<date>

<Doc ref id>

Committee for Veterinary Medicinal Products

Scientific overview[[1]](#footnote-1) of an application for the granting of a community marketing authorisation for Product name (EMEA/V/C/XXXXXX/0000)

Immunologicals

**Note to the (Co)**[**Rapporteurs**](https://www.ema.europa.eu/en/glossary/rapporteur):

The scientific overview document should not exceed 30-50 pages (including the LoQ). It will be updated by the rapporteur and co-rapporteur during the assessment process (e.g. following responses to a list of questions or list of outstanding issues), thus facilitating an easier review by CVMP members. It is the basis for the CVMP assessment report, which will be published within the EPAR (with the confidential information deleted) following the Commission Decision on the marketing authorisation.

Assessment reports and comments should be circulated **to the CNA mailbox (copy** Product Shared Mailbox: product.name-xxxx@ema.europa.eu and EMA procedure team).

**Guidance text** is in green italics.

**Examples** are given in blue.

**Assessment text**: Black; font: Verdana 9. Paragraph tab: alignment: left, outline level: body text, indentation: 0, spacing before: 0pt and after: 7pt; line spacing: at least, at: 14pt.
Rapporteurs should ensure that their final document only uses the black “assessment text”.

**General guidance**:

The Scientific overview document is a key document explaining why a marketing authorisation and each of the proposed indications can be approved or rejected and detailing the basis of the benefit-risk considerations for the product. It provides an explanation for the contents of the Summary of Product Characteristics (SPC), labelling and package insert that can be accepted.

This Scientific Overview document summarises the assessment of the major issues related to the individual product and any more detailed assessment on the individual studies will be found in the joint rapporteur and co-rapporteur’s assessment report. The document should be concise, written in a clear language and in a logical manner. Whenever possible, summarise various similar studies together in one paragraph.

A general description of the product should be included, once, in the Introduction of the document, to which the introductions to the different parts can make reference. In the beginning of parts 2, 3 and 4 only the relevant additional elements for the assessment of the quality, safety or efficacy of the product are highlighted, to understand the approach taken.

Address each heading even if little/no data are provided or available. In each section the rapporteur/co-rapporteur should give a summary/commentary, highlighting any unusual aspects (e.g. any deviation from relevant guidelines). Any headings not applicable for a particular product should be deleted (e.g. residues for products intended for companion animals).

Where scientific advice was requested for the product it should be commented in assessing the studies/section whether the advice was followed or not (particularly relevant for SMEs as regards fees).

Where the application has been granted an accelerated assessment timetable, please provide brief justification of why the applicant’s request was accepted. Where the application has been classified as “limited market” (Article 23) or “exceptional circumstances” (Article 25) and reduced data requirements as per CVMP guidelines apply, it should be commented in assessing the studies/section on whether the data package provided is acceptable or not with reference to the relevant limited markets/exceptional circumstances guideline. Details on the data which have not been provided by the applicant (i.e. the data gaps) should be listed (and will made publicly available in the European public assessment report).

If appropriate, assessors should comment on compliance with Directive 2010/63/EU on Protection of animals used for scientific purposes.

In the “Conclusions” section at the end of each main section (i.e. quality, safety, efficacy) summarise briefly the conclusions in respect to the compliance with requirements in accordance with Annex II to Regulation (EU) 2019/6 highlighting for each major heading the adequacy and completeness of the data provided and conclusions drawn (in general without giving details on studies) and identifying any deficiencies. The conclusions should be taken into account in the benefit-risk assessment or the SPC, as appropriate. The list of questions (day 120) or list of outstanding issues (day 180) should mirror the conclusions.

In case of considerations regarding deficiencies of certain data not preventing the granting of a marketing authorisation, such deficiencies may lead to post-authorisation measures (PAMs), including ‘Specific Obligations’ for applications under Exceptional Circumstances (Reg. 2019/6 Article 25). Any post-authorisation measure for the provision of data should be detailed in the appropriate section of the SO, then summarised in the conclusion of the relevant section (quality, safety or efficacy) and also included in the risk management section of the benefit-risk assessment; they may also be detailed in Annex II of the CVMP opinion. When a post-authorisation measure is added to the marketing authorisation, any statement pertaining to confirmation of benefit/risk balance is to be avoided.

‘Recommendations’ for the provision of data are not legally enforceable (and therefore not detailed in Annex II of the Opinion) and are usually only for unresolved issues, which are not critical but the results of which will further enhance the benefit-risk profile. They should be summarised as the very last point of the relevant conclusion section (usually quality); this will also facilitate the rapporteurs, assessors and EMA managing these in the future. Recommendations would not be included or noted in the benefit-risk assessment.

Avoid the use of commercial names of comparator products within the assessment. However, inclusion of the commercial name of the reference product for generic applications is acceptable (see Introduction).

Avoid references to “the applicant” where CVMP has assessed the data and made the ultimate decision.

Within the assessment, provide reference to studies by study identification or report number and to publications by author and year (author, year) in text.

There is a separate template for the assessment of any ASMFs which contains separate sections for the detailed assessment and Lists of Questions for both the applicant’s and (confidential) Restricted parts. Therefore, questions on the ASMF should not be included in this document, however the more general information pertaining to the ASMF and its applicant’s part which should be included here is given below. Where there is more than one ASMF cited in the dossier, a separate report is provided for each ASMF.

[Introduction 6](#_Toc88491943)

[Scientific advice 7](#_Toc88491944)

[Vaccine Antigen Master file (VAMF) and vPTMF 7](#_Toc88491945)

[Multi-strain dossier 8](#_Toc88491946)

[Limited market status 8](#_Toc88491947)

[Part 1 - Administrative particulars 9](#_Toc88491948)

[1.1 Summary of the Pharmacovigilance System Master File 9](#_Toc88491949)

[1.2 Manufacturing authorisations and inspection status 9](#_Toc88491950)

[Overall conclusions on administrative particulars 10](#_Toc88491951)

[Part 2 - Quality 12](#_Toc88491952)

[Quality documentation (physico-chemical, biological, and microbiological information) 13](#_Toc88491953)

[Qualitative and quantitative composition 13](#_Toc88491954)

[Container and closure system 13](#_Toc88491955)

[Product development 14](#_Toc88491956)

[Description of the manufacturing method 16](#_Toc88491957)

[Production and control of starting materials 17](#_Toc88491958)

[Starting materials listed in pharmacopoeias 17](#_Toc88491959)

[Starting materials not listed in a pharmacopoeia 18](#_Toc88491960)

[Control tests during the manufacturing process 21](#_Toc88491961)

[Control tests on the finished product 21](#_Toc88491962)

[Batch-to-batch consistency 23](#_Toc88491963)

[Stability 23](#_Toc88491964)

[<New active substance> 25](#_Toc88491965)

[Overall conclusions on quality 26](#_Toc88491966)

[Part 3 – Safety documentation (safety and residues tests) 28](#_Toc88491967)

[General requirements 28](#_Toc88491968)

[Safety documentation 28](#_Toc88491969)

[Pre-clinical studies 30](#_Toc88491970)

[Safety of the administration of one dose 30](#_Toc88491971)

[Safety of one administration of an overdose 31](#_Toc88491972)

[Safety of the repeated administration of one dose 32](#_Toc88491973)

[Examination of reproductive performance 33](#_Toc88491974)

[Examination of immunological functions 34](#_Toc88491975)

[Special requirements for live vaccines 35](#_Toc88491976)

[User safety 38](#_Toc88491977)

[Study of residues 39](#_Toc88491978)

[<MRLs> 40](#_Toc88491979)

[<Withdrawal period> 40](#_Toc88491980)

[Interactions 41](#_Toc88491981)

[Clinical studies 42](#_Toc88491982)

[Environmental risk assessment 44](#_Toc88491983)

[<Considerations for the environmental risk assessment> 45](#_Toc88491984)

[<Environmental risk assessment for products containing or consisting of genetically modified organisms> 47](#_Toc88491985)

[Overall conclusions on the safety documentation 48](#_Toc88491986)

[Part 4 – Efficacy documentation (pre-clinical studies and clinical trials) 51](#_Toc88491987)

[General requirements 51](#_Toc88491988)

[Challenge model 51](#_Toc88491989)

[Efficacy parameters and tests 52](#_Toc88491990)

[Efficacy documentation 52](#_Toc88491991)

[Pre-clinical studies 53](#_Toc88491992)

[Clinical trials 57](#_Toc88491993)

[Overall conclusion on efficacy 61](#_Toc88491994)

[Part 5 – Benefit-risk assessment 62](#_Toc88491995)

[Introduction 62](#_Toc88491996)

[Benefit assessment 63](#_Toc88491997)

[Risk assessment 64](#_Toc88491998)

[Risk management or mitigation measures 67](#_Toc88491999)

[Evaluation of the benefit-risk balance 68](#_Toc88492000)

[Conclusion 69](#_Toc88492001)

