28 January 2022
EMA/CVMP/IWP/544053/2021
Immunologicals Working Party (IWP)

Overview of comments received on "Guideline on data requirements for vaccine antigen master files (VAMF)" (EMA/CVMP/IWP/258755/2021)

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

Stakeholder no.	Name of organisation or individual
1	Vaxxinova The Netherlands b.v.
2	AnimalhealthEurope

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1. General comments – overview

Stakeholder no. *(See cover page)*	General comment (if any)	Outcome (if applicable)
1	The chapters of the VAMF have been deduced from Part 2 from a product dossier but the result is confusing: - Part 2E is missing, which is logical but potentially may result in an error using the VNeeS checker upon building the VAMF into an e-submission - Part 2F has nothing to do with antigen stability but final product stability – antigen stability usually was included in Part 2D of a product dossier. It is therefore proposed to revise the "V"AMF by creating a stand-alone chapter format (this format can be adapted in due time for the "S"olvent Master File): Part 1: Summary of the dossier Part 2: Quality documentation 2.V.1 **Active substance** description 2.V.2. Description of the manufacturing method 2.V.3. Production and control of starting materials 2.V.4. Control tests during the manufacturing process 2.V.5. **Antigen** Batch-to-batch consistency 2.V.6. **Antigen** Stability tests 2.V.7. Other information, if applicable.	Comment noted. The folder structure and standard files for an electronic application for a Vaccine Antigen Master File (VAMF) have been defined in the draft 'Guideline on the specifications for provision of an electronic submission (e submission) for a veterinary medicinal product' (Table 6) that has been published eSubmission: VET eSub (europa.eu) In brief, the structure follows the structure of the quality part of a MAA for an IVMP relevant to the active substance.
2	AnimalhealthEurope welcomes the publication of the draft Guideline on VAMF. The concept as it now stands offers relevant flexibility (non-mandatory for all antigens in a given combined vaccine, applicability to vaccines registered by any procedure - centralised, mutual recognition, decentralised and national procedures - and can also be used in applications for multi-strain dossiers, etc). As such, it is expected to be used by the Veterinary Vaccine Industry going	Comment noted.

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	forward, especially if the procedural guidance and the certification process (timing, cost and practicality) are attractive, too.	
2	**Comment:** The content of the VAMF consists in quality parts (part 2), while some clinical safety data may also be more relevant to active substances than to the formulated vaccine. Therefore, it would be of interest to have the option to include these studies (related to the characterisation of the vaccine strain, especially the special requirements for live vaccines conducted at the strain level, such as reversion to virulence, spread and dissemination of the vaccine strain) in the VAMF and avoid re-assessments in the context of inclusion in subsequent application for MAs. **Proposed change:** Please include a recommendation to have the opportunity to optionally include the safety studies specifically related to the strain included in active substances as part of the VAMF.	Annex II, section V.2 of Reg. 2019/6 refers to the quality part of a dossier only. Therefore, the proposed change was not considered.
2	As detailed information on sites is given in Part 1 of the VAMF dossier and GMP certificates are added as well, it is advised to clarify in the Guideline on data requirements for vaccine antigen master files (VAMF) that this information is no longer needed to be included in Part 1 of the final product dossier in order to retain the stand-alone aspect of the VAMF (see also comments on lines 95-97 below).	A statement is included in section 5 of the GL.
2	As detailed information of the starting materials, including TSE information and applicable CEPs, are already included in Part 1 of the VAMF dossier, it is advised to clarify in the Guideline on data requirements for vaccine antigen master files (VAMF) that this information is no longer needed to be included in Part 1 of the final	TSE information and applicable CEPs should be provided in Part 2C. of the VAMF when used for the production of the active substance, not in Part I. A statement is included in section 5 of the GL.

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	product dossier in order to retain the stand-alone aspect of the VAMF (see also comments on lines 95-97 below).	
2	Although not included in the draft Guideline on data requirements for vaccine antigen master files (VAMF), when detailed and critical summaries (DACS) are added to the VAMF, one should be able to leave the details about the antigen out of the DACS of the final product (see also comments on lines 95-97 below).	Applications for VAMF for new antigens will be done in the context of a new full MAA where DACS are required. For antigens authorised in existing vaccines, DACS were submitted at the time of the initial MA (and for any relevant change to the MA afterwards). If the applicants wish to include a DACS in the package for the VAMF relevant for the corresponding antigen/active substance, then a cross-reference in the DACS included in the new full MAA dossier is acceptable in order to avoid duplication. No change in the text of the guideline is considered necessary.

