20 May 2022
EMA/CVMP/45571/2022
Veterinary Medicines Division

Overview of comments received on 'Procedural advice for veterinary vaccine antigen master file (VAMF) certification' (EMA/CVMP/127488/2021)

Interested parties (organisations or individuals) that commented on the draft document as released for consultation.

Stakeholder no.	Name of organisation or individual
1	AnimalhealthEurope

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1. General comments – overview

Stakeholder no.	General comment (if any)	Outcome (if applicable)
1	AnimalhealthEurope welcomes the opportunity to comment on this procedural advice. We appreciate the clarity and the requirements proposed for the VAMF certification. In general, we believe that the procedural aspects make good sense and, assuming that the fees are attractive, the VAMF certification is likely to be implemented by Industry. However, especially keeping the original intent in mind *i.e.*, reducing complexity and administrative burden, there are a number of potentially significant disincentives in the current draft, detailed below. We would appreciate if these could be solved to a large extent in the final document. In general, there are still a lack of clarity if the (original) application of a VAMF for an existing product will automatically lead to a technical reassessment of the respective quality part for the corresponding antigen. Such an assessment will in consequence trigger further variations as there will be always additional questions by the competent authorities resulting in amendments, changes *etc*. It is also not completely clear if a registered VAMF to be included in a new combination will lead to a technical re-assessment, resulting in further changes and potentially leading to variations of existing products. We would like to refer on this topic to the following extract of the technical guideline: "*The main benefit is that once a VAMF is 'approved' there should be no re-assessment when presented in the context of a subsequent application for MA. Further benefits concern variations to modify a VAMF and the introduction of the updated VAMF in the respective MAs.*"	The Commission Implementing Regulation (EU) 2021/17 of 8 January 2021 establishing a list of variations not requiring assessment in accordance with Regulation (EU) 2019/6 of the European Parliament and of the Council foresees that the inclusion of an already certified VAMF in

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	Additionally, a significant disincentive is the requirement to submit two sequential variations every time there is a change to an existing VAMF). At least, the system should "strongly favour" the "2nd variation" to be a VNRA-only. This could be done by tackling any potential impact on finished products within the "1st variation" (*i.e.*, the variation changing the content of the VAMF "across the range of products"). There should not be situations in which 2 sequential VRA's are required, as this may end up in additional requests (in the worst case) that the Applicant would need to submit yet other variations (if there is a need to change anything concerning the 1st variation retrospectively). A similar comment applies for the first introduction of a new VAMF to existing products: the "first assessment" should tackle any impact/difference for the respective authorized products, so that only an administrative variation with no scientific assessment and with predictable outcome can happen as a "second step". The length of the process (when done outside the new MA CP route), the possibility to apply it to nationally only products, and the possibility to apply it in the context (or in parallel) to DCP/MRP are other important considerations. A couple of clarifying rewordings are suggested in the "specific comments" below, as well as the following other comments/questions: 1. A clearer understanding of the actual certificate has not been provided in this document. Referring to the draft guideline the certificate of compliance is "…a document summarising the parts of the dossier that are assessed and accepted and will not be re-	the marketing authorisation dossier of a veterinary medicinal product is affected through a variation not requiring assessment provided that the changes shall not affect the properties of the finished product. 1. Please note that in the final version of the 'Guideline on data requirements for vaccine antigen master files (VAMF)' EMA/CVMP/IWP/258755/2021, a certificate of compliance of the VAMF is defined as 'a document that confirms compliance of the VAMF with the EU legislation and applies

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	assessed for a vaccine, that contains the same active substance". Please consider providing additional clarity on this topic. 2. Please provide feedback if the CoC will follow an EPAR process (with the evaluation report as a basis)? 3. Could you please clarify whether/to which extent VAMF certificates will be published, together with the list of relevant products, evaluation reports, etc? 4. When filling in the eAF for the submission of a new MA it is required to provide a VAMF application number. It is unclear what the trigger is for the generation of this VAMF application number, as this is not the notification of the intent to use the VAMF certification system to EMA.	throughout the EU. This certificate accompanied by the evaluation report should be included in the MA application dossier for which the use of a VAMF is intended.' The actual certificate will be of administrative nature and will not include a summary of the parts of the dossier assessed and accepted during the VAMF certification. This information will be covered in the accompanying VAMF evaluation report. 2. The CoC will not follow an EPAR process. For transparency, for CAPs, the quality information relevant to the antigen included in the VAMF will be recorded in the EPAR of the product. 3. VAMF certificates, linked products, evaluation reports will not be published on the EMA website. 4. The VAMF application number will be confirmed by EMA once the intention to submit letter is submitted.

