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Guideline on data requirements for vaccine platform technology master files (vPTMF)

Draft

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Executive summary

The main aim of the guideline is to address the type of data to be included in a vaccine platform technology master file (vPTMF).

Furthermore, the guideline addresses the omission of information and /or possible reductions on data requirements for subsequent dossier submissions for marketing authorisations (MA) based on a vPTMF after its first evaluation and certification.

1. Introduction (background)

The concept of a vaccine platform technology master file is introduced for the first time in European Union (EU) legislation in Annex II of the Regulation (EU) 2019/6 (Commission Delegated Regulation (EU) 2021/805 of March 2021 amending Annex II to Regulation (EC) No 2019/6 of the European Parliament and of the Council).

This is a new concept in EU legislation for immunological veterinary medicinal products (IVMPs) that anticipates the unnecessary re-submission and re-evaluation of data relating to a vaccine platform technology used in an authorised IVMP for the authorisation of subsequent vaccines based on this platform.

The vPTMF is a stand-alone part of the dossier for an IVMP, which will remain unchanged regardless of the antigen(s)/gene(s) of interest included in the platform.

Once a vPTMF for a given platform technology has been approved for the first time after scientific and technical evaluation (as part of a full MA application), a certificate of compliance will be issued, accompanied by an evaluation report. Re-submission and re-assessment of data and/or parts of the dossier included in a certified vPTMF will not be necessary for other products using the same platform for the same listed target species.

The details of the content of this vPTMF will be outlined in the present guideline.

Vaccine platform technologies have the potential to lead to the development of multiple vaccines with the same 'backbone carrier'. Therefore, it is expected that this procedure will allow for the omission of already certified information in future dossiers and consequent reductions in data to be submitted by the applicant. This avoids the re-evaluation of parts of the dossier already assessed and certified in the first vPTMF; in turn speeding up subsequent authorisations and also helping to increase the availability of vaccines.

2. Scope

Guidance is provided on the type of data that may be included in a vPTMF and also on data requirements for subsequent dossier submissions for MAs based on a vPTMF after first evaluation and certification.

Procedural guidance for the submission, evaluation and certification of vaccine PTMFs will be developed in parallel by the European Medicines Agency (the Agency). This task is out of the scope of the present guideline.

3. Legal basis and relevant guidelines

This guideline should be read in conjunction with the introduction and general principles of Annex II to Regulation (EU) 2019/6 relevant to IVMPs, and all other relevant EU, VICH guidelines and European Pharmacopoeia (Ph. Eur.) texts and monographs applicable to IVMPs. These include but are not limited to:

- CVMP/IWP/07/98-FINAL Note for guidance DNA vaccines non-amplifiable in eukaryotic cells for veterinary use (under revision).
- EMEA/CVMP/004/04-FINAL Guideline on live recombinant vector vaccines for veterinary use.
- EMEA/CVMP/VICH/811/04 VICH GL40 Test procedures and acceptance criteria for new biotechnological/biological veterinary medicinal products.
- EMA/CVMP/IWP/600275/2020 Guideline on data requirements for multi-strain dossiers for inactivated vaccines.

4. Definitions and general principles

Vaccine platform technology: A collection of technologies that have, in common, the use of a 'backbone' carrier or vector that is modified with a different antigen or set of antigens for each vaccine derived from the platform. This includes, but may not be limited to, protein-based platforms (virus-like particles), DNA vaccine platforms, mRNA-based platforms, replicons (self-replicating RNA) and viral and bacterial vector vaccines.

More detailed descriptions and definitions for the types of platforms in current use are included in annex I to this document.

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, which are then used to produce a vaccine. The gene of interest may consist of one or more complete or partial gene sequences. The active substance obtained is blended with adjuvants and/or excipients in a fixed formulation to manufacture finished products with certain defined properties.

