July 2020
EMA/377884/2015-Rev.2
Veterinary Medicines Division

Validation checklist for initial MAA – immunologicals (applicable to submissions under Art. 12(3) of Directive 2001/82)

1. Background on the product

(Invented) Name and procedure number: **INN or common name:**

Indication applied for:

This validation checklist is used by the Agency to validate initial marketing authorisation applications for immunologicals and applicants should use it as a means to review in advance of their submission that standard requirements are fulfilled.

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

For the below table, please fill out by referring to the application form one line for each presentation per strength and form. Check consistency with the SPC. This is aimed at having the correct count for the fees.

Pharmaceutical Form (2.2.1 in AF)	**Strength (2.2.1 in AF)**	**Content (concentration) (2.2.1 in AF)**	**Package size (2.2.3 in AF)**
The pharmaceutical form is expressed in accordance with standard terms of the EDQM https://standardterms.edqm.eu/ (user name and password needed, request them from the library/information centre)	*The expression of the strength is in accordance with http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2010/01/WC500056428.pdf In case of liquid, single/partial use is important for expression of strength --> check section 4.9 of SPC (summary of product characteristics)*	*Mostly for liquids only*	
For example:concentrate and solvent for suspension for injection	For example:2.9 - 3.9 log10 PFU/dose	For example:ampoule of 1000 doses	For example:5 ampoules
For example:concentrate and solvent for suspension for injection	For example:2.9 - 3.9 log10 PFU/dose	For example:ampoule of 2000 doses	For example:5 ampoules
For example:concentrate and solvent for suspension for injection	For example:2.9 - 3.9 log10 PFU/dose	For example:ampoule of 4000 doses	For example: 5 ampoules

2. **Summary of Flags to PM:** (For internal use only)

3. Background documentation:

Topic	Document
User guide for the electronic application form for a marketing authorisation (veterinary)	http://www.hma.eu/fileadmin/dateien/Veterinary_medicines/CMDv_Website/Procedural_guidance/General_info_on_applications/eSubmission/User_Guide_for_the_electronic_application_form_for_a_marketing_version_3.pdf
Notice To Applicant volume 6B Part 1	https://ec.europa.eu/health/documents/eudralex/vol-6/
EDQM database of TSE/chemical certificates (CEPs)	https://extranet.edqm.eu/publications/recherches_CEP.shtml
In case of doubts regarding a submitted proof of establishment, contact VROS	
Veterinary e-submission guidelines	http://esubmission.ema.europa.eu/tiges/vetesub.htm
Link to the European Pharmacopoeia	http://online.pheur.org/EN/entry.htm
COMMISSION REGULATION (EU) No 37/2010 of 22 December 2009 on pharmacologically active substances and their classification regarding maximum residue limits in foodstuffs of animal origin	http://ec.europa.eu/health/files/mrl/mrl_20101212_consol.pdf
ATCvet codes	https://www.whocc.no/atcvet/atcvet_index/
EDQM standard terms: (It is used to check the dosage form (=pharmaceutical form) and route of administration.)	https://standardterms.edqm.eu/
Process for handling new standard term requests received from applicants in the pre-submission phase (or from other sources, also during any procedure):	If a new term (e.g. pharmaceutical form or unit of measurement) or a request for an update of an already existing term is needed in order to complete the eAF, a request should be submitted through the SPOR Portal - http://spor.ema.europa.eu/rmswi/#/ providing as much supporting documentation as possible (e.g. name of the product concerned, SPC, etc).

Topic	Document
EUTCT: to check the target species	http://eutct.ema.europa.eu/eutct/showAvailableListsDisplay.do?guestuser=true
Ph. Eur.: if the applicant declares that the reference for a substance (active substance or excipient) is the Ph. Eur. There is a need to check that they use the name in the Ph. Eur and not any other equivalent name.	
ASMF templates for letter of access and submission letter:	https://www.ema.europa.eu/documents/template-form/template-active-substance-master-file-procedure_en.doc

4. Checklist

Definitions:

VSI: Validation Supplementary Information. Information that will be requested by the Agency to the applicant during the validation period and that should be resolved before the start of the procedure, if not indicated otherwise.