[List of questions 72](#_Toc88492002)

[Part 1 72](#_Toc88492003)

[1.A Comments on administrative particulars 72](#_Toc88492004)

[Pharmacovigilance System Master File 72](#_Toc88492005)

[Manufacturing authorisations and inspection issues 72](#_Toc88492006)

[GMP inspection(s) 72](#_Toc88492007)

[GCP inspection(s) 73](#_Toc88492008)

[1.B Comments on SPC and labelling 73](#_Toc88492009)

[Major objections 73](#_Toc88492010)

[Other concerns 73](#_Toc88492011)

[Part 2 73](#_Toc88492012)

[2.A.1 <Title> 73](#_Toc88492013)

[2.A.2 <Title> 74](#_Toc88492014)

[Part 3 74](#_Toc88492015)

[3.A.1 <Title> 74](#_Toc88492016)

[Part 4 74](#_Toc88492017)

[4.A.1 <Title> 74](#_Toc88492018)

Introduction

For all submissions, choose one of the following options

Option 1: Falls under Art. 42(2) of Regulation 2019/6 (mandatory scope):

The applicant <Applicant name> submitted on <submission date> an application for a marketing authorisation to the European Medicines Agency (The Agency) for <Product name>, through the centralised procedure under Article 42(2) <a><b><c><d><e> of Regulation (EU) 2019/6 (**mandatory scope**).

The eligibility to the centralised procedure was agreed upon by the CVMP on <CVMP meeting date> as <Product name>

For option a) has been developed by means of a biotechnological process, i.e. using <recombinant DNA technology (Article 42(2)(a)(i))> or < controlled expression of genes coding for biologically active proteins in prokaryotes and eukaryotes including transformed mammalian cells (Article 42(2)(a)(ii))> or <hybridoma> <and> <monoclonal antibody> method<s> (Article 42(2)(a)(iii))>.

For option b) is primarily intended for use as performance enhancer in order to promote the growth of treated animals or to increase yields from treated animals (Article 42(2)(b)).

For option c) contains an active substance which has not been authorised as a veterinary medicinal product within the Union at the date of the submission of the application (Article 42(2)(c)).

For option d) is a biological veterinary medicinal product, which contains or consists of engineered allogeneic tissues or cells (Article 42(2)(d)).

For option e) is a novel therapy veterinary medicinal product (Article 42(2)(e)), in accordance with Article 4(43) <(a) - a veterinary medicinal product specifically designed for gene therapy, regenerative medicine, tissue engineering, blood product therapy, phage therapy> <b) - a veterinary medicinal product issued from nanotechnologies><(c) - any other therapy which is considered as a nascent field in veterinary medicine>.

Option 2: Eligible under Art. 42(4) of Regulation (EU) 2019/6 no other marketing authorisation has been granted for the veterinary medicinal product within the Union, (optional scope):

The applicant <Applicant name> submitted on <submission date> an application for a marketing authorisation to the European Medicines Agency (The Agency) for <Product name>, through the centralised procedure under Article 42(4) of Regulation (EU) 2019/6 (**optional scope**).

The eligibility to the centralised procedure was agreed upon by the CVMP on <CVMP meeting date> as no other marketing authorisation has been granted for the veterinary medicinal product within the Union.

At the time of submission, the applicant applied for the following indication<s>:

<indication>

The active substance of <Product name> is <vaccine common name>, a <class of active>, which <describes mode of action>. The target species <is, are> <target species>.

<Product name> <presentation> contains <concentration(s)> <vaccine common name> and is presented in packs containing <pack sizes>.

If applicant is registered as SME:

The applicant is registered as an SME pursuant to the definition set out in Commission Recommendation 2003/361/EC.

For all submissions:

The rapporteur appointed is <rapporteur name> and the co-rapporteur is <co-rapporteur name>.

The dossier has been submitted in line with the requirements for submissions under.

For all submissions: choose one of the following options:

<Article 8 of Regulation (EU) 2019/6 – full application*>*

<Article 20 of Regulation (EU) 2019/6 – a combination veterinary medicinal product application.>

<Article 21 of Regulation (EU) 2019/6 – an informed consent application.>

<Article 22 of Regulation (EU) 2019/6 – a bibliographic application.>

<Article 23 of Regulation (EU) 2019/6 – an application for limited markets.>

<Article 25 of Regulation (EU) 2019/6 – application in exceptional circumstances>

Scientific advice

<The applicant received scientific advice (SA/….) from the CVMP on <date>. The scientific advice pertained to the insert as appropriate: <batch potency test> <quality>, <safety> <and> <clinical development> <quality and bioequivalence studies> of the dossier.>

<Rapporteur to include text on whether or not the advice was followed by the applicant>

If scientific advice was received, briefly confirm if the applicant followed the scientific advice or not. If not, state whether a reasonable justification was provided to allow accepting this deviation.

Details on the scientific advice should be addressed in the relevant sections of this report; e.g. if the study design deviated from CVMP GLs and was agreed beforehand by the CVMP in a SA, or if extrapolation to another dossier was accepted in a SA prior to submission of the dossier.

Vaccine Antigen Master file (VAMF) and vPTMF

If a new VAMF/vPTMF was submitted for evaluation and approval, or if existing VAMF/vPTMF are used in support of the marketing authorisation application, it should be stated and described here.

Multi-strain dossier

The application has been submitted in accordance to Annex II to Regulation (EU) 2019/6 and for which CVMP has published guidance (EMA/CVMP/IWP/105506/2007). <x>strains of <xxx>virus/bacteria are included in the dossier, namely <name of the different virus/bacteria strains>. The vaccine may contain up to <3> types of strains of inactivated, viral/bacterial antigens, chosen from the <7> strains included in the dossier depending on epidemiological need.

Limited market status

The applicant requested classification of this application as limited market by the CVMP.

The Committee confirmed on <date> that limited market status would apply as <target species> is not listed in Art 4(29)b of Regulation (EU) 2019/6><<indication> in <target species> is considered to be an indication for the treatment or prevention of diseases that occur infrequently or in limited geographical areas, as per the requirements of Art. 4(29)(a) of Regulation EU 2019/6>.

The CVMP also confirmed that the application would <qualify to be submitted under Art. 23 of Regulation (EU) 2019/6 (limited market), as the benefit of the availability on the market of the veterinary medicinal product to the animal or public health outweighs the risk inherent in the fact that certain documentation has not been provided. The data requirements in the relevant CVMP guideline(s) for applications for veterinary medicinal products intended for limited markets submitted under Article 23 of the Regulation (EU) 2019/6 would be applicable when assessing the application.>

or

<not qualify to be submitted under Art. 23 of Regulation (EU) 2019/6 (limited market), as it is not considered that the benefit of the availability on the market of the veterinary medicinal product to the animal or public health outweighs the risk inherent to the fact that certain documentation has not been provided.>

Part 1 - Administrative particulars

1.1 Summary of the Pharmacovigilance System Master File

EMA to complete the section.

If the validation indicates that the summary of the PSMF is acceptable:
<The applicant has provided a summary of the pharmacovigilance system master file which fulfils the requirements of Article 23 of Commission Implementing Regulation (EU) 2021/1281. Based on the information provided the applicant has in place a pharmacovigilance system master file (PSMF) with reference number <enter reference number>, has the services of a qualified person responsible for pharmacovigilance, and has the necessary means to fulfil the tasks and responsibilities required by Regulation (EU) 2019/6. >

If the validation indicates deficiencies of the summary of the PSMF, add the following text (and add the outstanding issues to the draft list of questions):
<The applicant has provided a summary of the pharmacovigilance system master file in accordance with Article 8(1C) or Regulation (EU) 2019/6. The information < in the summary of the pharmacovigilance system master file is not in accordance with Article 23 of Commission Implementing Regulation (EU) 2021/1281 - description of unclear or outstanding information> < is not conclusive><has not been provided>.

<Rapporteur to include further text, if applicable>

1.2 Manufacturing authorisations and inspection status

<Rapporteur to include text>

**Active substance**

Repeat the paragraph below as many times as number of manufacturers involved in the manufacture of the active substance(s). Always indicate what activities are performed at each site. Include confirmation of GMP compliance from QP(s) at the EEA site(s) where the active substance is used as a starting material (e.g. manufacturer of dosage form in the EEA) and/or responsible for batch release of finished product. The sterilisation of an active substance is considered the first step of the finished product manufacturing and has to be conducted under GMP Part I. EMA will delete the names of manufacturing sites that are considered commercially confidential information at EPAR stage but all should be included in the scientific overview and CVMP assessment report.

<Manufacture><quality control><primary packaging> <secondary packaging><release> of the active substance <active substance> take(s) place <outside the EEA> at <name, brief address>.

