28 January 2022
EMA/CVMP/IWP/618280/2021
Immunologicals Working Party (IWP)

Overview of comments received on the draft guideline on data requirements for vaccine platform technology master files (vPTMF) (EMA/CVMP/IWP/283631/2021)

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. *(See cover page)*	General comment (if any)	Outcome (if applicable)
1	AnimalhealthEurope welcomes the specific guideline for the practical implementation of the technology platform concept, set in the new veterinary regulation, and the opportunity to comment on this draft guideline. We are looking forward to a guideline that will detail the registration procedures and expect that the benefit of the abridged dossier for the vPTMF updates as detailed in this guideline, will extend to the setting of a shorter assessment timeline. This guideline which will be in place, before much experience is gained from practical examples, seems too detailed and in some aspects, somewhat restrictive. This may prevent the Platform Technology concept from having a significant positive impact on vaccine availability. For example, several sections make this Guideline only applicable to monovalent vaccines with no change in manufacture except the inclusion of a different gene of interest, including identical excipients, adjuvants and a fixed formulation. To have a significant positive impact on vaccine development, provided relevant scientific and regulatory justification are given, this guideline should include more flexibility to allow differences for example in the formulation of the final product including different antigen content, different excipient and adjuvant composition... The omissions/reductions of requirements as described in this Guideline should then be adapted accordingly. AnimalhealthEurope would propose a focus group meeting is organised to discuss the comments received on the guideline and	**Noted** EMA procedural guidance for vPTMF certification is currently under development and will be published on the EMA website in due course. We have taken into account AHE comments about introducing more flexibility into the guideline (please see specific comments). The proposal for a meeting to discuss the comments is noted. Given the timeframe for the completion of the guideline and noting that most of the comments raised have now been addressed, an information session **after** publication of the guideline will be considered. This will avoid a delay in the publication and availability of the guideline.

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	how we can improve on the draft ahead of the finalisation of the guideline. As this is a new concept with little practical experience, we suggest that a revision date is set in the guideline to update it after experience is gained with the first procedures using this new concept. We would suggest this should occur once at least one product has been through the procedure.	
	Annex II (V.4.1.1) mentions that a vPTMF is for one 'backbone' carrier and attached technologies, later on (V.4.1.3), it mentions that a vPTMF should be certified for a technology and a given target species. Depending on the applicant's choice, the guideline should also set a situation where, it is applicable to the technology alone, not comprising species and route(s) of administration. This would allow all manufacturing/analytical parts to be set in a vPTMF certificate and the applicant, in subsequent applications, would add all relevant data for the vaccine to be registered in this or that species. Suggestion: please add flexibility in the different parts of the text where the species is mentioned.	**Partially accepted.** We can include the flexibility to add "route of administration", and also to revise possible sections affected in the guideline (see below in specific comments). About adding other routes of administration, it is possible in the present text, by way of variation. About adding or changing target species different from the one/s accepted in the first certified platform, it has to be noted that in the Delegated Regulation EU 2021/805 the following is indicated: A full dossier is required for the first product from a manufacturer based on a particular platform technology for a particular target species.
	We would also welcome the guideline mentioning that it will also be applicable to existing vaccines (with some specificities that could be set in a specific section later on).	**Noted**, as it is indicated in section 4. Definitions and general principles: In the case of existing MAs, MAHs may initiate the vPTMF certification process. The data submitted for certification should correspond to the data already approved for the

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		relevant platform technology in the linked MA. **Further details will be provided in the procedural guideline**.
	The principle of annex I and II, giving examples of technology and examples of data to submit is useful. However, the technical and scientific future evolution might be in contradiction with the listed examples. Additionally, although numerous examples are given, they might not encompass all the existing technologies that may be eligible for this scheme. We suggest two possibilities: either removing these appendices completely or if kept, adding a sentence in the beginning of Annex I and Annex II confirming that these described examples and situations are "illustrative and non-binding".	**Agreed** to add "illustrative and non-binding". On this point it is noted that the proposal for "specific annexes" was originally made by AHE in comments received on the concept paper.