Expression system: System used to express a gene of interest, whether in vivo or in vitro, e.g. a baculovirus system, a nucleic acid delivery system, a virus or a bacteria that has itself an immunological activity.

Gene of interest: Full or partial gene coding for the targeted antigen.

Construct: Combination of expression system and gene of interest.

Initial platform product: A fully licensed product that establishes the platform product and presents the components and principles indicated in point 5 of this guideline.

Vaccine Platform Technology Master File: a file that contains all data relative to the platform for which there is reasonable scientific certainty that they will remain unchanged regardless of the antigen(s)/gene(s) of interest added to the platform. The nature of the data to be included in the vPTMF will be defined by the applicant depending on the type of platform.

Certificate of compliance of the Vaccine Platform Technology Master File: a document 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.

For the initial platform product based on a particular platform technology for a particular target species where no vPTMF already exists, a full MA dossier is required from a manufacturer.

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 relevant platform technology in the linked MA. Further details will be provided in the procedural guideline.

5. Authorisation of initial platform product and certification of vPTMF

For an initial platform product, the standard requirements described in Section IIIb Requirements for immunological veterinary medicinal products of Annex II to Regulation (EC) 2019/6, in relevant guidelines and Ph. Eur. texts are applicable.

At the time of the application for authorisation of the first (full) dossier based on the platform technology, the applicant is encouraged to apply in parallel for a vPTMF.

The nature of the data to be included in the vPTMF will be defined by the applicant depending on the type of platform. 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(s)/gene(s) of interest 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.

A scientific and technical evaluation of the vPTMF will be carried out by the Agency. A positive evaluation will result in a certificate of compliance with Union legislation for the vPTMF, which will be accompanied by the evaluation report. The certificate will apply throughout the EU.

The following sections detail further which information may be included in a vPTMF.

5.1 Quality

General principles: 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.

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.

The documentation to be presented in this part, as defined by the applicant, could include:

- The expression system, including all reagents, seeds, sequences, and cells to propagate the final construct.
- The inserted gene of interest, including a defined procedure for creating new constructs.
- Standardised manufacturing system for consistency in the manufacture and formulation of finished product.
- Minimum and maximum antigen content - amount of antigen per dose as determined by a measurable quantity.

An example of data that may be included in the quality part of a vPTMF of viral or bacterial vector platforms is included in Annex II of this guideline.

5.2 Safety and efficacy documentation

The documentation to be presented in these parts of the vPTMF, as defined by the applicant, could include:

- Safety and efficacy data for the initial construct (minimum age, dose volume, specific route of administration, target species).

- In safety: maximum antigen content per dose.

- In efficacy: minimum antigen content per dose.

6. Authorisation of subsequent products after vPTMF certification

Applications for MAs of IVMPs manufactured using an approved vPTMF are considered to be eligible for:

- Omission of information already included in the initial vPTMF as certified
- Reduction of some data requirements (quality, safety and/or efficacy), mainly based on the data already available in the certified vPTMF

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 target species and route of administration**.**

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.

Any change to the standardised method of manufacture included in a certified vPTMF must be evaluated by way of variation prior to incorporation of the change to the initial product and this may require the establishment of a new vPTMF.

The request for additional claims for use of an authorised platform product, either in a different target species category or a different route of administration in the same target species will be considered as for any traditionally authorised product and will require safety and efficacy studies.

The following sections summarise the content of the different parts of the dossier of a subsequent product.

6.1 Quality

The standard requirements described in Section IIIb.2 Part 2: Quality documentation of Annex II to Regulation (EU) 2019/6, in relevant guidelines and Ph. Eur. texts remain applicable but only data related to the new insert need to be provided.

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.

Where the tests and validation studies are already performed and remain unchanged, in the quality part of the new dossier which are based in a vPTMF, then a cross reference to the vPTMF should be included.