Blocking issue: An issue that has been identified during the validation period and that should be resolved before the start of the procedure, otherwise it would prevent validation of the application.

Part 1a: Application Form ***Please ensure that all details given in the application form on product and applicant (incl. address) are consistent throughout the document*** **GENERAL CONSIDERATIONS**		
Has correct version of **Application Form** been used?	Select	*From July 2015, use of the e-application form is mandatory. Check first page of application form against the) latest version. If not request relevant missing/changed parts; suspend validation of these parts until update received:* *Alternatively, the applicant can provide the correct version of the AF within responses to validation issues plus missing documents.*
Product (Invented)Name: Has submitted name been agreed with the CVMP/ Invented Name Check? Is the name the same as indicated in section 2.1.1 and in the Product information.	Select	*The invented name should be agreed by CVMP prior submission. However, this is not a validation issue if name not agreed yet.* *Note: although it is recommended that the invented name is written with the first letter in upper case and the rest as lower cases, it is ultimately the choice of the applicant/ MAH (either upper or lower case), as long as it is written in a consistent format throughout the PI and is consistent with how the invented name will appear on the printed artwork.* *Reference: Compilation of QRD Decisions on stylistic matters –*

Part 1a: Application Form *Please ensure that all details given in the application form on product and applicant (incl. address) are consistent throughout the document* GENERAL CONSIDERATIONS		
		https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/compilation-quality-review-documents-decisions-stylistic-matters-product-information_en.pdf
Cover letter:	Select	*For electronic submissions via EMA eSubmission Gateway or Web Client, no hard-copy cover letter is required.*
Declaration on manufacturing sites (attachment to the cover letter) where the applicant confirms that: • The detailed information in relation to the manufacturing sites contained in Part 2/Module 3, is correct in terms of names, addresses and manufacturing activities, and • This information is consistent throughout the dossier, in particular with the corresponding information contained in Part 1 (electronic Application Form, flow-chart in Annex 5.8, QP declaration in Annex 5.19, GMP certificates in Annex 5.9, MIAs or MIAs equivalents in Annex 5.6).	Select	

Part 1a: Application Form *Please ensure that all details given in the application form on product and applicant (incl. address) are consistent throughout the document*		
Cover page: Is the person authorised to communicate on behalf of the applicant the same as indicated in formatted table and in section 2.4.2 of the application form and is a **letter of authorisation** attached for this person (Annex 5.4)?	Select	*If not, or letter not provided/not correct, request corrected application form/letter.*

Part 1a: Application Form ***Please ensure that all details given in the application form on product and applicant (incl. address) are consistent throughout the document***		
Cover page: Is **signatory** on behalf of the applicant either CEO of company, member of management board etc. or a person authorised to communicate on behalf of the applicant, i.e. the designated person as indicated above?	Select	*In case person is different from above ('person authorised to communicate on behalf'*
1.1 Eligibility ticked as agreed by CVMP and date correct?	Select	*Check correctness in DREAM (scope, Date):* *http://docs.eudra.org/webtop/component/main?_dmfClientId=1387548142425&_dmfTzoff=0* *If in doubt, consult with PM*
1.3 Legal basis	Select	*Check something is ticked.*
1.3.7 Article 13c - Informed consent application • **The scope of the application is the same as the reference product.** If informed consent is ticked as the legal basis for the application, information on the reference medicinal product is given below (Product invented name, pharmaceutical form(s), strength(s, Marketing authorisation holder, MA Number(s) and Date of authorisation) Annex 5.2 is ticked in the eAF and the letter of consent from marketing authorisation holder of the authorised (parent) product is attached in Part 1a Complete administrative data is provided in the application (including SPC and mock-ups)	Select Select Select Select Select	*If informed consent is not ticked as the legal basis, select N/A. Only a complete administrative data must be provided in the application, with consent to use the pharmaceutical, safety, (pre-clinical) and clinical data of the reference product given by the parent MA holder. In this case, there is no need to submit quality, safety and efficacy detailed and critical summaries.* *If the parent product belongs to the same MAH (so called "self-informed" consent), the letter of consent must still be provided - it is not correct when the applicant justifies that this is not applicable.*
1.4 MRL status: Has the applicant provided information for the active substance(s) (pharmaceutical products) or the adjuvant (immunological products)	Select	*Only to be completed when the target species is/are (a) food-producing animal(s). Only applicable to food-producing animals (check target species in section 2.1.4 of the AF). For immunologicals, information on the adjuvant(s) as per SPC point 2 has to be included.* *Information can be provided either in the field - "Maximum Residue Limits (MRLS) according to*