2. Specific comments on text

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
52	1	**Comment:** See the general comment on the platform/species and per vaccination route as mentioned in lines 160-162. It should be the choice of the applicant whether the platform includes one or different administration routes. The certificate should reflect this. The platform and vPTMF should be a bit more flexible, the applicant deciding, whether the vPTMF covers only manufacturing or manufacturing and safety. In the latter case, it should have all relevant information on the safety and the administration route(s). **Proposed change:** ….in a certified vPTMF will not be necessary for other products using the same platform for the same technology or for the same technology and listed target species **and vaccination route(s)**.	**Accepted with slight modification.** It could be acceptable to include also "vaccination routes" in line 52, but also to include/revise this point in sections 5 and 6 of the guideline. Left as "**route of administration**" On this point, it should be noted (as stated in the guideline) that: The request for additional claims for use of a licensed platform product, either in a different target specie category or route of administration in the same target species will be considered as any traditionally licensed product and will require safety and efficacy studies.
55	1	**Comment:** the term 'backbone carrier' should be defined in paragraph 4. **Proposed change:** **'backbone carrier': single vector or expression system**	**Accepted**
59	1	**Comment:** We suggest adding at the end of the introduction a revision clause (see general comment), to take into account the gaining of experience in the early life of this guideline. **Proposed change:** **This guideline should be reviewed in 2023 at the latest, after experience has been gained from its application**.	**Not accepted** The proposed statement is not considered necessary in the guideline. Noting that the vPTMF concept is new and that there is limited experience of platform technology assessment in the veterinary area, the CVMP will, by the end of 2023 at the latest, review the experience gained from the application of

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			this guideline and reflect on the need for revision of the guideline.
80	1	**Comment:** We suggest adding the following definitions: • *'backbone carrier'* • *'Replicative and non-replicative platforms'* **Proposed change:** **backbone carrier: single vector or expression system** **Replicative platforms: platforms that are able to form when reaching their targets (cells or other media in the vaccinated animal) a new replication-competent organism that can reproduce itself and infect new targets (cells…) to transfer genetic material.** **Non-replicative platforms: platforms that are not able to form any replication-competent organism that can reproduce itself and infect new targets and transfer genetic material, to replicate further.**	**Accepted**
84	1	**Comment:** …*mRNA-based platforms, replicons (self-replicating RNA)*: **Replicon**: the term "Replicon", also mentioned in Annex II of the regulation, as an example, targets a self-amplifying RNA vaccine with a certain 'RNA-carrier' technology (based on a virus-like particle allowing the RNA to enter the target cells). There are other self-amplifying RNA vaccines that are not based	**Accepted**

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		on this principle (using lipid carriers to enter the target cells). **self-replicating RNA**: as later mentioned in the document (line 271), the term "**self-amplifying**" should be used instead of "self-replicating". We believe this later term better reflects the scientific reality of these RNA vaccines as there is no 'replication' per se, which is more usually used for an organism replicating from cell to cell in the vaccinated animal. **Proposed change:** …mRNA-based platforms, replicons **and other** self-**amplifying** ~~replicating~~ RNA)…	
90	1	**Comment:** Besides the master seed, a master sequence or a construct can be the origin of the vaccine; in the definition list (line 98), 'construct' is mentioned and it is not necessarily based on a seed lot system. In the annexes it seems that this is understood (see line 341 for example) **Proposed change:** In practice, a vaccine platform is a manufacturing process that relies on a single vector or expression system ("backbone carrier") and a standard process for inserting a gene or genes of interest into the system to generate different recombinant master seeds**, master sequences or constructs**, which are then used to produce a vaccine.	**Accepted**

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92-93	1	The active substance obtained is blended with adjuvants and/or excipients in a fixed formulation to manufacture finished products with certain defined properties. **Comment:** It is proposed to change this sentence in order to allow flexibility on the formulation steps. As mentioned in lines 121-124, "The vPTMF shall contain all data relative to the platform for which there is reasonable scientific certainty that that part will remain unchanged regardless of the antigen/gene added to the platform. The format of the vPTMF shall follow the normal dossier format, including only those sections that will remain unchanged for subsequent products derived from the platform." In addition to this: for any vaccine there is a need to adjust formulation to reach the required efficacy claim(s). Moreover, a range can be defined for the active substance instead of a fixed formulation target; what is important is that when the platform is registered, the maximum content of active substance (and excipients) are set so the safety 'data package' allows establishing a range of formulation instead of a fixed one. The omissions/reductions of requirements should be adapted depending on the level of similarity with the initial product. **Proposed change:** The active substance obtained is blended with adjuvants and/or excipients to obtain s ~~in a fixed formulation to manufacture~~ finished products with certain defined properties.	**Accepted**