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Sections of the Quality part	***Information about the new insert***	***Possible omissions /reductions***
2A: PRODUCT DESCRIPTION 2:A1: Qualitative and Quantitative composition	Modification of the composition to include the new antigen An explanation of the choice of the new gene of interest	Information of product development could be reduced Only data about the gene of interest are needed, (no information is needed about the vector)
2B: DESCRIPTION OF MANUFACTURING METHOD	New flow charts are needed, with the incorporation of the new sequence/ gene of interest	The parts already described in the vPTMF and that are similar should not be included again Cross-references to the certified platform is sufficient If inactivation is performed, no new inactivation kinetics study is required, if adequately justified
2C: STARTING MATERIALS	Information about the origin and manufacturing of the new sequence/ gene of interest, including details of the synthesis and insertion process of the gene	All other starting materials already described in the vPTMF should not be included again Cross-references to the certified platform is sufficient
2D: CONTROL TESTS DURING MANUFACTURING PROCESS	Identification and quantification (specifications and validation) of the new antigen related to the new sequence/ gene of interest Only new tests not performed in the original vPTMF and related with the new insert will be described and validated	The description and validation of all other tests performed and already described in the vPTMF should not be included again Cross-references to the certified platform is sufficient
2E: CONTROLS TESTS ON FINISHED PRODUCT	Identification and quantification of the new antigen related to the new sequence/ gene of interest should be described and validated	The description and validation of all other tests performed and already described in the vPTMF should not be included again Cross-references to the certified platform is sufficient
2F: BATCH TO BATCH CONSISTENCY	Should be demonstrated with batches of the new sequence/gene of interest product	At least 2 pilot/R&D batches

Sections of the Quality part	*Information about the new insert*	*Possible omissions /reductions*
		Results of a 3rd batch at industrial scale should be provided post-authorisation
2G: STABILITY	Should be demonstrated with batches of the new sequence/gene of interest product	No specific studies are needed pre-authorisation. Same shelf life as the initial product could be authorised, but stability data obtained with the new product should be provided post-authorisation

6.2 Safety and efficacy

Safety and efficacy studies should be performed with the new product containing the new gene/sequence of interest and manufactured as defined in Part 2 (quality), and in general in line with requirements included in Parts 3 and 4 of section IIIb of Annex II to Regulation (EU) 2019/6.

6.2.1 Safety

Part 3A (General Safety Requirements) is in general applicable.

Safety with the new product construct should be demonstrated for the most sensitive category of each species and for each recommended route of administration.

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.

Sections of SAFETY Part	***To be performed***	***Possible omissions/ reductions***
NON-REPLICATIVE	With batches of the new product	No user safety and interaction studies
3B PRECLINICAL	1 dose and repeated dose	Studies for the examination of reproductive performance and immunological functions may be omitted (based in original vPTMF)
3C CLINICAL	---	No study needed (based on the original vPTMF)
3D ERA	---	No study needed (based in original vPTMF)
3E GMO	---	No study needed (non-replicative)s indicated in Directive 2001/18/EC
3F Residues	---	No study needed (based on original vPTMF)

REPLICATIVE	With batches of the new product	No user safety and interaction studies
3B PRECLINICAL	1 dose and repeated dose and overdose Special requirements for live vaccines (reversion to virulence and biological properties should be performed)	Studies for the examination of reproductive performance and immunological functions may be omitted (based on original vPTMF) Shedding and dissemination studies may not be needed in subsequent dossiers, if adequately justified
3C CLINICAL	---	No study needed (based on original vPTMF)
3D ERA	---	No study needed (based on original vPTMF)
3E GMO	To be performed	As indicated in Directive 2001/18/EC
3F Residues	---	No study needed (based on original vPTMF)

6.2.2 EFFICACY

Efficacy studies should be performed with the new product containing the new gene of interest and manufactured as defined in Part 2 (quality), and in line with requirements included in Part 4 of section IIIb of Annex II to Regulation (EU) 2019/6.