2. Specific comments on text

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
52-53	1	**Comment:** we suggest rewording for clarity. **Proposed change:** "*The use of the VAMF certification system is optional. For combined vaccines, the vaccine antigen(s) to be included in VAMF(s) shall be specified and a separate VAMF shall be required for each of* ***those selected by the Applicant*** ~~*them*~~*."*	Accepted.
75-77	1	**Comment:** We suggest clarifying the text to make it clear that it applies not only to multivalent vaccines (which the term "novel combination" may suggest), but that it also applies to monovalent vaccines (for example, a new formulation of one authorized vaccine containing already one existing antigen). A concrete example of this is Suvaxyn Circo (authorized in EU around 2017 with SP Oil adjuvant) which "replaced" the original formulation – Suvaxyn PCV (authorized around 2009 with SLCD adjuvant). The antigen was still the same. **Proposed change:** "*The same will also apply to vaccine antigen****(s)*** *included in a new vaccine,* ***whether monovalent or multivalent*** ~~*in a novel combination*~~*, irrespective of whether or not one or more of those vaccine antigens are part of vaccines already authorised in the Union."*	Partly accepted. The text used in the guidance quotes Section V.2.3.2 of Annex II to Regulation (EU) 2019/6 which refers explicitly to new combinations of 'vaccine antigens' so it is not possible to change it. Nevertheless, it is considered that the possibility to apply for a VAMF in the context of a new MAA for active substance/s already authorised should exist in case that an applicant, for any reason does not want to introduce the VAMF(s) in an existing product. The following text has been added: "*The same will also apply to vaccine antigens (…). It is also possible to evaluate a VAMF application as part of an initial marketing authorisation for a vaccine containing antigen(s) included in authorised vaccine(s) if, for any reason (e.g. new formulation), the introduction of VAMF(s) in the existing vaccine(s) is not envisaged.*
82-83	1	**Comment:** The VAMF concept described in the Guideline on data requirements for vaccine antigen master files (VAMF) (EMA/CVMP/IWP/258755/2021) offers relevant flexibility in particular about its applicability to vaccines registered by any procedure *(p 107-108 "The VAMF is*	Not accepted. The text in the Guideline on data requirements for vaccine antigen master files (VAMF) (EMA/CVMP/IWP/258755/2021) should be interpreted in the sense that once a VAMF for a particular antigen is certified it can be used to support

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		applicable to vaccines registered by any procedure (centralised, mutual recognition, decentralised and national procedures and can also be used in applications for multi-strain dossiers"). If the vaccines registered solely via national procedures are excluded from the VAMF certification, its use will be less attractive than expected. **Proposed change:** please delete the following sentence ~~The use of the VAMF certification system is not foreseen for antigens that form part of vaccines authorised solely via the national route~~	marketing authorisation applications of vaccines containing the antigen and submitted by any authorisation route. In the procedural guidance, the text has been included to discourage the submission of VAMF applications for antigens in vaccines authorised by the national route only and therefore evaluated by one national competent authority (e.g. old dossiers).
89-90	1	*"Either the same change is made to all linked MAs or the particular MA in question is removed from the system"* **Comment:** The above sentence is unclear. Could you please clarify if this will lead to the withdrawal of the respective product? Is there an opportunity to withdraw products from the VAMF (decoupling) or is this process irreversible (*i.e.*, leading to corresponding product withdrawal)?	The point has been clarified in the text: *"Either the same change is made to all linked MAs or the particular MA in question is removed from the **VAMF** system".* If the change to a VAMF is not introduced in all the linked MAs, then the particular MA(s) will be removed from the VAMF system, but this should not entail the withdrawal of the respective product. However, additional variation procedure(s) may be needed to remove a product from the VAMF certification scheme (e.g. to update the quality part of the 'decoupled' MA dossier).
93-94	1	**Comment:** same comment as in lines 75-77. **Proposed change:** *"In the framework of a new MAA assessment via the centralised procedure for a vaccine with a new antigen or an existing antigen in a novel combination of antigens **or in a new vaccine formulation**."*	Accepted.