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105	1	**Comment:** It seems odd that a "certificate of compliance" is a "document that summarises the parts of the dossier that….". We suggest that the certificate is granted on the basis of a positive assessment of the vPTMF. Also, the definition given is a repetition of the definition given just before on vPTMF. **Proposed change***:* a document that is granted after a positive assessment of a ~~that summarises the parts of the dossier that have been assessed and accepted and that will not be re-assessed for subsequent products based on that~~ vPTMF.	**Accepted and amended in line with VAMF guideline.** **Certificate of compliance of the Vaccine Platform Technology Master File:** a document that confirms compliance of the vPTMF with the EU legislation and applies throughout the EU. This certificate accompanied by the evaluation report should be included in the MA application dossier for which the use of a vPTMF is intended.
129	1	**Comment:** Word missing **Proposed change:** Quality **Documentation**	**Accepted**
134-136	1	It is then expected that there will be no changes in adjuvants and other excipients (fixed formulations) and no changes in starting materials (including e.g. cell lines used), except the ones used for new inserts. **Comment:** It is proposed to be less restrictive on the standardisation of the manufacturing process in order to allow more flexibility on the manufacturing steps from the antigen to the finished product. The omissions/reductions of requirements should be adapted and justified depending on the level of similarity with the initial product. **Proposed change: The maximum level of standardisation of the manufacturing process being** ~~It is then expected that there will be~~ no changes in adjuvants and other excipients (fixed formulations) and no changes in starting materials	**Accepted with amendments** The text to be included is proposed as follows: It is important in the quality part of the dossier of a vPTMF to ensure/confirm as far as possible standardisation of the manufacturing process, regardless of the sequence/gene inserted in the future. This is the key point to allow certification of a vPTMF and reference to that certified vPTMF in subsequent MA applications.

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		(including e.g. cell lines used), except the ones used for new inserts.	
138	1	**Comment:** As explained earlier (see line 90), seeds might not be relevant **Proposed change:** The expression system, including all reagents, ~~seeds,~~ sequences, and **if relevant,** seeds and cells, to propagate the final construct.	**Accepted**
143	1	**Comment:** antigen is not the correct term as in some technology the active substance (or active ingredient) is not made of antigen(s) but rather of genetic material. **Proposed change***:* -Minimum and maximum ~~antigen - amount of antigen~~ **active substance** content per dose….	**Accepted**
161-162	1	**Comment:** see earlier general comment (line 52) Ideally the applicant should be able to set the limits proposed for the vPTMF; it should be also possible to build a vPTMF solely for a manufacturing process (the data relevant for the target species and administration route would be in the additional; files); in the current setting, this is probably not possible…Flexibility is required here, depending on the submitted package **Proposed change***:* Once a vPTMF is certified, the certificate may be used to fulfil the relevant data requirements in subsequent applications for MAs based on this platform **and intended for the same technology (for a different gene of interest in a different target species) or for a different gene of interest in** the same target species **and same**	**Partly accepted.** With modifications We cannot accept the first part of the proposal as the target species should be the ones already existing in the certified vPTMF, as indicated in the Delegated Regulation EU 2021/805 new Annex II of the new Regulation. If the applicant wants to change the target species, this can be done, by variation. As indicated above in the text of the guideline: *The request for additional claims for use of a licensed platform product,* ***either in a different target species*** *category or route of administration in the same target species will be considered as any traditionally licensed product and will require safety and efficacy studies.*

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		route(s) of administration if those latter are already included in the vPTMF.	Then the paragraph is proposed as follows: Once a vPTMF is certified, the certificate may be used to fulfil the relevant data requirements in subsequent applications for other products using the same platform for a different gene of interest and intended for target specie and for route(s) of administration already accepted for the vPTMF.
163 & 167	1	**Comment:** 'antigen' to be replaced by 'active substance' **Proposed change***:* 163: Registration ~~Licensure~~ of products containing new ~~antigens~~ can be streamlined… 167: the manufacturing process or ~~antigen~~ active substance content	**Accepted**
163-167	1	Licensure of products containing new antigens can be streamlined based on some of the studies conducted with the initial product, provided there are no changes in manufacture except the inclusion of a different gene of interest. Subsequent constructs must be produced with an identical expression system, using the same method of production as for the initial product. There should be no changes to the manufacturing process or antigen content. **Comment:** It is proposed to be less restrictive on the standardisation of the manufacturing process in order to allow more flexibility on the manufacturing steps from the antigen to the finished product. The	**Accepted with amendments** Taking into consideration the proposals made by AHE, we can have two types of vPTMF certifications and subsequent dossiers: First one, with "fixed" final formulation (excipients and adjuvants)", where Quality, safety and efficacy omission/reductions indicated in the guideline for subsequent products are applicable Without fixed final formulation, where these reductions are not fully applicable, and then only some parts of Quality