<A GMP declaration for the active substance(s) manufacturing site was provided from the Qualified Person (QP) at <the EU batch release site><and/or> the EEA site(s) where the active substance is used as a starting material: e.g.<manufacturer of dosage form><on behalf of all QPs involved>. The declaration was based on an <on-site> audit by <a third party> <the manufacturing site responsible for batch release> <which has taken into consideration the GMP certificate available for the active substance site issued by <name of competent authority> following inspection.>

**Finished product**

Repeat the paragraph below as many times as number of manufacturers involved in the manufacture of finished product. Always indicate what activities are performed at each site and their manufacturing authorisation and GMP status. EMA will delete the names of manufacturing sites that are considered commercially confidential information at EPAR stage but all should be included in the scientific overview and CVMP assessment report.

<Manufacture><sterilisation><quality control testing (<microbiological>,<chemical/physical>, <biological>)>, <primary packaging> <secondary packaging><importation><batch release> of the finished product take(s) place <outside the EEA> at <name, brief address>.

Only applicable to sites in the EEA: <The site has a manufacturing authorisation issued on <date> by <name of competent authority>>.

Applicable to all sites EEA and non-EEA:<GMP certification, which confirms the date of the last inspection and shows that the site is authorised activities indicated above, has been provided.><As there is a mutual recognition agreement in place for Good Manufacturing Practice (GMP) between the EU and <name of country with an MRA>, the site was considered appropriately certified as complying with GMP requirements.>

For pre-approval inspections to verify GMP compliance – usually for sites outside the EEA.

<A request for GMP inspection <is required><has been adopted> for the following site(s) in order to verify the GMP compliance status. The outcome of this/these inspection(s) is required for the Committee to complete its examination of the application.>

And/or

For pre-approval inspections to cover product or process related issues – for both kinds of sites in and outside the EEA.

<A request for GMP inspection <is required><has been adopted> for the following site(s) in order to provide further product specific information. The outcome of this/these inspection(s) is required for the Committee during its examination of the application.>

Overall conclusions on administrative particulars

<Rapporteur to include text>

<The summary of the pharmacovigilance system master file is considered to be in line with legal requirements.>

<The GMP status of the active substance(s) and of the finished product manufacturing sites has been satisfactorily established and are in line with legal requirements.>

<Additional information is requested in regard to <the summary of the pharmacovigilance system master file ><GMP certification of the manufacturing sites>.>

Part 2 - Quality

The text below indicates the type of information and level of detail that should be included in the quality part of the CVMP AR for new applications in order to ensure consistency of CVMP report format and style, but it is not exhaustive.

More information will need to be included depending on the specificities of each product e.g. active substances derived through biotechnology, non-standard manufacturing processes, novel QC methods to control quality steps, novel starting materials (adjuvants and/or excipients), presentations or delivery systems etc.

In general the Rapporteur should confirm compliance with the Ph.Eur where relevant or comment on the appropriateness and relevance of in-house methods and the proposed specifications.

Any shortcomings, omissions or deviations from the Ph.Eur or Regulation should be highlighted and the rational for acceptance explained and justified.

**Please note:**

The assessment report should follow the guidance provided below even if the format of the dossier of the applicant follows a different structure i.e. production of the antigen (seed material through to active substance) should be included in 2B. Validation for test methods should be included in the relevant sections for in-process and final product tests (2D and 2E respectively). Stability data (active ingredient, shelf-life and in-use stability should be included in 2G.

Solvent and diluent are equivalent terms, but the preference is the term solvent.

Starting materials and raw materials are equivalent terms but the preference is the term starting materials.

Where the application has been submitted in accordance with the multi-strain dossier it should be stated together with information on the strains included in the dossier and the proposed possible combinations up to a defined maximum number of antigens per formulation.

For applications under exceptional circumstance (e.g. BTV and AI) or for multistrain dossiers reference to the appropriate GLs) should be made in light of the data submitted in support of the application.

For in vivo studies and tests the Rapporteur should on any 3Rs issues of concerns that may suggest non-compliance with Directive 2010/63. Comment is particularly relevant regarding in vivo challenge tests for potency or the use of animal models to demonstrate the absence of virulence/toxicity.

Quality documentation (physico-chemical, biological, and microbiological information)

Qualitative and quantitative composition

<Rapporteur to include text>

Mention the compositions of the product, specifying the concentration/ strength (potency/titre) of the active substance and the mass/volume of the adjuvant(s) and listing the excipients, indicating in general terms their function in the formulation .e.g. adjuvant, preservative, excipient. Comment may be necessary whether or not the use of a preservative and colorants is justified.

If there are any formulation overages (for antigen stability and/or volume) state what they are and whether justified or not. Details of the studies to establish the antigen overage should be included under 2G Stability.

Provide details of the solvent/diluent and its composition and where relevant details as described above for any antigen, adjuvant and excipient included in the solvent/diluent.

It is not necessary to refer to Compliance of starting materials with Ph. Eur. or other EU pharmacopoeial monographs or Directives in this section – this will be dealt with in the relevant section under Part C “Control of starting materials”.

Examples:

<The finished product is presented as <pharmaceutical form(s)> containing of <active ingredient> as active substance at potency/titre <> per dose of <>. The product contains <> as adjuvant.>

<Other ingredients are: <list of excipients as described in section 2 of SPC.>>

<The vaccine is intended to be available in multidose presentations and consequently contains <> as a preservative.>

Include information on pack sizes indicating the primary and secondary packaging as described in section 5.4 of the SPC. Briefly mention any devices (measuring and/or administration) supplied if part of the presentation of the product.

<The product is available in <primary packaging> in <secondary packaging> as described in section 5.4 of the SPC>.

<The pack sizes are consistent with the dosage regimen and duration of use.>

Container and closure system

<Rapporteur to include text>

Add a brief description of the primary (immediate) packaging (including its closure), including information on the quantity of product contained in each container (if not included in section above and where relevant). Include brief reference to the specifications of the immediate container (and closure), e.g., whether the immediate packaging complies with the relevant Ph. Eur./other EU pharmacopoeial monographs. If the primary container is pre-sterilised give brief details.

If the primary containers/stoppers are sterilised give brief details and refer to provided validation reports.

Include a phrase/sentence confirming whether certificates of analysis have been supplied demonstrating compliance with the proposed specifications.

If any administration device is supplied with the product brief details should be included here on its design, quality and the adequacy of its specifications.

Examples:

<The product is filled into 11 ml type I neutral glass vials and 50 ml type II glass vials (in accordance with Ph. Eur. chapter 3.2.1) containing 50 and 200 doses respectively. These are closed with chlorobutyl rubber stoppers (type 1 in accordance with Ph. Eur. chapter 3.2.9) and aluminium seals.>

<Frozen, cell-associated virus suspension in sealed glass ampoule (containing 1000 and 2000 doses) and diluent in stoppered polypropylene bottles (containing 200 ml and 400 ml) or sealed plastic bags (containing 200 ml, 400 ml, 600 ml)>.

<The vaccine is filled into type I glass ampoules with a volume of 2 ml which are subsequently flame sealed, frozen and stored in liquid nitrogen. The ampoules are compliant with the Ph. Eur. The diluent is filled into polyethylene (PE) or multilayer plastic (MLP) bags of 400 ml or 800 ml volume. These materials are Ph. Eur. compliant.>

<The pack /container sizes are consistent with the vaccination schedule and intended use.>

<The containers and closures are in compliance with the pharmacopoeial requirements and their sterilisation is adequate.>

<Specifications for the stoppers are in accordance with Ph. Eur. chapter 3.2.9 are presented in Annex X and a document from a supplier (company y) also indicating the specifications is provided in Annex 2a.4.>

Product development

<Rapporteur to include text>

Give a critical summary of the development of the active substance(s), e.g. why the particular antigen (s)/strain(s) was chosen and its relevance to the field situation in the EU and/or the proof of concept of the mechanism of action of the biological active substance to trigger the intended immune response and its relevance in the pathogenesis of the disease. Give the rationale for combined products where there is more than one active substance in the final formulation.

Explain briefly how the biological characteristics of the seed materials have been taken into consideration and how they are relevant to the development of the active substance in the finished product e.g. for gene deleted vaccines the rationale for the development of a vaccine that enables a diagnostic test to differentiate between infected and vaccinated animals (DIVA).

Give a critical summary of the rationale for the development of the product and the significant process validation and developmental clinical studies that led to the choice of the final formulation. Assessment of the validations studies should be included in the relevant sections as outlined below (manufacturing processes under 2B and tests under 2D or 2E as appropriate).

Choice of the active ingredient (antigen) concentration – where relevant: target titre, minimum protective titre, minimum release titre, maximum release titre.

Choice of adjuvants and excipients which are either critical to the development of the finished product should be mentioned here together with their function. Briefly explain the container-closure system selected. If any device is supplied with the product brief details should be included here on its performance data.

Choice of any preservative(s) should be described with comment on the suitability of the preservative for the formulation (preservative efficacy validation should be described under 2G Stability).

Comment on the chosen manufacturing process for the product and how the development studies assure the quality of the finished product.