With regard to demonstration of efficacy, no reduction of requirements is foreseen for the new platform product, except in the following cases:

- Applications for multi-strain dossiers as defined in Annex II to Regulation (EU) 2019/6, using an approved vPTMF. In this case, the efficacy requirements mentioned in the guideline on multi-strain dossiers are applicable.
- For live vectors (replicating in the target animal) authorised and certified in the first vPTMF with one or more gene of interest and in the subsequent dossiers with a different gene of interest (addition and/or change), only efficacy data for the new antigen(s) is expected. The efficacy already demonstrated with the live vector in the target species should not be re-submitted again, if it is demonstrated and/or justified that the new insert does not interfere with the efficacy.

7. References

USDA veterinary Services Memorandum 800.213. Licensing Guidelines for Production Platform Technology-Based, Non-Replicating, Nonviable Vaccines (March 12, 2018)

Vaccine Platforms: State of the Field and Looming Challenges (2019 Johns Hopkins University). Summary of Workshop Dec11, 2018

Novel Vaccine Technologies in Veterinary Medicine: A Herald to Human Medicine Vaccines. V. Aida *et al.* Front Vet Sci. 15 April 2021

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Annex I - Examples of platforms

1. Viral and bacterial vector platforms:

Recombinant live vector vaccines are preparations of one or more types of live bacteria or viruses that are non-pathogenic or have a low pathogenicity for the target species. They one or more genes encoding antigens inserted and stimulate an immune response which is protective against other micro-organisms.

The heterologous antigen gene included in the vector may be of viral, bacterial or parasitic origin. The heterologous gene may comprise sequences coding for an entire antigen, a fragment of an antigen or more than one antigen.

They can include replication-defective as well as replication-competent vectors.

Replication-defective vectors may have a natural host-restriction such as the canarypox viral vectors in mammals, or they may have been attenuated by laboratory passage to be replication-incompetent in animals, or they may have a specific genetic modification (often the deletion of a gene[s] necessary for replication) that limits their replication (abortive replication).

Replication-competent vectors can give protection against wild-type microorganisms, from which the vector is derived, and may also be sought and against the inserted gene of interest.

Examples of authorised veterinary vaccines in EU with vector platforms: porcine circovirus, myxoma vectored vaccine, fowlpox, turkey herpesvirus.

As seen from the examples given, most of the veterinary recombinant vaccines authorised have been based on viral vectors.

Bacterial vector vaccines have also been used in the veterinary field to develop a double protective immune response, against a heterologous antigen and against the vector itself (e.g. *Erysipelothrix rhusiopathiae, Mycoplasma gallisepticum, Corynebacterium pseudotuberculosis*).

2. Protein-based platforms:

Protein based platforms generally consist of self-assembling recombinant proteins (virus-like particles, VLPs) that function as a scaffold to which any antigen can be linked. The design of specific VLPs may enhance stability or modulate the immune response. Well characterized viral, bacterial and/or parasite proteins and polypeptides can be obtained by recombinant techniques and linked to the virus-like particles to form the final vaccine antigen.

3. Nucleic acid vaccines:

Nucleic acid vaccines can be subdivided into DNA and mRNA categories, and their synthesis methods may be very similar.

DNA vaccine platforms:

DNA vaccination involves the inoculation of a gene(s) encoding a relevant antigen against which an immune response is desired, under the control of a promoter, which will permit its expression in the vaccinated animal. This gene construct is usually contained, for manipulation and for manufacturing purposes, within a bacterial plasmid DNA molecule although shortened linear DNA sequences blocked at either end with synthetic hairpin nucleotides have also shown promise.

A DNA vaccine for use in fish is already authorised in the EU, consisting in a DNA plasmid with no adjuvant. More DNA vaccines are expected in future submissions.

RNA vaccine platforms:

mRNA –non replicating, and replicons (self-replicating)

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.