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		omissions/reductions of requirements should be adapted depending on the level of similarity with the initial product. **Proposed change:** Licensure of products containing new antigens can be streamlined based on some of the studies conducted with the initial product, **depending on the level of similarity with the initial product**.~~provided there are no changes in manufacture except the inclusion of a different gene of interest~~. Subsequent constructs must be produced with an identical expression system, using **whenever possible** the same method of production as for the initial product. **The omissions/reductions of requirements should be adapted to the** ~~There should be no~~ changes to the manufacturing process or ~~antigen~~ active substance content.	and/or Safety omission/reductions will be applicable, and in general Safety and Efficacy omission/reductions will be not applicable and a case by case decision will be made. Then the text proposed here will be as follows: 'Registration of products containing new active substances can be streamlined based on some of the studies conducted with the initial product. The level of standardisation of manufacturing process (similarity) with the initial vPTMF certified should be sufficiently described by the applicant. If it is intended that the vPTMF relates to a fixed final product formulation and that subsequent product applications are based on this same final product formulation (with the exception of gene of interest), the possible omission/reductions included in sections 61. (Quality) and 6.2 (Safety and efficacy) are applicable. However, if the applicant decides not to include a final product fixed formulation only some points of quality and/or safety reduction/omission will be applicable, depending on the level of similarity of subsequent dossiers with the initial product, and this will be a case by case decision.
184	1	**Comment:** The omissions/reductions of requirements listed should be adapted depending on the level of standardisation of the manufacturing process. **Proposed change:** **The omissions/reductions of requirements listed in the Table hereafter should be adapted depending on the level of similarity with the initial product.**	**Accepted with amendments** See previous comment

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181	1	**Comment:** what about regulators such as the promoter(s)? **Proposed change***:* Each subsequent construct with a different gene of interest should be identical to the initial vPTMF construct, with the exception of the sequence of the inserted gene **and if justified the promoters**.	**Accepted.**
185	1	**Comment:** 2A1: addition of backbone 2B: addition of the possibility to have new promoters adapted to the new gene of interest. 2C: when insertion is the same as described in the vPTMF, why describe it again? 2E: when the already-approved test has been validated and approved, why re-validate it, an applicability test should be sufficient. **Proposed change***:* 2A1: Only data about the gene of interest are needed, (no information is needed about the vector **or backbone nucleic sequence**) 2B: Information about the origin and manufacturing of the new sequence/gene of interest**/promoters**, including details of the synthesis and insertion process of the gene	**Partially accepted** (see details below) 2A1: **Accepted** 2B and 2C (promoters): **Accepted**

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		2C: Information about the origin and manufacturing of the new sequence/ gene of interest, **including when changes occurred**, details of the synthesis and insertion process of the gene 2E: Identification and quantification of the new antigen related to the new sequence/ gene of interest should be described ~~and validated~~**; test applicability should be confirmed.**	2C: **Accepted** **Not accepted.** In part 2C CONTROL TESTS DURING MANUFACTURING PROCESS, we include the possible flexibility. Only new tests not performed in the original vPTMF and related with the new insert will be described and validated. Here in part 2E Finished Product we want to measure the new antigen, then the tests are expected to be new for the identification and quantification (potency), and as such, should be validated.
195-196	1	Some reductions of requirements in safety studies are possible and are listed in the following table depending on the capacity of the platform product to replicate or not. **Comment:** The omissions/reductions of requirements listed should be adapted depending on the level of standardisation of the manufacturing process. **Proposed change:** Some reductions of requirements in safety studies are possible and are listed in the following table depending on the capacity of the platform product to replicate or not. **The omissions/reductions of requirements listed in the Table hereafter should be adapted and justified depending on the level of similarity with the initial product.**	**Accepted with amendments.** See previous comments