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		Commission Regulation (EU) No. 37/2010" when the MRL has been established by the European Commission or *- "Application for a Maximum Residue Limit has been made to the EMA" when the MRL application has been submitted however MRL(s) has not yet been established.* *Additional substances (excipients) may have been declared on the application form, however are not checked at validation.*
1.4 MRL status: Is the information concerning established MRLs and/or submitted MRL applications correct?	Select	*There must be a status for each target species (e.g. bovine, porcine, all mammalian species, all food producing species) and/or relevant food commodity (milk, eggs, honey). E.g. if target species is dairy cattle, an MRL for milk is applicable; if target species is laying hens, an MRL for eggs is applicable.*
1.5 Additional requests for consideration: Has the applicant provided documents in support of their request for exceptional circumstances, or market protection or data exclusivity?	Select	
1.5.2 Has **accelerated review** been granted**?**	Select	*If not ticked, select n/a.*
2.1.3 ATCvet code and Group	Select	*Check correctness on the following link:* *http://www.whocc.no/atcvet/atcvet_index/* *The pharmacotherapeutic group would usually be the 4th group. It is not the name of the substance.* *Example:* *Active substance: Canine Parainfluenza virus Type 2, strain CPiV2-Bio 15* *ATCvet code: QI07AD08* *Group: Live viral vaccines* *If an ATC vet code is published by the WHO, but it is not used in the application, a justification should be provided.*

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2.1.4 Target species	Select	*Should be in line with product information* *If a new target species or a request for an update is needed in order to complete the eAF, a request should be submitted through the SPOR Portal – http://spor.ema.europa.eu/rmswi/#/ providing as much supporting documentation as possible (e.g. name of the product concerned, SPC, etc).*
2.2.2 Route of administration: In line with Standard Terms?	Select	*Check against standard terms (EDQM)* *If a new term (e.g. pharmaceutical form or unit of measurement) or a request for an update of an already existing term is needed in order to complete the eAF, a request should be submitted through the SPOR Portal – http://spor.ema.europa.eu/rmswi/#/ providing as much supporting documentation as possible (e.g. name of the product concerned, SPC, etc).*
2.2.3 Container, closure and administration device(s) Are information provided in line with Part 2 and Product Information? Annex 5.17 is ticked in the eAF.	Select	*The container should be selected from the List of Standard Terms published by the EDQM.* *The Annex 5.17 should contain short description (names) of mock-ups or samples / specimens sent or provided with the application.*
2.3 Legal status: Has the applicant proposed a legal status for its medicinal product?	Select	*Applicant to propose i.e.* *- non-prescription* *- restricted* *- special*
2.4.1 Proposed MAH: Is the name and address (if mentioned in the proof of establishment (PoE)) of the proposed MAH exactly the same as in the PoE?	Select	*Annex 5.3 has to be provided and the details should be exactly the same as in section 2.4.1. as far as they are given in the PoE. Ignore section for national/decentralised applicant (should be kept unticked/empty)*