2. Specific comments on text

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
32-35	2	**Comment:** As mentioned elsewhere (lines 87-91), for combined vaccines, it is allowed to have the VAMF concept implemented for one or more antigens, but not all. The current sentence is misleading ("each of the active substances"). We suggest a rewording: **Proposed change:** "The concept of a VAMF was firstly introduced through Directive 2001/82/EC as amended, Annex I, Title IV, as a stand-alone part of the marketing authorisation (MA) application dossier, which contains all relevant information on quality concerning ~~each~~ **one or more** of the active substances, which are part of this vaccine."	**Not accepted.** This text quotes the definition of VAMF given in Directive 2001/82/EC (which is the same in Annex II of Regulation 2019/6). To avoid confusion, the second part of the sentence (", which …..this vaccine.) is deleted. In section 'Principles', it is clearly stated it is allowed to have the VAMF concept implemented for one or more antigens, but not all.
39-41	2	**Comment:** The reference to the fact the VAMF certification has not yet been applied for in the human field is not adding any value, to our opinion. It is rather negative, and could eventually become outdated (should one or more Companies decide to apply it in the future). We would suggest removing these sentences. **Proposed change:** ~~For human vaccines, the concept of VAMF was introduced with Directive 2001/83/EC as amended, Annex I, and guidance on scientific data requirements as well as requirements for VAMF certification were published. So far, no VAMF certification has yet been applied for in the human field.~~	**Accepted.**
84-85	2	**Comment:** "The main benefit is that once a VAMF is "approved" there should be no re-assessment when	**Accepted.**

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		presented in the context of a subsequent application for MA". As highlighted in line 99, there will be no re-assessment for the VAMF once approved. **Proposed change: "**The main benefit is that once a VAMF is "approved" there ~~should~~ **will** be no re-assessment when presented in the context of a subsequent application for MA."	
87-88	2	**Comment:** In some cases, the protection of the animals by vaccination can be improved by inclusion of different antigen subtypes within a vaccine. Related to the fact that the characteristic and production of subtypes often are close to each other, the separation of VAMF of these subtypes brings no value and increase the hurdles to the applicant to use VAMF for vaccines. **Proposed change:** Therefore "For combined vaccines, the active substance(s) intended to be included in a VAMF shall be specified and a separate VAMF shall be required for each of them." should be adapted to "For combined vaccines, the vaccine antigen(s) to be included in Vaccine Antigen Master File(s) shall be specified and **by default** a separate VAMF shall be required for each of them. **A special case is when protection against a microbial organism requires multiple antigens, in which case one VAMF may cover multiple antigens**."	**Not accepted.** The provisions in Annex II of the Regulation 2019/6 indicate "Vaccine Antigen Master Files corresponding to each single vaccine antigen for which the use of a Vaccine Antigen Master File is intended" so there is no scope to include more than one antigen in a VAMF.
95-97	2	**Comment:** "In the case of existing MAs, MAHs may initiate the VAMF certification process. The data submitted for certification should correspond to the quality data already approved for the relevant antigen	**Not accepted.** A VAMF is a stand-alone part. Even for antigens authorised in centralised MAs, the application data package for a VAMF

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		in the linked MA. Further details will be provided in the procedural guideline." – According to line numbers 45 to 47, EMA is responsible for scientific evaluation and certification of VAMFs. In case of existing MAs issued in a centralized procedure led by EMA it seems redundant to re-submit all data for certification of a VAMF. It should be clarified in general which data has to be included in the marketing authorisation dossier and in the certified VAMF respectively to avoid redundancies and administrative burden due to double submission and evaluation. (See also general comments above).	should contain the relevant information as described in the GL. The same is valid for MRP/DCP products.
95-97	2	**Comment:** Is the case of non-fully harmonised MA dossiers containing the same vaccine antigen planned to be addressed in the procedural guideline for VAMF ? The data submitted for certification will correspond in the whole to the Quality data already approved, but may need to be updated in some linked MAs when non-fully harmonised marketing authorisation application dossiers are concerned (registered in the past by National Procedure for example). 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? See also lines 102-103 indicating that the VAMF can be used for the "fall out" and "built up" vaccines and lines 111-112. **Proposed change:** The data submitted for certification should correspond to the quality data already approved for the relevant antigen in linked MA	**Partly accepted.** It is up the applicant to decide in the case of a VAMF application for an antigen included in different authorised vaccines and differences in the quality data for the antigen: - To harmonise these quality data of the different dossiers before applying for a VAMF or - choose one of the MAs to prepare the initial VAMF and then harmonisation should be done based on the certified VAMF.