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93-94	1	**"...**In the framework of a new MAA assessment via the centralised procedure for a vaccine with a new antigen or an existing antigen in a novel combination of antigens…" **Comment:** According to the draft procedural guideline, it is only possible to apply for a VAMF for a new product if the corresponding product is authorised through the centralised procedure. Following the approach as described in trigger 2 with a subsequent procedure of + 150 days represents a time loss, plus potential changes in the already assessed product. There will continue to be new vaccines for which Applicants will prefer to choose the DCP or MRP (*e.g.,* vaccines against geographically restricted diseases and a few MS concerned.). Therefore, extending this concept to DCP and MRP would be welcome. **Proposed change:** Please consider including the option for a shorter notification procedure without re-assessment directly after the outcome of MRP/DCP or enable parallel assessment.	Not accepted. A shorter notification procedure is not foreseen. Please note that in case a VAMF is applied for a recently authorised DCP or MRP product (i.e. no changes in the VAMF data package compared to the quality data assessed through MRP/DCP), it would be expected that the adoption of the VAMF certificate takes place on Day 90. The time required for the VAMF certification should be put in the context of the long-term benefit of using the VAMF certification scheme. In this regard, a certification procedure of 90 days (which would be expected in most of the cases) is considered very reasonable. Parallel assessment of a MRP/DCP MAA by NCAs and a VAMF application by EMA is not foreseen in the framework laid out in Regulation (EU) 2019/6.
101-104	1	*"For applications for VAMFs linked to the submission of an initial MAA, the intention to use VAMF shall be confirmed in the pre-submission request form (i.e. to confirm eligibility for the centralised procedure) to be submitted four months prior to the submission of the MAA or, in any case, via notification to the Agency submitted no later than 2-3 months prior to the submission of the MAA."* **Comment:** The above sentence is difficult to understand. We propose to reword. **Proposed change:** *"For applications for VAMFs linked to the submission of an initial MAA, the intention to use VAMF shall be confirmed ~~in the pre-submission request form (i.e.~~*	Accepted.

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		~~to confirm eligibility for the centralised procedure) to be submitted four months prior to the submission of the MAA or, in any case, via notification to the Agency submitted~~ no later than 2-3 months prior to the submission of the MAA, ***either via notification to the Agency or via inclusion in the pre-submission request form****."*	
106	1	**Comment:** We propose to add the clarification for the combined vaccines, that the intended use of the VAMF may be restricted to one or several, but not all, antigens. **Proposed change:** *"Intent to use the EU VAMF certification system.* ***For combined vaccine, identification of the antigen(s) for which the use of VAMF is intended."***	Accepted.
107-109 and 165-167	1	**Comment:** it is unclear why the manufacturing site information should be provided in addition (or as part of) the letter of intent submission. The requested inspection information and supportive information will be presented as part VAMF, and it is unclear how knowledge on the manufacturing sites and their inspection status prior to the submission of the VAMF is of added value. **Proposed change:** Please remove the requirement to provide information on the manufacturing sites of the antigen as part of the submission of the letter of intent.	Accepted.
128-129	1	**Comment:** It should be confirmed that in this case, the VAMF is included as such for this vaccine and no VNRA is needed to include the certificate in the dossier. **Proposed change**: Please consider adding: ***"In this case, the VAMF is included as such for this vaccine***	Partially accepted. The proposed text has been reworded and placed under 4.1.5 – Certification (Instead of 4.1.3 – Evaluation): *"At the end of the certification procedure, the certified VAMF will effectively form part of the MA dossier of the vaccine. A*