Part 1a: Application Form ***Please ensure that all details given in the application form on product and applicant (incl. address) are consistent throughout the document***		
Annex 5.3: Proof of establishment: Does the Annex 5.3 duly establish the applicant as being in the EEA?	Select	*Should not be older than 6 months but can be in any language as long as EN translation is provided*
2.4.1 Proposed MAH: Is a person identified at the MAH address (for centralised procedure)?	Select	*It can be that the email address is a generic email address. In that case it should be confirmed with the company (can be in the cover letter) that it is a dedicated email address which will reach the allocated person 24h/day.* *If section 2.4.2 is filled in, a personal email address should be included.*
2.4.1 SME status: If yes is ticked, is the Qualification as SME in Annex 5.21 still valid? Information provided in the application are the same in Annex 5.21 and in the formatted table.	Select	
2.4.4 Qualified person for PhV Is the CV of the qualified person attached in Annex 5.20.	Select	*Data needs to be correct & complete for SIAMED entry.* *Name, Address, Telephone number, personalized email address should be included.* *It might be that the email address is in a format such as EUQppv@company.com but in that case it should be confirmed with the company that it is a dedicated email address which will reach the QPPV24h/day.* *If CV of qualified person is missing(no Annex 5.5 nor inclusion in Annex 5.20, issue VSI*
2.5.1.1 Has a person responsible for **product defects and recalls in the EEA** been named along with contact details? (should include at least name / surname, address with postcode and country, 24H tel. # and e-mail address)	Select	*Person has to be located in the EEA.*
2.5.3 ASMF and CEP are not applicable to vaccines, all the information on the active substance should be provided in	Select	*Only CEPs for TSE are applicable to vaccines (see 2.6.2). In this section both should be ticked*

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the dossier		*with "no"*
2.6.1 Qualitative and Quantitative composition: Is the information in this section in agreement with the relevant information in Part 2, 2a-qual-quant-partic?	Select	*For liquids, not only concentration per 1 ml needs to be given but also the container size/volume of the product. This can be found either in the AF point 2.2.3 (or 2.2.3.1) or 2.6.1.* *If VSI - Pharmacopoeia terminology should be used.* *This excludes components that are not present in the final dosage form.* *There is no information that can be withheld as confidential in providing a regulatory submission to the Agency. E.g. composition of tablet coating mixtures.*
2.6.1 Qualitative and Quantitative composition: **Cross-check with** in Part 2, 2a-qual-quant-partic Active substance Overages	Select	*Notes:* *- Complete composition to be provided; no information can be confidential – all to be disclosed to the Agency. E.g. for commercially available tablet film-coating mixtures quantitative composition needs to be provided (through confidentiality agreement between the applicant and the mixture manufacturer).* *- For liquids, not only concentration per 1 ml needs to be given but also the container size/volume of the product.* *- Reference to Ph.Eur. for excipients is preferable. If reference to USP/NF or JP is used instead, VSI (but not a blocking issue if not provided with the responses)* *- Overages – extra amount of the active substance or excipients added to compensate for losses during manufacture/storage. Generally discouraged* *- Overfill should not be stated in the Application Form – if it is = to be removed.*
2.6.2 Materials of animal origin	Select	*All material of animal origin should be stated*

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Cross-check with Part 2, 2c4-bio-origin.		*including reagents in the active substance manufacture.*
2.6.2 TSE certificate: If applicant has ticked and given the number of a Ph. Eur. Certificate of suitability, is it/are they duly annexed in 5.12?	Select	*Information on excipients to be consistent with Part 2, 2c4-bio-origin (TSE table A and table B). TSE tables applicable only for materials of animal origin* *In EDQM database, it is better to search for the Certificate number (Certificate of suitability for TSE)* *Check the EDQM certificate database online at https://extranet.edqm.eu/publications/recherches_CEP.shtml* *Lactose is out of the scope of TSE requirements, as TSE transmission was never confirmed through milk. If Lactose is contained in the product, it never has a Certificate, only statement from the manufacturer (appendix to AF 5.12) that it is sourced in the same way as milk for human consumption. However, the option "animal origin susceptible to TSE" still needs to be ticked in the Application Form.*
4.1 Other MAA (for national applications only)	Select	*This section should be left blank for centralised procedures.*
4.3 Multiple application: If the company is submitting a duplicate/multiple, has the letter of authorisation from the EC been provided?	Select	*Only possible to validate a multiple application in case a letter from EC, with or without conditions to be fulfilled, is attached.*
Annexes: Mock-ups: Is list of mock-ups attached in Annex 5.17 to the application form?	Select	