Regarding the current use of conventional mRNA (also referred to as non-replicating or non-amplifying mRNA) vaccine technology, there are already authorised vaccines for humans (against Covid-19) in the EU and other countries and other vaccines against infectious diseases and cancers have been investigated in animals (e.g. rabies virus) and in humans.

mRNAs do not interact with the host-cell DNA, so they avoid the potential risk of genomic integration posed by DNA-based vaccines but can still encode any protein antigen of choice.

The final synthetic mRNA contains a protein-encoding open reading frame (ORF) flanked by two elements essential for the function of mature eukaryotic mRNA: A poly(A) tail that can either be incorporated from the 3′ end of the pDNA template, or added enzymatically after in vitro transcription as well as 5′ and 3′ untranslated regions (UTRs), which increase translation and stability. The optimisation of the ORF entails GC enrichment.

The RNA contains modified N1-methylpseudouridine instead of uridine to minimise the indiscriminate recognition of the mRNA by pathogen-associated molecular pattern receptors (e.g. TLRs).

Self-amplifying saRNA vaccines are genetically engineered replicons derived from self-replicating single-stranded RNA viruses.

Replicon vaccines are self-amplifying viral mRNA sequences that, in addition to the sequence encoding the antigen of interest, contain all elements necessary for RNA replication. Vaccination results in high levels of in situ antigen expression and induction of potent immune responses. Both positive and negative-stranded viruses have been used to construct replicons, and they can be delivered as DNA, viral replicon particles with the saRNA packaged into the viral particle, or as a completely synthetic saRNA produced after in vitro transcription (naked RNA)-complexing this with cationic lipids or polymers. The last one is the important in this definition.

saRNA is derived from the genome of certain viruses like alphaviruses (including Venezuelan equine encephalitis virus (VEEV), Semliki Forest virus (SFV), and Sindbis virus) and flaviviruses and has the capacity of self-amplification due to the fact that it expresses a viral replicase (Rep), while the genes coding for the viral structural proteins have been substituted by the transgene of interest.

As a result of their self-replicative activity, saRNAs can be delivered at lower concentrations than conventional mRNA vaccines to achieve comparable antigen expression.

Annex II: An example of data that may be included in the quality part of a vPTMF of viral or bacterial vector platforms

Below is an example of the data requirements for existing or currently known platforms of viral or bacterial vectors. This may be used as a guide for submission of the quality part of a vPTMF.

For platforms consisting of viral or bacterial vectors

Qualitative and quantitative particulars of the constituents (Section IIIb, Part 2.A)

The complete and exact name of the active substance of the one present in the first vPTMF (e.g. virus or bacteria strain, plasmid) shall be provided.

Information on product development relevant to the platform (engineering of the vector/plasmid), including the justification of the use of the selected backbone, information on the choice of vector and/or plasmid, the origin of the heterologous antigen gene(s) and the elements concerning the expression of the transgene(s).

Also, information and a justification about the method of integration of the antigen of interest should be provided. Any genetic material used in the construction, the inserted gene(s) and the final construct should be described in detail.

It should be explained and justified what are the sections that are expected to remain unchanged in future dossiers and which ones are only applicable to the present insert.

The origin of the inserted sequences should be described and documented.

Description of the manufacturing method (Section IIIb., Part 2.B)

The description of the manufacturing method for the active substance/ platform shall be provided including validation of the key stages of production and justification, if relevant, of any intermediate storage proposed.

It should be explained and justified what are the sections that are expected to remain unchanged in future dossiers and which ones are only applicable to the present insert.

A full description of manufacturing method should be provided in the vPTMF for its first certification, including –where relevant-:

- All intended and unintended genetic modifications such as site-specific mutations, insertions, deletions and/or rearrangements to any component as compared with their natural origin counterparts should be detailed.
- For a vaccine construct that incorporates transcriptional or translational elements to control the expression of a transgene summary evidence should be provided to demonstrate such specificity from a product characterisation and control viewpoint.
- The origin, synthesis and insertion process of the gene to be inserted should be detailed. The method of integration of the inserted gene (and possible future ones) should be standardised.