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		(unless justified exception, for example to allow for harmonization of the corresponding dossier sections – covered by the VAMF - for the same product authorized nationally in different Member States). Further details will be provided in the procedural guideline.	
109-112	2	**Comment:** "The inclusion of an already certified VAMF in the marketing authorisation dossier of an authorised vaccine when changes do not affect the properties of the finished product is included in the list of variations not requiring assessment in accordance with Regulation (EU) 2019/6 (Commission Implementing Regulation (EU) 2021/17)." – It is appreciated that the inclusion of a VAMF is possible via a variation not requiring assessment. Nevertheless, it should be clarified how this specific variation would work in practice. Additionally, it should be clarified in general which data has to be included in the marketing authorisation dossier and in the certified VAMF respectively to avoid redundancies and administrative burden due to double submission and evaluation. (See also general comments above).	Comment noted. The processing of variations not requiring assessment is not in the scope of this GL and will be addressed in the context of separate procedural guidance. This GL describes what should be included in a VAMF. A statement is included that the information provided for the active substance in a VAMF does not need to be included in Part 1 or Part 2 of the final product dossier. Please consider also the EMA procedural advice (Procedural advice for veterinary vaccine antigen master 4 file (VAMF) certification - https://www.ema.europa.eu/en/procedural-advice-veterinary-vaccine-antigen-master-file-vamf-certification#current-version-section).
127	2	**Comment:** Structure to be followed of an VAMF is not open to CTD like optional mentioned in Section I of ANNEX II to Regulation (EU) 2019/6. **Proposed change:** Therefore "The following structure should be followed:" should be adapted to "The following structure **or an equivalent structure in CTD** should be followed"	**Accepted.**

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147-148	2	**Comment:** We are aware that the sentence is a copy-paste from the annex II requirements, but at the same time, the most recent part I requirements (application form) require a QP declaration, as follows: "For each active substance, attach a Qualified Person declaration that the active substance is manufactured in compliance with the detailed guidelines on good manufacturing practice for starting materials". In our opinion, this sentence is providing definitive clarity on expectations and we suggest to use it as such. **Proposed change:** We suggest to use a similar wording as above: "For each active substance, a Qualified Person declaration that the active substance is manufactured in compliance with the detailed guidelines on good manufacturing practice (GMP) for starting materials shall be provided. ~~The manufacturing processes for the active substance(s) shall comply with Good Manufacturing Practice (GMP). Corresponding GMP certificates shall be provided~~."	**Partly accepted.** The proposed sentence is included. The sentence on providing corresponding GMP certificates is not deleted in line with section 1 of Annex II.
Line 151	1	Comments: The VAMF concerns an active substance, therefore it is proposed to amend the header of section 5.2 Proposed change (if any): "**5.2. Active substance description (Part 2.A.)**"	**Not accepted.** See general comments.
153-158	2	**Comment:** It might be difficult to present the qualitative composition for Biological active substances as it is quite complex to define precisely	**Accepted.**

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		(subjected to further treatments). This requirement should not lead to provide the full list of starting materials (all the constituents mentioned in the text) involved in the manufacture of the active substances (redundant with information presented in part 2.C) and should be limited to the description of the active substance only, recognizing that all other information will be provided in the other sections. **Proposed change:** "~~The qualitative composition of all the constituents of the active substance shall be given.~~ The complete and exact name of the active substance (for example, virus or bacteria strain, antigen) shall be provided, in the same way as mentioned in any finished product. The nature of the antigen should be described (inactivated, live, recombinant, …). Any information on titre/potency specifications at specific production steps should be addressed in the corresponding sections of antigen production. **Any information on the starting materials should be addressed in the corresponding sections of the VAMF."**	
Line 156	1	Comment: It is not clear if one VAMF can be used for an active substance both in a live- as well as in an inactivated form. Proposed change (if any):	One VAMF cannot be used for an active substance both in a live- as well as in an inactivated form.
Line 160	1	Comment: Section 2.A.2 should only focus on the relevance of the active substance for the EU. The	**Accepted.**