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		and no VNRA is needed to include the certificate in the dossier.”	*variation not requiring assessment (VNRA) to add the VAMF to the MA dossier is not needed in this case (Trigger 1).”*
130-132 and 185-187	1	**Comment:** VAMF is simply a means to allow for easier logistics *etc* - *Per se*, the use of a VAMF should not be determinant in authorities asking for an inspection It is assumed that for trigger 1 inspections will be handled when deemed necessary for a new product submission but not due to VAMF. Likewise, for trigger 2, the scope being products already approved in the EU by definition (and by extension satisfying EU GMP/inspections), the VAMF in itself should not be a trigger for an inspection. **Proposed change:** Please consider removing the paragraph on inspections.	Accepted.
144-147	1	**Comment:** As minor editorial differences between dossiers (quality part) may exist depending on the type of procedure and the date of registration, this should not prevent the VAMF certification process if these differences are not significant and without impact on the quality. Hence, the preliminary harmonisation of the dossiers would be required in case of significant differences. In addition, in case of significant differences, would it be possible, for example, to use a MA of reference for the certification and to allow harmonisation by the mean of the VAMF considering also that VAMF can be used (among others) for the “fall out” and “built up” vaccines *(lines 111-112 -The VAMF concept described in the Guideline on data requirements for vaccine antigen master files (VAMF) (EMA/CVMP/IWP/258755/2021)).* **Proposed change:** *In the case of a VAMF application for an antigen included in different authorised vaccines where*	Accepted but proposal slightly re-worded. *“In the case of a VAMF application for an antigen included in different authorised vaccines where **relevant** differences in the quality data packages exist, the MAH may consider harmonising the respective dossiers before applying for a VAMF. **Alternatively, the applicant could choose one of the MA dossiers to apply for the initial VAMF and then consider harmonising the rest of the dossiers based on the approved VAMF certificate.”***

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		significant/major *differences in the quality data packages exist, the MAH may consider harmonising the respective dossiers before applying for a VAMF.* ***Alternatively, the applicant may consider harmonising the corresponding dossiers based on an approved VAMF certification.***	
163-164	1	**Comment:** Same comment as for line 106. **Proposed change:** "*A list of MAs, to which the respective VAMF will apply, with the corresponding Member States (MS) of authorisation.* ***For combined vaccine, identification of the antigen(s) for which the use of VAMF is intended.***"	Accepted. For the sake of clarity, a bullet point has been added to clarify that the identification of the antigen for which the VAMF is intended needs to be specified. A separate VAMF application will need to be submitted for each antigen for which a VAMF is intended. Therefore, the reference to combined vaccines and to 'antigen(s)' in plural as in the proposed text is not appropriate here.
168-172	1	Appointment of rapporteurs under trigger 2 ("For the evaluation of the VAMF, one rapporteur and one co-rapporteur will be appointed by the CVMP") **Comment:** This text is redundant (see 152-154). Among the selection criteria of rapporteurs under trigger 2, it may be considered to facilitate the choice of the rapporteur(s) coming from (one of) the Authorities who are RMS of the corresponding product(s). Comparable to the centralised procedure, the initial assessments are made by the RMS in the MRP/DCP. **Proposed change:** "***4.2.1.2. Appointment of rapporteur(s)*** *For the evaluation of the VAMF, one rapporteur and one co-rapporteur will be appointed by the CVMP. The*	Accepted (slightly reworded). *'For antigens contained in a vaccine authorised by the DCP/MRP route only, rapporteurs will be appointed by the CVMP considering the Member State acting as reference Member State (RMS) in the original DCP/MRP procedure for the corresponding product(s).* *The rapporteurs will be responsible for the evaluation of the VAMF certification application on behalf of the EMA.'*