Production and control of starting materials (Section IIIb., Part 2.C)

Information on the active substance (virus/bacteria vector, or plasmid), the substrate/s used (i.e. 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.

As far as possible, all starting materials (mandatory for virus/bacteria vector, and/or plasmid; and cells or other culture substrates used) should be kept for subsequent authorisations after first vPTMF certification or proposed differences highlighted and justified.

Virus and bacterial vectors and cells used are based on a seed lot system.

The vPTMF dossier shall include the specifications, information on the processes implemented and the tests to be conducted for the quality control of all batches of starting materials and results for a batch for all components used.

TSE and extraneous agents (EA) risk assessment shall be provided, where applicable. It is to be noted that the target species retained for the finished products making reference to the VPTMF shall be considered for the TSE and EA risk assessment. Warnings or restrictions of use may be brought in at the vPTMF level depending on the information presented, which may be mitigated during the risk analysis at the level of the finished product.

For the platforms where active substance is obtained by recombinant techniques, all corresponding relevant data on the genetically modified virus/bacteria should be provided, in line with Directive 2001/18/EC.

The use of antibiotic markers encoding resistance to antibiotics used for therapy should be avoided wherever possible. Article 4 of Directive 2001/18/EC should be taken into consideration. Transfer of the encoding resistance to the final vector vaccine is unacceptable.

Control tests during the manufacturing process (Section IIIb, Part 2.D)

The standard requirements described in Section IIIb.2D shall apply for the in-process control tests carried out during the manufacture of the active substance, including validations of key control tests and, if relevant, any intermediate storage proposed (prior to blending).

The corresponding controls to be implemented during the construction process, in particular, the controls to be implemented to verify that each construct will be correct and stable must be described and the corresponding validation methodology should be provided.

The description, validation and specifications of all the tests that are relevant for the platform (independently of the insert) should be included, and insofar as possible should remain unchanged, potentially excluding the specifications, for subsequent dossiers.

It should be explained and justified which tests, validations and specifications are expected to be kept in future dossiers and which ones are only applicable to the present insert.

These relevant tests may be (not limited to):

- Identification and quantification of the active substance.
- Purity/sterility of the active substance.
- Controls on product- and process–related impurities from the manufacturing process that can be present in finished product, as well as their safety profile, should be implemented (e.g. residual host cell proteins, residual host cell DNA, residual reagents-including inactivating agents).
- For non-replicating vectors, data relevant to demonstrate the absence of replication should be provided.
- For inactivated active substances, data relevant to the inactivation step, including the validation of the inactivation process shall be provided.

Where a test has been carried out with satisfactory results on the bulk vaccine, the test may be omitted on the final lot.

Control tests in finished product (Section IIIb, Part 2.E)

The standard requirements described in Section IIIb.2E shall apply.

The description, validation and specifications of all the tests that are relevant for the platform (independently of the insert) should be included and should be as standardised as possible in this first vPTMF, and maintained as far as possible for future dossiers.

Even if this part is difficult to maintain in future dossiers, it should be explained and justified which test methods, validation studies and specifications are expected to remain unchanged in future dossiers with different sequences/genes and which ones are only applicable to the present insert.

These relevant tests may be (not limited to):

- General characteristics:
- Identification and assay of adjuvants and/or preservative.
- Sterility and/or purity test.
- Identification of active substance/s and batch titre or potency should also be included in the first dossier for authorisation of the product and are in general product specific.

Batch-to-batch consistency (Section IIIb Part 2.F)

The standard requirements described in Section IIIb.2F shall apply for the demonstration of consistency in the manufacture of the antigen.

Stability (Section IIIb Part 2.G)

The standard requirements described in Section IIIb.2G to demonstrate the stability of the antigen and, where relevant, any intermediate storage, shall apply.