suggest rephrasing the paragraph: *~~The relevance of the a~~Already existing data on safety as provided by testing of the "old" Master seed ~~should be~~ may be used when their relevance is justified. For live attenuated vaccines, when new master seed re-established at the same or higher passage level as the old seed and by conventional methods ~~proof of the stability of the attenuation characteristics of the seed has to be given~~, satisfactory batch safety results obtained with the finished product suffice.*	Not accepted. When the vaccine is outside old MSV+5 or if the maximum subcultures are exceeded for the vaccine, the proof of stability of the attenuation is needed. It is considered that the increase of the number of passages could potentially affect the characteristics of the vaccine strain.
Section **6.2** ***Efficacy***	1	**Comments:** *"The relevance of the existing data on efficacy as provided by ...* *... If a Ph. Eur. monograph is applicable, the efficacy test should*	

Line No. or location	Stakeholder No.	Comment and Rationale; proposed changes	Outcome
		be performed with a vaccine batch produced with the new master seed." See the first comment on Section 4.2 *Efficacy*. **Proposed change:** We would suggest the following changes: *~~The relevance of the~~ ~~a~~A*lready existing data on efficacy as provided by testing of the "old" MSV ~~should be~~ may be used when their relevance is justified ~~and confirmed by experimental data.~~ When the new master seed is re-established at the same passage level as the old one, or when maximum passage level for finished product remains unchanged, satisfactory batch potency results obtained with the finished product suffice.* *~~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.~~*	Accepted. Nevertheless, if no correlation between the batch potency test and the efficacy is shown, an immunogenicity test is needed.
Section **6.3**	1	**Comments:** *"6.3 Replacement by a master seed obtained from a post-master seed passage not exceeding the maximum number of subcultures"* It is not likely that a MAH would apply for a new master seed in such a case. With sufficient working seed available for production within the maximum allowed number of subcultures, there is no need for a new master seed. With production starting within, but extending beyond the maximum number of subcultures (option not mention in draft	

Line No. or location	Stakeholder No.	Comment and Rationale; proposed changes	Outcome
		GL), only extension of this maximum number for live vaccines will trigger the need for additional efficacy data. **Proposed change:** IFAH-Europe would appreciate the complete removal of section 6.3 (see also Key Point 4).	The different strategies of replacement and requirements are presented taking into account all the possibilities. Then, the MAH can choose the appropriate strategy to replace the MSV.
Section **7**	1	**Comments:** In the table of section 7 the heading in the first column *"Replacement with"* and the specification *"Pre-master seed"* suggests that only a pre-master seed can be used as new master. The Table should be updated according to the comments given above. Because the requirements for new virus and new bacterial master seed are comparable, these are combined in a new proposed Table in order to prevent unnecessary repetition. **Proposed change:** *IFAH-Europe would like to suggest adding the following (please see also new proposed Table at the end of this document):* *Replacement <u>of existing seed</u> with <u>new master seed derived from</u>*	The table has been amended.
General	1	If section 4.3. is maintained at all, we would like to propose the following changes :	
Section **4.3**	1	**Comments and proposed change:** Please remove "*4.3*" before the heading "*4.3 Replacement by ....*"	Accepted

Section **4.3.1** ***Title***	1	**Comments:** *"Post master seed obtained from old MSV + 1 to MSV + 4 and vaccine still below old MSV + 5."* The title of this section should be clarified. In fact, if new MSV= old MSV + 4, vaccine can not be below old MSV + 5 (see also remark at Key Point 5). **Proposed change:** Please adapt the title so that it reads: *Post master seed obtained from working seed lot derived from old MSV ~~+ 1 to MSV + 4~~ and vaccine still produced within the maximum allowed number of passages ~~below old MSV + 5.~~*	Accepted
Section **4.3.1** ***Quality***	1	**Comments:** When the new master seed is derived from the old one (post-master seed level), it is not justified to re-perform the whole purity testing since compliant raw materials will be used and GMP standards applied. Therefore reduced testing should be sufficient. More specifically: sterility and mycoplasma testing should suffice. **Proposed change:** IFAH-Europe suggests adding the following sentence: *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. Data already existing on the quality testing of the "old" master seed may be used when their relevance is justified.*	Accepted
Section **4.3.2**	1	**Comments:** *"4.3.2 Post-master seed obtained either from MSV+5 or more"* If Section 4.3 is kept at all, Section 4.3.2 needs clarification as Section 4.3.1 provides guidance on the requirements for	