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196	1	**Comment:** the capacity of the platform product to replicate or not should be described. **Proposed change:** Please add a definition of replication as per 2001/18	**Partially accepted**. Already included in definitions (replicative and non-replicative) To be noted that in Directive 2001/18 (GMOs), there is not a specific definition of replication, but it is for "micro-organisms".
197	1	**Comment:** The repeated dose safety test should be required only when relevant. REPLICATIVE: Special requirements for live vaccines (reversion to virulence and biological properties should be performed): we believe that there are occasions when the reversion to virulence test is not needed for a new replicative construct, if well justified. **Proposed change***:* NON REPLICATIVE 3B PRECLINICAL 1 dose **and when relevant** repeated dose REPLICATIVE 1 dose and overdose and **when relevant** repeated dose Special requirements for live vaccines (reversion to virulence and biological properties should be performed, **unless justified**)	**Partially accepted** For repeated dose safety test **when relevant** (meaning, in line with vaccination schedule) **could be added**. For live vaccines, the special requirements included in Annex II have to be addressed. Therefore, here **we do not accept to include "unless justified".**
225	1	**Comment:** The principle of annex I giving examples of technology is useful. However, the listed examples may be in contradiction with the scientific and technical evolution and progresses. Besides, although	**Accepted**

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		numerous, those examples might not encompass all the technologies that may be eligible for this scheme. We suggest that a sentence should be added at the beginning of Annex I confirming that these described examples and situations are "illustrative and non-binding" **Proposed change:** **The examples here list, in a non-exclusive manner, different existing technologies that could fit in the vPTMF scheme. They are illustrative and non-binding and do not preclude other existing technologies and future scientific and technical progresses.**	
271	1	**Comment:** See comments for line 84 **Proposed change:** …mRNA – non ~~replicating~~ **amplifying, self amplifying RNA (like replicons and other synthetic RNA vaccines)**	**Accepted**
272-274	1	**Comment:** Clarification is required for the different RNA vaccines and the technology used to make them: RNA vaccines are currently of two types, mRNA and self-amplifying RNA vaccines. None of them are replicative platforms, as they are not able to form any replication-competent organism that can reproduce itself and infect new targets and transfer genetic material. They are two ways to produce RNA vaccines: mRNA vaccines are produced in a synthetic manner, not using any conventional vaccine-manufacturing means, like cell-line system…	**Accepted**

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		Self-amplifying RNA vaccines can be produced, following a synthetic process (like for mRNA vaccines) or a more conventional way (transfection of cell line). **Proposed change:** ~~There are currently two different types of synthetic RNA vaccines: conventional mRNA and self-amplifying RNA (saRNA). Conventional mRNA and synthetic saRNA vaccines are essentially produced in the same manner.~~ **There are currently two different types of RNA vaccines: mRNA and self-amplifying RNA (saRNA). They are manufactured following a synthetic production process (mRNA and certain saRNA vaccines)or a more conventional manufacturing technologies (other sa-RNA (replicon) vaccines, produced using with cell lines).**	
288	1	**Comment:** Self-amplifying RNA vaccines are either based on a replicon system (produced in transfected cells) or on a synthetic saRNA embedded in lipidic carrier. **Proposed change:** Self-amplifying saRNA vaccines are genetically engineered ~~derived~~ from single-stranded RNA viruses ~~replicons derived from self-replicating~~ **and either based on a replicon system (produced in transfected cells) or on a synthetic saRNA embedded in lipidic carrier.**	**Accepted**
290	1	**Comment:** Not all self-amplifying RNA vaccines are based on a replicon system.	**Accepted**

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		Proposed change: ~~Replicon vaccines are s~~**S**elf-amplifying **RNA vaccines** are viral mRNA sequences that, in addition to the sequence encoding the antigen of interest, contain all elements necessary for RNA replication.	
305	1	**Comment:** The principle of annex II giving examples of dossier content is useful. However, taking into account the absence of direct experience of this scheme at the time this guideline is set, we suggest that a sentence is added at the beginning of Annex II confirming that these described examples are "non-binding" **Proposed change:** **The listed examples are illustrative and non-binding and do not preclude the specific content of the dossier for each technology fitting the vPTMF scheme.**	**Accepted**