The manufacturing overages should be described with comment on the proposed limits and whether justified or not (e.g. setting of relevant final product specifications).

Filling volume overage should be justified.

For active substance the overage should be justified. Specific comment on the validation studies to justify the limits should be included in the relevant section 2G.

Examples:

<An explanation and justification for the composition and presentation of the vaccine has been provided. …>

<The diluent used for the vaccine is the same as the one already used with various others of the company’s vaccines. The information on the diluent was recently updated and approved by all European Member states>

<As the vaccine will be introduced in 2,000 and 4.000 doses presentations, only the 400 ml and 800 ml presentation of the diluent will be registered with the vaccine>

<The multi-dose oral presentation provides advantages in that it requires the preparation of only one vaccine solution which is subsequently administered by drenching or via drinking water to the herd. Moreover, the multi-dose presentation and the combination of the two vaccine strains (bivalent vaccine), instead of having two monovalent vaccines administered at the same period, has also the advantages of reducing the handling of multiple vials during the preparation of the single vaccine solution by the user, but also reducing the preparation time, the quantity of shipping material and wastage of empty containers. The combination of the two vaccine strains also reduces the risk for preparation errors, misadministration and mis-dosing>

<Reasonable justification is given regarding the relevance of the chosen vaccine strain within the EU.>

<X is attractive for the use as a vector, as it hardly spreads, is fully apathogenic and not infectious for non-avian species. The advantage of the recombinant product is that there is no need for the application of a live vaccine which prevents the development of latently infected carrier animals.>

<The applicant explains that the vaccine was originally developed in the US. Presently, a US frozen form of the vaccine, which is produced by a different manufacture, is under authorization process in that country. For the European market, the vaccine, which is freeze dried, is manufactured by X.>

<The strain in the vaccine expresses antigen X and is toxin-negative. It was isolated from a healthy animal at the Y Institute in 2008. The strain is non-pathogenic for animals and humans since it is negative for Z-toxins and virulence genes. The wild-type strains are endemic in the EU and commonly affect herds of dairy/fattening animals>

<The strain originated from an ill animal during an outbreak in the Region of X, Country Y in 2006 and was selected for optimal antigen supply for an inactivated vaccine. The identity of the strain was confirmed by RT-PCR on the Master Seed Virus>

If all the excipients are not critical, please use the following standard sentence:

Example:

<All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 2 of the SPC.>

Comment on relevance of formulation used during development

Example:

<The formulation of batches used during clinical studies is the same as that intended for marketing>

If different formulation(s) have been used for the clinical trials explain the differences and on what basis they have been accepted e.g. bioequivalence study, in vitro comparison data, other theoretical justification.

Description of the manufacturing method

<Rapporteur to include text>

Please note: Do not include information on the manufacturing and test sites here. These are included in Part 1.

Please note: Details of production of the active substance from seed material through to active substance/bulk antigen, formulation, blending and filling of the finished product should be included in this section (2B).

Include a brief description of the method of manufacture highlighting any critical steps e.g. inactivation process for inactivated vaccines, blending and filling processes (note, inactivation validation assessment and in process and final product tests under 2D and 2E) and stating whether they are adequately controlled.

Discuss the adequacy of the validation data of specific manufacturing steps (including hold times) and any justification related to the production process e.g. in relation to the manufacturer’s experience with the specific process. Include details of whether or not the validation studies were performed on full production-scale batches or pilot batches at each proposed manufacturing site.

Provide manufacturing details of any solvent included with the product identifying any critical steps and the adequacy of any in process controls.

Novel manufacturing processes may require more detail including comment whether justified or not. Reference to critical or novel process validation steps should be described and comment provided on the suitability of the validation studies e.g. purification, or other critical process steps as appropriate. Include reference to manufacturing steps for other substances used during manufacture (e.g. adjuvants) including the specifications to ensure a homogenous and consistent starting material.

Examples:

<The manufacturing process consists of <number> main steps: <list and briefly discuss the steps>. <The process is considered to be a <non->standard manufacturing process.>

<Major steps of the manufacturing process have been validated by a <number> of consecutive batches. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible and consistent manner. The in-process controls are adequate for this <type of manufacturing process> <pharmaceutical form>.>

Production and control of starting materials

<Rapporteur to include text>

For all components and substances used in the manufacture of the product should have the relevant information as per Commission Delegated Regulation (EU) 2021/805 should be provided according to their classification in the order below.

As a general point relevant to all sections under “C Production and Control of Starting materials” any shortcomings, omissions or deviations from the Ph. Eur. or legal texts should be highlighted and the rational for acceptance explained and justified.

Starting materials listed in pharmacopoeias

<Rapporteur to include text>

All starting materials listed in a pharmacopoeia should be presented with an indication as to which Pharmacopeia they are listed under and if they are compliant. Include a sentence confirming whether the proposed specifications are in accordance with the Ph. Eur. or not and if certificates of analysis have been supplied.

For non-Ph. Eur. monographs (e.g. EU National pharmacopoeias) include a sentence confirming whether the proposed specifications are in accordance with the Ph.Eur. or not and if certificates of analysis have been supplied.

The function of the material should be described, its method of identification and any particular issues of note e.g. storage period/stability.

Examples:

<Certificates of analysis have been provided and all conform to specifications in the <Ph. Eur>.>

<The nature of the starting materials, controls and treatments applied guarantee sterility of the vaccine and absence of introduction of any extraneous agent.>

Starting materials not listed in a pharmacopoeia

*<e.g. active substance, adjuvants, cell seeds and some excipients>*

Starting materials of biological origin

<Rapporteur to add product specific details here>

All starting materials of biological origin not listed in a pharmacopoeia e.g. master and working cell seeds, viral bacterial or other microbial/parasite seeds and other starting materials of biological origin e.g. bovine serum, trypsin, lactose, peptides, recombinant products should be presented here. Include a brief description of the material, the species of origin and geographical region from which it is sourced. The function of the material should be described.

For seed materials include a brief summary of the species of origin, history and geographical origin include details of method of preparation of the master and working seeds including the cell cultures and the master and working seeds involved. Include details of the tests on MSV/MBS, WSV/WBS and MCS/WCS including compliance with the relevant monographs or GLs (e.g. Ph. Eur. 5.2.4, Ph. Eur. 5.2.5, Ph. Eur. 0062) and whether any specific issues were identified. A summary of the tests conducted for identity, extraneous agents, purity, sterility, absence of mycoplasma and retroviruses should also be included. Storage conditions should be briefly indicated. For live attenuated vaccines, proof of stability of the attenuation characteristics of the seed has to be given.

Comment on the in-house controls tests implemented to ensure the quality & consistency of the starting material and their specifications. Include comment on whether a certificate of analysis (where relevant) has been included and is in compliance with the in-house specifications. Comment on how the material is in compliance with the requirements of Ph. Eur. 5.2.5 “Substances of animal origin for the production of immunological veterinary medicinal products”. Comment on the source of the starting material and any significant processing and/or testing to remove the risk of extraneous agents.

For genetically engineered starting materials include information on any added or deleted genes, biological properties, gene expression and genetic stability of the final construct. This information shall include details such as the description of the starting cells or strains, the construction of the expression vector, control of the inserted sequences, details of the plasmid vector if applicable.

Any starting materials of human and/or animal origin which fall within the scope of Ph. Eur 5.2.8 “Minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products” & the TSE Note for Guidance (EMEA/410/01 <version>) including seed materials, cell seeds, batches of serum and other materials originating from relevant TSE-risk species should be identified here and reference included how TSE compliance for each was demonstrated by the applicant, for example, by TSE certification and/or via scientific documentation. Comment should be made on the overall TSE risk assessment for the product taking account of all the starting materials and the intended use of the product in the target species. Where necessary highlight any specific TSE issues that were addressed in relation to the application that may be considered high risk e.g. ruminant derived starting material used to prepare ruminant vaccine.

Examples:

<The product does not contain any materials derived from human or animal origin.>

<None of the starting materials used for the active substance or the finished product are risk materials as defined in the current version of Ph. Eur 5.2.8 and the Note for guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products (EMA/410/01 <version>). The product is therefore out of the scope of the relevant Ph. Eur. monograph 5.2.8 and the Note for guidance.>

<Valid TSE declaration<s> from the manufacturer<s> of the <active substance> <excipients> <finished product> confirming compliance Ph. Eur. monograph and the Note for guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products (EMA/410/01 <version>), <has> <have> been provided.>

<The only material of animal origin used in the product <or in the production of the <active substance> is lactose monohydrate<milk / milk derivatives, including lactose>. It is confirmed that the lactose… is produced from milk from healthy animals in the same condition as those used to collect milk for human consumption and that the lactose has been prepared without the use of ruminant material other than calf rennet according to the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents Via Human and veterinary medicinal products (EMA/410/01 <version>).>.