		establishing a new MSV somewhere between MSV+1 and MSV+4, but the vaccine antigen passage is still within MS+5. Section 4.3.2 heading should be changed to make it clear that the requirements described are intended to support post-master seed virus obtained from old MSV+1 to MSV+5, but the vaccine antigen passage level is to be beyond MS+5 from the old MSV. **Proposed change:** IFAH-Europe would appreciate the following change : *"4.3.2 Post-master seed obtained either from MSV+1 to MSV+5 ~~or more~~ but vaccine antigen is above MS+5, or post-master seed obtained from old MS+5 or more."*	Accepted
Section **4.3.2.** ***Quality***	1	**Comments:** See comments on Section 4.3.1 *Quality*. **Proposed change:** IFAH-Europe suggests adding the following sentence: *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. Data already existing on the quality testing of the "old" master seed may be used when their relevance is justified.*	Accepted
Section **4.3.2** ***Safety***	1	**Comments:** For live vaccines, when the new master seed is re-established at a higher passage level as the old seed, the additional proof of stability of the strain attenuation does not seem justified. **Proposed change:** IFAH-Europe suggests deleting the following sentence: *~~For live attenuated vaccines, proof of the stability of the attenuation characteristics of the seed has to be given.~~*	Not accepted. When the vaccine is outside old MSV+5 or if the maximum subcultures are exceeded for the vaccine, the proof of stability of the attenuation is needed. It is considered that the increase of the

			number of passages could potentially affect the characteristics of the vaccine strain.
Section **4.3.2** ***Efficacy***	1	**Comments:** What is meant by *"the requirements"* in the sentence "*The requirements as indicated in section 4.2 apply accordingly*"? Was it intended to state that "*The ~~requirements~~ assumptions as indicated in section 4.2 apply accordingly"?* With our proposal to remove most of the text at 4.2, the last sentence at 4.3.2 can also be deleted. **Proposed change:** IFAH-Europe suggests deleting the last sentence in this section: ~~*The requirements as indicated in section 4.2 apply accordingly*~~	Accepted.

Proposed change for the table:

7. Summary of data requested

New situation		Data required			
Replacement of existing seed with new master seed derived from	**New finished product level compared to approved passage level**	**Analytical**	**Safety**	**Efficacy/Potency[1]**	**Finished product batch release (including batch safety test and batch potency test)**
Vaccine organism (virus, bacteria, fungus) Master Seed					
Pre-master seed	Within	Virus: Sterility and Mycoplasma Bacteria: Identity and purity	Live: only in case finished product from new master seed is at level below that for which safety was demonstrated, or; Live and inactivated: when new master seed is obtained by other than normal passage methods, i.e. involving cloning steps or rDNA techniques.	-	+
Pre-master seed	Beyond	Virus: Sterility and Mycoplasma Bacteria: Identity and purity	Live and inactivated: only when new master seed is obtained by other than normal passage methods, i.e. involving cloning steps or rDNA techniques.	Live: Immunogenicity test Inactivated: -	+
*Post-master seed obtained	Within	Virus: Sterility and	-	-	+

[1] Efficacy data is required only if the batch potency test was not validated correctly and the efficacy test was not performed using the reference batch of old MS.

from MS+1 to maximum passage / subculture level allowed in MA		Mycoplasma Bacteria: Identity and purity			
**Post-master seed obtained from MS+1 to maximum passage / subculture level allowed in MA	Beyond	Virus: Sterility and Mycoplasma Bacteria: Identity and purity	-	Live: Immunogenicity test Inactivated: -	+
*Post-master seed obtained beyond maximum passage / subculture level allowed in MA	Beyond	Virus: Sterility and Mycoplasma Bacteria: Identity and purity	-	Live: Immunogenicity test Inactivated: -	+
Master Cell Seed					
Pre-master seed	Within	Sterility and Mycoplasma	-	-	+
Pre-master seed	Beyond	Sterility, Mycoplasma and Biological characteristics	-	-	+
*Post-master seed obtained from MCS+1 to maximum passage level allowed in MA	Within	Sterility and Mycoplasma	-	-	+
**Post-master seed obtained from MCS+1 to maximum passage level allowed in MA	Beyond	Sterility, Mycoplasma and Biological characteristics	-	-	+
*Post-master seed obtained beyond maximum passage level allowed in MA	Beyond	Sterility, Mycoplasma and Biological characteristics	-	-	+

* In these situations it is not likely that a MAH would apply for a new master seed. Preferably to be omitted from Table (see Key Point 4)

** Situation not covered by draft guideline. Not likely that a MAH would apply for a new master seed. Preferably to be omitted from Table (see Key Point 4)