General Application Form checks		
Is the information on product name, active substance, strength(s) and pharmaceutical form(s) given consistently between cover page of the application form, sections 2.1.1, 2.1.2 and 2.2.1 of the application form and PI?	Select	*If No, request corrected application form and/or PI, as appropriate.*
Confirm Product Shared Mailbox, SIAMED, EURS, DREAM Product Folder are consistent with the Product Name given in the Application Form	Select	*EMA internal process*
Are all Annexes as ticked in section '5- Annexed documents' provided?	Select	*Double check with boxes ticked in the individual sections, too. If an Annex is missing issue VSI*

Part 1 – excluding application form		
1b SPC, Labelling and Package Leaflet: Are they provided in EN for all of the applied for forms/ strengths? Is Word version of the PI provided (in folder 'add-info')? Is the correct (QRD) format (latest version) used for the product literature? If combined PL, is the justification present?	Select Select Select Select	*Note: If Word version not provided, not a VSI but necessary to be received by day 1 of the procedure.*
1b. Mock-up: Have the mock-ups been provided?	Select	*Mock-up for PL not needed, only labelling (outer and inner)*
In English	Select	*For validation purposes the Agency requests that all applications for a Marketing Authorisation should include the labelling texts in English, together with one English mock-up and one multi-lingual mock-up ('worst case') of the outer and small immediate packaging for each pharmaceutical form in the smallest pack size.*
'Worst case' (e.g. trilingual pack or 3 x EN)	Select	*Even if 3 x EN is provided as the worst-case example, a separate EN mock-up is required as per the row above because this will be the reference mock-up during the assessment.*

Part 1c – Detailed and critical summary reports		
For new applications, statements justifying absence of data or specific parts/sections should be provided in the relevant detailed and critical summary. In case any of these docs need updating, updated expert signatures in Part 1c have to also be provided or updated docs have to be signed. ***For each report a signature of the expert with date, a CV and a declaration of the professional relationship is necessary. Expert does not need to reside within the EEA. If it is obvious from the CV of the expert that he/she is an employee of the applicant, the declaration of his/her professional relationship can be omitted.***		
1c1 Detailed and critical summary report - Quality: • Has the report been provided, together with: • CV of the expert • Declaration of his/her professional relationship to the applicant?	Select Select Select	
1c2 Detailed and critical summary report - Safety and Residues: • Has the report been provided, together with: • CV of the expert • Declaration of his/her professional relationship to the applicant?	Select Select Select	*Separate reports might be provided for safety, residues (not required for non-food producing species) and ERA.* *Short check if the headings of the main subsections (pharmacology, user safety, ERA and residues (for food-producing species only) are present.*
1c3 Detailed and critical summary report - Efficacy: • Has the report been provided, together with: • CV of the expert • Declaration of his/her professional relationship to the applicant?	Select Select Select	*Short check if headings of the main subsections are present (pre-clinical, including target animal safety and clinical).*

Part 2 – Quality ***Check for either documents in the appropriate indent or a justification for absence has been provided in the quality overview -> If neither is present => VSI.*** ***The purpose of Part 2 validation is to check presence or absence of documents***		
Part 2 ToC	Select	*Should be in P2 folder but outside any of the subfolders within P2. (this is also checked by the VNeeS checker)*
2A Qualitative and quantitative particulars of the constituents		*It is acceptable not to create one folder per subsection (i.e. 2a1, 2a2, 2a3, 2a4) It can be all included in the same document.* *The information in this section should be consistent with section 2.6.1 of the application form.*
2a1 Qualitative particulars	Select	
2a2 Usual terminology	Select	
2a3 Quantitative particulars	Select	
2a4 Product development	Select	
2B Description of the manufacturing method	Select	
2C Production and Control of starting materials		
C1 Starting materials listed in Pharmacopoeias	Select	
C2 Starting materials not listed in Pharmacopoeia	Select	
C2.1 Starting materials of biological origin	Select	*Tables A, B and C to be included here, if applicable. If there are no substances of animal origin the tables do not need to be included. The information here should be consistent with section 2.6.2 of the application form.*
C2.2 Starting materials of non-biological origin	Select	
2D Control tests during the manufacturing process	Select	
2E Control tests on the finished product		
E1. General characteristics of finished product	Select	