<A valid TSE certificate of suitability for <substance> from the stated manufacturer was provided.>

<The starting materials of animal origin used in the production of the final product comply with the current regulatory texts related to Ph. Eur. monograph 5.2.8 “Minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products” & TSE Note for Guidance (EMEA/410/01<version>)”>

<All starting materials of animal origin which do not fall within the scope of Ph. Eur. 5.2.8 are either tested for or treated to ensure that there are no contaminants or further assurance is given that there is no potential risk.>

Any ‘novel’ excipient (used for the first time in the EU in a veterinary medicinal product) should be clearly mentioned here if of biological origin (and the supporting, safety and efficacy data relating to it should be given in Parts 3 and 4 as appropriate).

Examples:

<All excipients are well known pharmaceutical ingredients and their quality is compliant with <Ph. Eur.><detail other> standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 2 of the SPC.>>

<If the product is GMO the information should refer to instructions contained in the relevant of CVMP guideline on live recombinant vector vaccines for veterinary use (EMEA/CVMP/004/04-FINAL): from point 3.2.1. to 3.2.5.>

Starting materials of non-biological origin

All starting materials of non-biological origin not listed in a pharmacopoeia should be mentioned here with information on their specifications and whether they conform to their certificate of analysis and if the presented documentation is adequate to be considered acceptable or not.

<Rapporteur to include text>

Any ‘novel’ excipient should be clearly mentioned here and the supporting safety and efficacy data relating to it should be given in Parts 3 and 4 as appropriate).The function of the material should be described, and any particular issues of note described.

Example:

<Certificates of analysis have been provided for … and all conform to in-house specifications.>.

In-house preparation of media and solutions consisting of several components

According to Commission Delegated Regulation (EU) 2021/805 culture media consisting of several components used for production of an active substance shall be regarded as one starting material. All components shall be listed in previous sections (starting material s). State if there are any risk that might be posed by the use of media and solutions.

A useful phrase (after summarising in-house preparation of media and solutions consisting of several components) is: <Information regarding the qualitative and quantitative composition of all culture media <and the stabiliser>, their treatment processes and their storage conditions is provided in the dossier. All components are either tested for or treated to ensure that there are no contaminants or further assurance is given that there is no potential risk.>

Control tests during the manufacturing process

<Rapporteur to include text>

This section should include details of the control tests performed at the various stage of the manufacturing process and their validation commencing at the control tests performed on the production seed through to any tests conducted on the bulk active substance.

This section refers to testing of any intermediates.

Include a brief overview of any control tests (and respective limits, if relevant) conducted during intermediate stages of the manufacturing process with comment on their validation, necessity and suitability to control consistency and homogeneity of production e.g. antigen content, sterility, CPE). In line with the Ph. Eur. controls relevant to this section also include inactivation controls, detoxification, physical tests, chemical tests, pH, etc.

Example:

<The applicant presented in-process data for the manufacture of three consecutive antigen bulks. During the manufacture of the antigen the following tests are carried out <CPE on production seed virus, CPE on harvest, inactivation controls, pH > Test descriptions and the limits of acceptance were presented. The relevant test methods for in-process controls are satisfactorily validated. The in-process tests are deemed to be sufficient to control all the critical steps in the manufacturing.>

Control tests on the finished product

This section includes tests on the final filled product and/or bulk formulated product where appropriate and justified.

Details of the finished product tests should be included in the relevant sections 1 – 7 below. The following details should be given for each test:

<Rapporteur to include text>

In general, give the objectives of the test with a reference to the Ph. Eur. if relevant, or the reference to any internal test method or standard, and a short description of the proposed test.

State whether the proposed specifications/limits for each control test are justified or not and whether they provide a satisfactory confirmation of the quality of the product. Include details of whether the control test is performed on the final product or bulk and whether the approach is acceptable or not.

Comment in particular on the tests to identify and quantify the active substance in the finished product.

Give brief information on the batch potency test including reference to validation studies provided and studies used for determination of release and/or end-of-shelf-life specifications. State whether the limits have been adequately justified.

State if all the analytical methods are well described, if any are Ph. Eur. or other EU pharmacopoeial methods, and for non-Ph. Eur methods if appropriately validated in accordance with current guidance (EU GLs or VICH GLs 1 & 2 [Validation of Analytical procedures] and VICH GL 40 [Test procedures and acceptance criteria for new biotechnological/biological veterinary medicinal products].

Finished product tests:

1) General characteristics of the finished product

List of tests performed and confirm compliance with the specifications.

Examples of tests provided here include appearance, volume, pH, viscosity etc.

2) Identification of the active substance(s)

A brief description of the method used to confirm the identity of the active substance. Confirmation that the methods used to identify the active substance(s) (e.g. strains/serotypes) are suitable.

For GMO active substances include a brief description of the method of identification including techniques for the identification and detection of the inserted sequence and vector

3) Batch titre or potency

A brief description of the potency test should be provided.

Validation is reliable to guarantee each batch will contain the appropriate potency or titre to ensure its safety and efficacy as in the pivotal safety and efficacy studies (in part 3 and 4) and that release specifications are justified. The rapporteur should confirm that the test is able to detect a sub-potent batch and the appropriateness of the test to ensure consistency of production.

4) Identification and assay of adjuvants

A brief description of the methods used to confirm the identity and quantity of the adjuvant where relevant.

5) Identification and assay of excipient components

A brief description of the methods used to confirm the identity of the excipient where relevant.

6) Sterility and purity tests

List the tests performed that confirm the sterility and purity of the finished product. Include reference to the Ph. Eur. for sterility, purity and mycoplasma (Ph.Eur. 2.6.1 and Ph. Eur. 2.6.7) and comment if a risk-based approach following Ph. Eur. 5.2.5 has been used to demonstrate the absence of extraneous agents.

7) Residual humidity (if relevant)

Each batch of lyophilised product shall be tested for residual humidity according to the Ph.Eur.

8) Filling volume

A Useful phrase (after summarising the finished product tests) is:

<The description of the methods used for the control of the finished product (vacuum, appearance, identity, purity, titre, residual humidity, filling volume) and the specifications were provided.>

Batch-to-batch consistency

<Rapporteur to include text>

Batch analyses results from three consecutive batches should be summarised with comment on whether they confirm consistency and uniformity of the product. Comment on whether pilot or industrial scale batches have been used to demonstrate consistency and highlight any deviations from the proposed method of production for routine batches.

The shelf life specifications should be detailed under “Stability”.

Example:

<The applicant presented finished product data for the manufacture of three consecutive finished product batches. During the manufacture of the active substance the following tests are carried out <CPE on production seed virus, CPE on harvest, inactivation controls, pH > Test descriptions and the limits of acceptance were presented. The relevant test methods for in-process controls are satisfactorily validated. The in-process tests are deemed to be sufficient to control all the critical steps in the manufacturing.>

Stability

<rapporteur to include text>

Include sections on the stability of:

- Active substance i.e. final bulk active substance before formulating as bulk finished product.

- Finished product including active substance(s) in final filled container in its final state.

- Solvent (if relevant).

The Rapporteur should confirm that the appropriate controls were used at the appropriate time points to establish the stability of the active substance, final finished product (including and in-use stability) and, where relevant, the solvent. If intermediate products obtained at various stages of the manufacturing process are stored, the intended conditions and duration of storage shall be adequately justified on the basis of the stability data available.

In general, for active substance and finished product, summarise the stability studies and significant findings. State conditions (storage at xx°C, container material) used, number of batches that had been produced, batch sizes (whether pilot scale/production scale) and immediate packaging material.

For finished product comment on the bracketing design (testing smallest and largest container).

The description should be concise and normally not more than a short paragraph. No tables of stability study results to be included. Briefly discuss the stability results and any out-of-specification results and mention the conclusions in this respect. Any shortcomings/omissions should be highlighted and justified.

If a preservative is included in the product include details of the preservative efficacy studies at the end of shelf life and comment on whether the test method and specifications are in compliance with Ph. Eur. requirements.

If an in-use period is proposed for the finished product, a comment on the stability data supporting the in-use period should be made in this section.

Stability of the solvent: the stability studies of the solvent should be confirmed, and where the solvent includes an active substance the full spectrum of observations as described above should be applied.

Examples:

For active substance:

<Data on the stability of the active substance was provided for <number of active substance batches/or finished product batches> that had/have been produced according to the described production process with active substance(s) stored at <°C> for <xx months before blending>. Data demonstrating stability up to xx months support the proposed shelf life for the active substance of <xx months>.