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		rationale for its use in different final products shall be included in the product dossier, not in the VAMF. Proposed change (if any): ~~Information on product development relevant to the active substance shall be provided.~~ The choice of the active substance and the choice of the constituents of the active substance, in particular relative to their intended functions, shall be described. The justification of the antigen/strain relevance should cover the situation in the EU, as the VAMF will be certified by the EMA, regardless of the authorisation procedure of the corresponding vaccine(s). The selection of the manufacturing process of the active substance shall be explained.	
174-176	2	**Comment:** We are not aware of a specific EU requirement relative to the number of active substances batches and the requirement for them to be consecutive. Requiring 3 consecutive active substance batches may be seen as a disincentive versus a "non-VAMF" containing vaccine(s). Up to now, for regular vaccines, Industry has been successful with two, non-consecutive, antigen batches (sometimes mixed with each other before finished product blending to document this practice into MA dossier). Knowing that the guiding principle of the VAMF is to reflect the corresponding sections (and content) of antigens, without adding new technical requirements, we would suggest to reword this sentence. Also, this requirement appears to contradict the "quality by design" approach.	**Accepted.**

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		Proposed change: "Results of ~~three consecutive~~ **two** active substance batches produced using the method of production described should be provided".	
180-185	2	**Comment:** "The standard requirements described in Section IIIb.2C of Annex II to Regulation (EU) 2019/6 and relevant to the active substance shall apply. For the purposes of this Part, 'starting materials' means all components used in the production of the active substance. Information on the active substance (for example, virus/bacteria strain), the substrate/s (cells, culture medium) and all the raw materials (pharmacopoeia or non-pharmacopoeia, biological or non-biological) used in the production of the active substance shall be provided." We recognize that the wording "starting materials" and "raw materials" is extracted from the Annex II (especially section V.2.2.4.2). However, the difference between both terms is not clear. We suggest to use "starting materials" as only term, consistent with wording of Annex II (section IIIb.2.C). **Proposed change:** Information on the active substance (for example, virus/bacteria strain), the substrate/s (cells, culture medium) and all the ~~raw~~ **starting** materials (pharmacopoeia or non-pharmacopoeia, biological or non-biological) used in the production of the active substance shall be provided.	**Accepted.**

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196	2	**Comment:** "Warnings or restrictions of use may be brought in at the VAMF level depending on the information presented, which may be mitigated during the risk analysis at the level of the finished product." We suggest an alternative wording to improve the reliability of VAMF outcomes. **Proposed change:** "**Outcome of EA assessment should** ~~Warnings or restrictions of use may~~ be brought in at the VAMF level depending on the information presented, which **should** ~~may~~ be mitigated during the risk analysis at the level of the finished product."	**Partly accepted.** The following amendment is proposed (so both aspects TSE and EA are included in line with the original text): It is to be noted that the target species retained for the finished products making reference to the VAMF shall be considered for the TSE and EA risk assessment. *The outcome of this risk assessment should be brought in at the VAMF level depending on the information presented, which should be mitigated during the risk analysis at the level of the finished product.*
201-209	2	**Comment:** For live genetically engineered starting materials, this information also has to be provided in Part 3.E of the dossier. In fact, when the final product is intended for the same target animal(s) and the same route(s) of administration is applied, part 3.E should also be part of the VAMF. As it has already been assessed and the live vaccine strain has been released for introduction into the environment, there should be no new information to be provided. Adding Part 3.E to the VAMF reduces the administrative and regulatory burden for industry and competent authorities for authorisation of vaccines and offers also greater consistency and predictability for the assessment of the live genetically modified antigen.	**Not accepted.** Annex II, section V.2 of Reg. 2019/6 refers to the quality part of a dossier only. Furthermore, Part 3.E is assessed by GMO authorities for each GMO IVMP independently. Therefore, the proposed change was not considered.

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		Note that in the past the information provided in Part 3.E had to be provided in Part II.H of the dossier.	
215-217	2	**Comment:** The description of the requirement for the inactivation or detoxification testing is not in line with the last revision of Ph. Eur. monograph 0062 which describes the possibility to conduct the test "after subsequent process steps enhancing the sensitivity of the test (e.g. concentration step)". *Extract from EP 0062:* *2-3-2-3. Residual live virus/bacteria and/or detoxification testing. For each production run, a test for complete inactivation and/or detoxification is performed immediately after the inactivation and/or detoxification procedure or after subsequent process steps enhancing the sensitivity of the test (e.g. concentration step).* **Proposed change:** "For inactivated or detoxified active substances, inactivation or detoxification shall be tested during each production run as soon as possible after the end of the inactivation or detoxification process and after neutralisation if this occurs, **or after subsequent process steps enhancing the sensitivity of the test** ~~but before the next step of production~~."	**Accepted.**
224-226	2	**Comment:** The recommendation to apply, for antigen consistency purposes, the annex II requirements as they apply to finished products, is not supported for the reasons described above. Please see the suggested change specific to lines 174-176 above.	**Accepted.**

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		Proposed change: Results of ~~three consecutive~~ **two** active substance batches produced using the method of production described should be provided.	