Part 2 – Quality ***Check for either documents in the appropriate indent or a justification for absence has been provided in the quality overview -> If neither is present => VSI.*** ***The purpose of Part 2 validation is to check presence or absence of documents***		
E2. Identification of active substance	Select	
E3. Batch titre or potency	Select	
E4. Identification and assay of adjuvants	Select	*Only applicable when adjuvants are in the composition of finished product.*
E5. Identification and assay of excipients components	Select	
E6. Safety tests	Select	*Not always present and it is acceptable. Batch safety test may be waived.*
E7. Sterility and purity test	Select	
E8. Residual humidity	Select	*Only applicable to lyophilisates.*
E9. Inactivation	Select	*Only applicable to inactivated vaccines*
2F Batch to batch consistency	Select	
2G Stability		
Stability of bulk antigen	Select	
Stability of finished product	Select	
Stability of reconstituted product	Select	*Not always applicable.*
2H Other information	Select	

Part 3 – Safety and Residues *Check that documents/cross-reference/justification for absence have been provided in the appropriate indent -> If none present => VSI*		
Part 3 Safety		
Table of contents present, clearly indicating cross-references to part 4 (if applicable)	Select	
A Introduction and general requirements	Select	
B Laboratory tests	Select	
B1. Safety of the administration of one dose	Select	
B2. Safety of an administration of an overdose	Select	
B3. Safety of the repeated administration of one dose	Select	
B4. Examination of reproductive performance	Select	
B5. Examination of immunological functions	Select	
B6. Special requirements for live vaccines	Select	*Only applicable to live vaccines*
B6.1. Spread of the vaccine strain	Select	
B6.2. Dissemination in the vaccinated animal	Select	
B6.3. Reversion to virulence of attenuated vaccines	Select	
B6.4. Biological properties of the vaccine strain	Select	
B6.5. Recombination or genomic reassortment of strains	Select	
B7. User safety	Select	
B8. Study of residues	Select	*Only applicable to food-producing species*
B9. Interactions	Select	
C Field studies	Select	

Part 3 – Safety and Residues *Check that documents/cross-reference/justification for absence have been provided in the appropriate indent -> If none present => VSI*		
D Environmental risk assessment	Select	
E Assessment required for veterinary medicinal products containing or consisting of genetically organisms	Select	*Only applicable to GMO products* *Should be a stand-alone application. The documents included should be those required under Annex IIIA of Directive 2001/18/EC:* *A. Objective* *B. General Principles* *C. Methodology* *D. Conclusions on the potential environmental impact from the release or the placing on the market of GMOs* https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-6/vol6c_gmo_guidance_2017_03.pdf

Part 4 –Efficacy *Check that documents/cross-reference/justification for absence have been provided in the appropriate indent -> If none present => VSI*		
Part 4 Efficacy		
Table of contents present, clearly indicating cross-references to part 3 (if applicable)	Select	
A. General requirements	Select	
B. Laboratory trials	Select	
• establishment of a challenge model	Select	*The establishment of a challenge model and determination of dose is often not included in vaccine dossiers, but these are replaced by the onset of immunity studies (OOI)*

Part 4 –Efficacy *Check that documents/cross-reference/justification for absence have been provided in the appropriate indent -> If none present => VSI*		
• determination of the vaccine dose	Select	*The establishment of a challenge model and determination of dose is often not included in vaccine dossiers, but these are replaced by the onset of immunity studies (OOI)*
• onset of protection	Select	
• the influence of maternal antibody on the efficacy of the vaccine	Select	*Usually not applicable – Not a VSI*
• duration of immunity	Select	
• additional studies	Select	
C Field trials	Select	

Part 5 –Particulars and documents *Usually missing and it's acceptable.*		
A. Introduction	Select	
B. Laboratory studies	Select	
C Field studies	Select	

Part 6 –Bibliographical references