For finished product:

<real time stability data of <number, scale> batches of finished product for <number> months at 2-8 ºC xx days were provided. The batches of <Product name> are <identical> <representative><different> to those proposed for marketing and were packed in the primary packaging proposed for marketing.>

<Stability studies include <number, scale> batches and encompass both the smallest and the largest presentation filled in <material> vials.><Samples were tested for <include the shelf life specifications if different from the release specifications>.> <The control tests demonstrate the final product/active ingredient is stable for X months.> <…no significant changes have been observed> <…observed biological and physicochemical changes were small, and not likely to have a significant effect on efficacy and safety of the product when used according to the directions in the SPC.>

<The proposed specifications regarding minimum shelf life titre (xx/dose) and release titre (xx cfu/dose) are adequately justified. Furthermore, an in-use shelf life of xx hours after first broaching/reconstitution is sufficiently demonstrated.>

<Based on the available stability data, the proposed shelf-life of <x months/years> and <storage conditions> as stated in the SPC are acceptable.>

for preservative efficacy:

<Preservative efficacy has been tested in accordance with Ph. Eur. 5.1.3 and Monograph 0062 criteria …. Efficacy of the preservative data at the end of the proposed in use shelf-life is available and it is considered satisfactory.>

for in-use stability:

<Stability data on the broached vial stored for 10hr at 30°C was provided and considered acceptable for the claimed xx hour in-use stability. It further supports that the product may be transported at room-temperature.>

<New active substance (NAS) status>

(if claimed by the applicant)

<Rapporteur to include text>

If the applicant claims that the active substance is a new active based on the nature, properties of the active substance, the outcome of the assessment of NAS status should be included in Part 2 of the scientific overview; if the applicant claims that the new active substance differs significantly in properties with regard to safety and/or efficacy in comparison to a known active substance already authorised, the outcome of the assessment of NAS status should be included in Parts 2, 3 and/or 4 of the scientific overview, as appropriate. The rapporteurs should assess NAS status based on the evidence and justification provided by the applicant usually included in Annex 5.21 of the dossier. In case of questions, these should be added to the LoQ section at the end of this document.

Scientific discussion as to why the NAS status claim was accepted (or rejected) should be included.

The applicant requested the active substance <vaccine common name> contained in <Product name> to be considered a new active substance <as it is novel and not hitherto authorised in a veterinary medicinal product in the European Union> <in comparison to the known <active substances> previously authorised in the European Union, and claimed that <active substance> differs significantly in properties with regard to <safety> <and> <efficacy> from the above-mentioned substance already authorised in the EU>.

Based on the review of the data provided, the CVMP considered that the active substance <active substance> contained in the veterinary medicinal product <Product name>

<is to be qualified as a new active substance considering <add justification>>

<could be qualified as a new active substance considering <add justification> provided that satisfactory responses are given to the concerns as detailed in the List of Questions.>

<is not to be qualified as a new active substance considering <add justification.> In case this option is chosen, please add justification.

<no conclusions can currently be taken on the new active substance status. The applicant is requested to update Annex 5.21 of the dossier and provide evidence and justification that the active substance is new.> In case this option is chosen, a corresponding question should be included in the LoQ.

If the applicant claims that the new active substance differs significantly in properties with regard to safety and/or efficacy in comparison to an already authorised active substance, rapporteurs should highlight here the relationship between the candidate and the already authorised active substance. The sections relating to NAS in Parts 3 and/or 4 of the Scientific Overview should be completed, as appropriate.

Overall conclusions on quality

<Rapporteur to include text>

Summarise briefly the conclusions in respect to the compliance with the Annex to Regulation (EU) 2019/6.

Confirm compliance with the relevant Ph. Eur. monographs, including general monographs and the general chapter highlighting the adequacy and completeness of the data provided in general (without giving details of studies) with any shortcomings/omissions highlighted and justified and the conclusions drawn.

Comment of critical areas including, the shelf life of the active ingredient and finished product, the appropriateness of the manufacturing method and in-process and finished product controls, the selection and testing of starting materials, including adjuvants, and other excipients and preservatives (where applicable) identifying any deficiencies and explaining the criteria for acceptance where there are gaps in the data or compliance with relevant requirements are identified.

The conclusions should be taken into account in the benefit-risk assessment and the SPC and product information, as appropriate. The list of questions (day 120) or list of outstanding issues (day 180) should mirror these conclusions.

Examples:

<Information on the development, manufacture and control of the active substance and the finished product has been presented in a satisfactory manner.>

<Biological and physicochemical aspects relevant to the performance of the product have been investigated and are controlled in a satisfactory way.> <Data has been presented to give reassurance on TSE safety>.

<Based on the review of the data on quality, the manufacture and control of <Product name> are considered acceptable.>

<The manufacturing process including appropriate in-process controls and quality controls on the finished product are described in sufficient detail to give confidence that the manufacture will yield a consistent immunological product.>

<In addition, the applicant is recommended to provide the following information <<post-authorisation><prior to marketing>>:

The applicant had provided both a protocol for the process validation study and a commitment to submit the data post-authorisation and the Committee considered this to be acceptable>.

Part 3 – Safety documentation (safety and residues tests)

General requirements

<Rapporteur to include text>

As introduction, the relevant elements pertinent to the safety assessment of the product under consideration should be presented, in order to understand the approach taken, without repeating the general description of the product (i.e. type of vaccine (live, inactivated, etc.), adjuvants, GMO, limited market).(If the vaccine is a live one reference can be made to the pathogenesis of the field strains, their impact on the target animals and specific points of concern, if applicable.) Reference can be made to the general description in the “Introduction” section of the scientific overview document.

A very brief summary of the type of data provided may be suitable as an introduction, e.g. that a complete set of safety data has been provided, as the application concerns a product with a new active substance not assessed before, or that the product is assessed under the multi-strain dossier guideline requirements or that the application has been qualified as eligible for an authorisation for limited markets one or is authorised under emergency circumstances, therefore certain derogations in requirements may apply.

If scientific advice was given, briefly outline what the advice related to. Comments whether the advice was followed or not should be made when discussing the relevant study and if not followed, explain the deviation and whether it was justified or not.

Examples:

<The active substance of <Product name> is <vaccine common name>, a <class of active>. <vaccine common name> is a new active substance not authorised for a veterinary medicinal product in the EU before. A full safety file in accordance with Article 8(1)(b) has been provided.>

If (a) novel excipient(s), that is to say (an) excipient(s) used for the first time in a veterinary medicinal product or by a new route of administration, is used in the product this should be stated in the introduction. Comments should be provided in the relevant sections, safety for the target animals and/or, user safety, section or in all of them depending on the study data provided and the results of these.

For all sections, if no data have been provided, the rapporteur / co-rapporteur should note this and comment on why this is or is not appropriate. If there are justifications for this omission i.e. limited market or emergency circumstances it should also be mentioned here.

Safety documentation

<Rapporteur insert text>

Provide briefly an overview of pivotal studies conducted to support the safety of the product.

If a study was not conducted according to GLP this should be stated. Summarise clearly the endpoints examined but avoid too detailed descriptions of the examinations conducted. Summarise clearly the findings of each study and present clearly the conclusions of the study and what it showed.

Examples:

<X> safety studies were conducted to investigate the safety of the product and included <z> pre-clinical studies investigating the safety of the administration of one and repeated dose, a <x fold> overdose, reproductive performance and <y> clinical trials. The vaccine was administered by the <> route, as <not> recommended. Pre-clinical studies were reported to be GLP compliant and carried out in <target animals> of the minimum age recommended for vaccination, using <pilot> <production> batches containing <>. <Production> <pilot> batches were used in the <clinical> trials.

<Non-GLP studies were performed for <non-target animal species><the evaluation of <immunological><biological><genetic properties> of the vaccine strain under adequately controlled conditions>. This is considered acceptable according to Annex II of Regulation (EU) 2019/6.

<Studies applicable to <live vaccines> <GMO> products were conducted to investigate the dissemination of a single dose of the vaccine strain, the spread from vaccinated animals to non-vaccinated contacts and reversion to virulence>.

Provide comment if there is a Ph. Eur. monograph elaborated which is applicable to the product which specifies the requirements for safety testing - and if the Ph. Eur. chapter 5.2.6 has been followed.

Alternatively, please populate the overview table for the purpose of providing a brief overview of the amount of data i.e. list of pivotal safety studies, including studies to fulfil the special requirements for live vaccines or studies specific to the product under consideration, (e.g. potential shedding by vaccinated animals, the risk to unvaccinated animals or to any other species as well as an assessment of the potential to revert to virulence of the strain used and genetic re-assortment)and any tailored study design for products classified as a GMO or novel immunologicals such as monoclonal antibodies).

| ***Study reference*** | ***Study title*** | ***Batch used*** |
| --- | --- | --- |
|  |  |  |
|  |  |  |

Other trials (supportive/pilot/exploratory...) should only be briefly summarised, if relevant. The assessor should indicate why studies could not be considered relevant (e.g. inappropriate study design, dose, etc.).

Describe the various <additional> tests designed to show the potential risks from the product, which may occur under the proposed conditions of use.