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		appointment of rapporteur(s) will be notified to the MAH. ***The rapporteur(s) will be responsible for the evaluation of the VAMF certification application on behalf of the EMA.*** *For antigens contained in a centrally authorised vaccine, the rapporteur(s) responsible for the authorised product will be appointed as rapporteur(s) for the evaluation of the VAMF application.* ***For any application other than that made in the framework of a new centralised MAA, rapporteur(s) will be appointed by the CVMP considering the RMS acting in a DCP/MRP for the corresponding product(s).*** *"*	
191-193	1	**Comments:** The consequences of the refusal to the linked existing MAs are not clarified. Is it possible to withdraw the VAMF application for all or for several linked MAs for example at Day 90?	It is possible to withdraw the VAMF application at any time during the VAMF application procedure with no direct consequences to the linked MAs. However, should a concern over the quality of the antigen be identified which puts the benefit-risk balance of the existing product(s) in question, it is expected this concern will be addressed in a separate procedure.
194-195	1	**Comment: "**The VAMF certificate holder will need to introduce the VAMF certificate in the corresponding MA(s) via the relevant variation." As commented in the general comments, At least, the system should aim for the "2nd variation" to be a VNRA-only. Any potential impact on finished products should be tackled in the "1st variation" (and assessed by the authorities, so that the outcome is clear and only a VNRA – with predictable outcome - can be submitted in the 2nd stage).	The point has been clarified in the text. The following text has been added: A variation not requiring assessment shall be submitted where the VAMF data package is identical to the corresponding sections of the authorised marketing authorisation dossier(s) or, if changes have been made, these do not have an impact on the finished product. A variation requiring assessment shall be submitted in case of changes in the VAMF data package that may have an impact on the finished product.

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		Proposed change: Please amend accordingly	In case of changes/harmonisation of data in a VAMF application, the applicant should include in the expert statement, an evaluation of possible impact of the changes introduced. Also, Rapporteurs may be able to signal the potential impact of changes on the finished product during the assessment of the VAMF application and therefore the type of variation that will be required to introduce the certified VAMF. In any case, the responsibility for applying for the correct variation type ultimately lies with the MAH.
218-219	1	**Comment:** We understand the requirement to submit a variation to introduce a new VAMF certificate in the corresponding MA(s) (following the trigger 2). However, for variations to the terms of an existing VAMF certificate, the proposed requirement to submit two sequential variations (each time there is a change in the VAMF content – *i.e.*, one variation to change the content of the VAMF and one variation to introduce the updated VAMF certificate) will certainly be a major disincentive for using the VAMF. As stated in the general comments, at least, the system should aim for the "2nd variation" to be a VNRA-only. Any potential impact on finished products should be tackled in the "1st variation" (and assessed by the authorities, so that the outcome is clear at the end of the 1st variation and only a VNRA – with predictable outcome - can be submitted in the 2nd stage). And in fact, ideally, when a procedure for variation to the terms of a VAMF certificate has been successfully closed,	Within the current framework a second variation to 'introduce' an updated VAMF into the corresponding MA will be necessary. The type of variation required i.e. variation not requiring assessment or variation requiring assessment, will depend on the impact of the change introduced in the VAMF on the finished product. In case of changes introduced to the VAMF through a VNRA (first stage) then it would be generally expected that a VRNA will also be relevant for the second stage. In cases where changes to the VAMF are introduced through a VRA (first stage), then the type of variation necessary for the second stage will depend on the impact of the change on the finished product. In any case, the responsibility to apply for the correct variation type ultimately lies with the MAH.

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		this would immediately include a process or procedure to allow the affected MA(s) to be updated instead of having to do this via a separate procedure (be it VNRA or VRA). Should this not be acceptable; a separate variation procedure is required to update the VAMF certificate in the affected MA(s), then, as commented above, the 2nd variation should be a "VNRA-only" and it is proposed to provide the classification of this procedure in this guidance, instead of referring to "relevant variation". **Proposed change:** Please consider the changes suggested above**.**	
243 diagram	1	**Comment:** We suggest some additional clarity in the wording (*per se,* an antigen is not "authorised", but rather the corresponding IVMP). See also comments above (please see comments on lines 93/94 re authorisation routes – Please consider reflecting further changes in the graph, too). **Proposed changes:** *New antigen(s) not ~~authorised~~* ***yet included in authorized*** *IVMPs in the EU or* ***existing antigen*** *included in a new vaccine combination* ***or in a new vaccine formulation. Corresponding IVMP MA submitted through CP****.* *Antigen* ***already included*** *~~authorised~~ in* ***authorised*** *CP, DCP, MRP IVMPs*	Accepted. Slightly reworded.