Pre-clinical studies

<Rapporteur to include text>

For each of the sections below, summarise key studies and significant findings. Any shortcomings/omissions should be highlighted and justified as appropriate and the (co)rapporteur’s conclusions on the adequacy of data provided and findings stated. Describe pivotal studies first and individually. The description of one study should be concise and normally not require more than 1 paragraph. If several studies and references have been provided, first summarise briefly how many studies were provided and separate these into pivotal and supportive. Assessors can refer to the requirements outlined in Ph. Eur. 5.2.6 and VICH GL 44 TAS for veterinary inactivated and live vaccines.

Alternatively provide a brief description of each pivotal study, using the study summary table located under clinical safety studies, as appropriate, to ensure consistency and that key information is included in the scientific overview.

Safety of the administration of one dose

<Rapporteur to include text>

Include information supporting the safety of the product when administered at the recommended dose containing the maximum titre, antigen content or potency (containing bacteria/virus at the least attenuated passage level, in case of live vaccines). Administration should be following the primary administration scheme by the recommended route(s) of administration, to an appropriate number of animals of each species and category for in which it is intended to be used, including animals of the minimum age (serological status where relevant) at the start of administration and pregnant animals, where appropriate. Also comment whether a pilot or production batch of the product containing the maximum release potency or, in the case where maximum release potency to be licensed is not specified, then a justified multiple of the minimum release potency was used. Finally comment on compliance with minimum safety requirements and any specific Eur. Ph. Monograph applicable to the product.

Observations and examinations for signs of systemic and local reactions shall be described as well as where appropriate post-mortem macroscopic and microscopic examinations. Results should be evaluated in a conclusion in relation to the safety of the administration of a recommended dose following the primary administration scheme.

Examples:

<One pivotal study and two supportive one-dose pre-clinical studies were provided.> <The <study was><studies were> <not> compliant with GLP standards>. <One> dose of a <pilot> or <production> batch containing the <maximum release> <potency, antigen content, titre> or, <justified multiple of the minimum release potency, antigen content, titre> was used. <One> dose containing the <highest recommended concentration> of the product was administered by the <route> which is <not> the recommended one in the <recommended species> <not recommended species> <species 1> (at x weeks) and <species 2> (at y and z weeks). The vaccine <contained> <did not contain> bacteria/virus at the least attenuated passage. Animals were <not> of the minimum age as required.>

<The following observations and examinations for signs of systemic and local reactions were performed in <target species> for <x days> after administering the <recommended> <dose> via the <administration route>>.

<Post-mortem macroscopic and microscopic examinations were performed on day <x>.

<Results showed that <…>>.

<On the basis of the results <no> <the following > safety concerns arose following the administration of the <recommended> <dose> to the <target species> of the <minimum recommended> <age>, <providing therefore a valid <demonstration> of the safety of a single dose of the primary <vaccination, administration> schedule of the product >. <The applicant should provide satisfactory answers/justifications to all identified safety concerns.>

Safety of one administration of an overdose

<Rapporteur to include text>

(Please note that this section is not applicable for inactivated vaccines as no overdose studies are required for those kind of vaccines). If studies are provided for inactivated vaccines please include here; otherwise use proposed text to clarify that no overdose studies are required for inactivated vaccines or for IVMPs for exceptional circumstances). At a minimum include information taking into account the need to use the recommended route(s) of administration to an appropriate number of animals of the most sensitive category of the target species and serological status if relevant. Comment on the dose administered and its justification (i.e. for live vaccine it is expected that a 10X dose of vaccine at the least attenuated passage level containing the maximum release titre for which the application is submitted shall be administered. In the case where the maximum release titre to be licensed is not specified, or if the vaccine is formulated at a fixed concentration of antigen and no minimum/maximum dose is applicable, the study should be conducted with a justifiable multiple of the minimum release titre. Finally comment on compliance with minimum safety requirements and any specific Eur. Ph. monograph applicable to the product.

Observations and examinations for signs of systemic and local reactions shall be described and, where appropriate, post-mortem macroscopic and microscopic examinations. Results should be evaluated in a conclusion in relation to the safety of the administration of an overdose dose following the primary administration scheme.

Examples:

<No overdose studies are required for inactivated vaccines.>

<<One> pivotal study and <two> supportive overdose pre-clinical studies were provided.> <The <study was> <studies were> <not> compliant with GLP standards>. <An overdose containing <x> titre of <product>, which exceeds <x> times the recommended dose was administered by the <route> which is <not> the recommended one in the <recommended species> <not recommended species> <species 1> and <species 2> (at y and z weeks).> < Animals were<not> of the minimum age as required.>

<The following observations and examinations for signs of systemic and local reactions were performed in <target species> for <x days> after administering the <recommended> <dose> via the <administration route>.>

<Post-mortem macroscopic and microscopic examinations were performed on day <x> >.

<Results showed that <>>.

<On the basis of the results <no> <the following > safety concerns arose following the administration of an overdose <x> times higher than the recommended dose to the <target species> of the <minimum recommended> <age>.<The applicant should provide satisfactory answers/justifications to all identified safety concerns.>

Safety of the repeated administration of one dose

<Rapporteur to include text>

Comment on the administration protocol and potency, antigen content or titre of the dose used.

Include information taking into account the need for the vaccination schedule to include the primary vaccination regimen plus an additional dose(not required for IVMPs in exceptional circumstances) via the recommended route of administration to animals of the most sensitive category of the target species. Comment whether a pilot or production batch of the product containing the maximum release potency, antigen content or titre was used. If not comment whether an acceptable justification was provided (i.e. in the case where maximum release potency to be licensed is not specified, then a justified multiple of the minimum release potency can be used). Comment if seronegative animals were used in case of live vaccines and if not whether reasonable alternatives were provided. In cases where seronegative animals are not reasonably available, alternatives should be justified. Finally comment on compliance with minimum safety requirements and any specific Eur. Ph. monograph applicable to the product.

Observations and examinations for signs of systemic and local reactions in injection sites shall be described, where appropriate post-mortem macroscopic and microscopic examinations. Comment on duration and frequency of examination taking into account that injection sites should be examined daily or at other justified intervals by inspection and palpation for a minimum of 14 days after each administration. Results should be evaluated in a conclusion in relation to the safety of the administration of a recommended dose following at least one additional vaccination after the primary vaccination scheme.

Examples:

<<One> pivotal study and <two> supportive repeated dose pre-clinical studies were provided.> <The <study was><studies were> <not> compliant with GLP standards>. <<One> dose of a <pilot> or <production> batch containing the <maximum release> potency or, <justified multiple of the minimum release potency> was used.>

<<One> dose containing the <highest recommended concentration>of the product was administered by the <route> which is <not> the recommended one in the <recommended species> <not recommended species><species 1> (at x weeks) and <species 2> (at y and z weeks), which represents <one> additional vaccination after the primary one. Animals were of <not of>the minimum age as required.>

<The following observations and examinations for signs of systemic and local reactions were performed in <target species> for <x days> after administering the <recommended> <dose> via the <administration route>.>

<Post-mortem macroscopic and microscopic examinations were performed on day <x>.>

<Results showed that <>.>

<On the basis of the results <no> <the following > safety concerns arose following the administration of the <recommended> <dose> <one> additional time after the primary <vaccination, administration> schedule to the <target species> of the <minimum recommended> <age>.><The applicant should provide satisfactory answers/justifications to all identified safety concerns.>

Examination of reproductive performance

<Rapporteur to include text>

Examination of reproductive performance shall be considered when the immunological veterinary product is intended for use or may be used in pregnant animals or laying birds and when data suggest that the starting material from which the product is derived may be a potential risk factor.

Comment on whether the examination of reproductive safety, was appropriate for the purpose of the study i.e. use of the recommended dose according to the proposed administration scheme, by the recommended route(s) of administration to the groups of animals used (whether numbers were sufficient and if control groups were included) and whether a pilot or production batch was used. Also comment whether the observation period was appropriate to determine reproductive safety. For vaccines recommended for use in pregnant animals comment whether the study(ies) covered the periods of gestation recommended for use and whether the observation period was extended to parturition, to examine any harmful effects during gestation or on progeny.

Any additional studies to determine the effect(s) on semen, including shedding of the live organism in semen should be described in this section.

Comment on whether reproductive performance is also examined in clinical safety studies and if it is supportive and consistent with the results of the pre-clinical ones.

If the reproductive safety studies are not performed, an exclusion statement must be included on the product information label, unless a scientific justification for absence of risk for use of the product in breeding animals is provided. If no studies have been conducted provide a brief justification.

In addition, since this section of the SO establishes the basis of the information in the SPC concerning use during pregnancy, lactation or lay, ensure that a relevant statement can be included on use during lactation, if applicable.

Summarise briefly and state whether the studies are adequate or not, to support the indications for use in the SPC. Depending on the results, consider potential contraindication in breeding, pregnant (consider the acceptability on use for the different stages of gestation) or lactating animals.>

Examples:

<The safety of the reproductive performance was investigated in <x> studies, where <one> dose containing the <highest recommended concentration> of the product was administered by the <route> which is <not> the recommended one in <female animals of the target species>< at x stage of gestation>, <male breeding animals of the recommended species>, < (at <y>weeks)>. The following observations and examinations for signs of systemic and local reactions were performed in <target species> for <x days> after administering the <recommended> <dose> via the <administration route>.

<Post-mortem macroscopic and microscopic examinations were performed on day <x>>.

Results showed that <…>.

On the basis of the results <no> <the following > safety concerns arose following the administration of the <non> <recommended> <dose> <one> <not> following the recommended schedule for <primary> vaccination to <female animals of target species<at x stage(s) of pregnancy>> <breeding males>. The SPC has therefore been updated accordingly <provide statement of section 3.3/3.7 of SPC>.

Or

<No reproductive studies were provided as the product is not indicated to be used during pregnancy and/or by <breeding males>. The SPC has therefore been updated accordingly<provide statement of section 3.7 of SPC>.

(i.e. The safety and efficacy of the veterinary medicinal product has not been established during pregnancy. Do not use in<>).

Examination of immunological functions

<Rapporteur to include text>

Please provide a brief description of the tests on the immunological functions in cases where the product might adversely affect the immune response of the vaccinated animal or of its progeny.

If no tests have been conducted provide justification and relevant wording of the SPC in section 3.8.

Examples:

<The following studies were conducted to investigate the effects of the product in immunological functions. Studies examined the effect of the product in <>. <No> evidence of adverse effects from the use of the product as recommended on immunological functions was observed in <any of> the studies. The SPC has been updated accordingly in section 3.8.>.>

Or

<No further studies were conducted to investigate the effects of the product on immunological functions but <no> adverse effects were observed in <any of> the safety or efficacy studies. It is therefore <un>likely that this vaccine will have an adverse effect on immunological functions due to the nature of the product (i.e. inactivated vaccine, or live vaccine without any known immunosuppressive effects)>.

Special requirements for live vaccines

<Rapporteur to include text>

Relevant guidelines include: Ph. Eur. chapter 5.2.6 and VICH GL41 Target Animal Safety - Examination of Live Veterinary Vaccines in Target Animals for Absence of Reversion to Virulence – Annexes Spread of the vaccine strain

Spread of the vaccine strain

<Rapporteur to include text>

Please provide a brief description of the investigations into the spread and shedding of the vaccine strain from vaccinated to unvaccinated target animals using the recommended route of administration most likely to result in spread. Additionally, it may be appropriate in this section to describe the investigations into spread to non-target species which could be highly susceptible. Investigations to examine the spread of an antibiotic resistance gene into the environment, if relevant, can also be included in this section. Comment on whether the investigations and the data provided were adequate to characterise the risk of spread and whether an acceptable risk has been adequately demonstrated.

Examples:

<The spread of the vaccine strain from vaccinated to unvaccinated <animals> was investigated in <x> studies in which <animals of the target species> of <age> were vaccinated with <dose> according to the recommended vaccination schedule by the <recommended route> and left in contact with unvaccinated sentinels for up to <x> days. <The vaccine strain was isolated from <tissues> of <x> sentinels after <x> days contact.> <The vaccine strain was not found in any of the sentinel tissues sampled>

<It is concluded that the vaccine <virus, bacteria> can<not> spread to in-contact unvaccinated animals. Studies were <not> carried out to investigate spreading to other non- target species>.

Dissemination in the vaccinated animal

<Rapporteur to include text>

Please provide a brief description of the tests in faeces, urine, milk, oral, nasal and other secretions for the presence of the vaccine organism as well as the bio-distribution of the organism and its dissemination in the body’s predilection sites for replication. In the case of live vaccines against zoonotic diseases for food-producing animals these studies are obligatory and include an assessment of persistence at the injection site. Comment on whether the investigations and the data provided were adequate to characterise the risk of dissemination and whether an acceptable risk has been adequately demonstrated.

Examples:

<Dissemination of the vaccine strain in vaccinated animals was also investigated in <x> number of studies.>

<The vaccine strain was <not> isolated from the <tissue description > of <x%> vaccinated animals for at least <x> days post-vaccination.>

<In conclusion the virus strain <does>< not>disseminate following vaccination by the <recommended> route at a dose of <> in animals of the <target> species at <minimum> <recommended age> and therefore can <not>be shed from vaccinates <x >days post vaccination.>

<Although <Product name> is a live vaccine, the active substance(s) is/are non-pathogenic are not able to colonise non-target species, including humans; therefore studies to determine the persistence of the organism at the injection site are not necessary>

Increase in virulence of attenuated vaccines

<Rapporteur to include text>

Please provide a brief description of the tests with material from the passage level that is least attenuated between the master seed and the final product. Comment on whether the master seed was used and if not whether adequate justification was provided (i.e. if sufficient quantity of the master seed was not available for testing). Generally, for each target species, the most sensitive class, age, sex and serological status of animals should be used. Comment on the route of administration, which should be using a recommended route of administration or natural route of infection that is the most likely to lead to reversion to or increase in virulence and result in recovery of the organism following replication in the animal. The route used must be justified. In cases where alternative approaches are used, alternatives should be justified. Comment on the groups and number of animals used and whether appropriate for this type of study. Comment on whether the inoculum and the passages used were appropriate (i.e. initial one should contain the maximum release titre expected in the recommended dose or, in the cases where the maximum release titre to be licensed is not specified, then a justifiable multiple of the minimum release titre can be used). Comment on whether the clinical observations were typical for the disease which could indicate reversion to or increase in virulence. If signs consistent with the target disease were observed, confirm whether there was any evidence of an increase in virulence, indicative of reversion, with passage and whether the test organism is suitable for use as a live vaccine. Provide a conclusion as to whether the applicant adequately demonstrated an acceptable risk with respect to reversion to virulence.

Examples:

<The reversion to virulence of the vaccine strain was investigated in <x> studies in accordance with the requirements of Ph. Eur. 5.2.6 and Ph. Eur. relevant specific monograph respectively>.

<Sequential passage of vaccine strain through <x> groups of <animals> was investigated; a single dose of test vaccine was administered to <target species> in the first group by the <e.g. oculo-nasal> route and at passages <e.g 2, 3, 4 and 5>. <x> ml of <e.g. tracheal mucosa suspensions> prepared from <e.g. birds> of the preceding passage was administered to each <animal> by the same route.>

<<Animals> were <x> days of age at the start of the study and the time between passages was <x> days. Each passage group consisted of <x> animals.> <The vaccine strain was recovered at passage<e.g. 1> but could not be recovered at passages <2, 3, 4 or 5>... <The vaccine strain was recovered at <e.g. all 5 passages>.<There were <no> clinical signs of disease observed at <any> of the passage levels.>

<Passage was inoculated into <x> animals to prepare a larger volume of the virus () which was evaluated for safety for <e.g the respiratory tract and kidneys and safety for the reproductive tract.>

<Results: <No> abnormalities were found in the animals vaccinated either with material used for the first passage or material recovered from the final passage. <No> inflammatory lesions in <e.g. the kidneys> were seen in either the group inoculated with material used for the <1st> passage or in the group inoculated with virus recovered from the final passage.>

<It is concluded that <no> <slight> reversion to virulence was observed following <e.g. five> passages in vivo.>

Biological properties of the vaccine strain

<Rapporteur to include text>

Please provide a brief description of any other tests that may be necessary to determine as precisely as possible the intrinsic biological properties of the vaccine strain (e.g. neurotropism). Information on the characterisation of the live virus strains and the stability of the attenuation can also be included in this section (detailed description should be already addressed in part 2C-starting material of biological origin). Were other tests necessary in relation to the properties of the vaccine strain? If so, were they adequately performed?

Provide a conclusion as to whether the biological properties of the vaccine strain have been adequately presented and whether on the basis of this data the safety profile of the strain is acceptable>.

Examples:

<<No> specific studies have been conducted to determine the intrinsic biological properties of the vaccine strain. In the studies conducted, the vaccine strain did <not> cause, <clinical signs>, <lesions>, etc. to vaccinates.>

<On the basis of the data presented the safety profile of the strain can <not> be considered acceptable>.

Recombination or genomic reassortment of the strains

<Rapporteur to include text>

Please provide a brief discussion of the probability of recombination or genomic re-assortment with field or other strains. Include information on whether the genetic stability of the vaccine strain(s) was <were> demonstrated to be consistent and stable in in vitro passaging. Further describe if the strains are attenuated and of low virulence.

Provide a brief analysis of the potential scenarios for genomic re-assortment. Conclude on the level of risk posed by the potential recombination and whether it is acceptable or not.>.

User safety

<Rapporteur to include text>

Relevant guideline: CVMP guideline on user safety for immunological veterinary medicinal products ([EMEA/CVMP/IWP/54533/2006](https://www.ema.europa.eu/en/user-safety-immunological-veterinary-medicinal-products)). Where a more detailed user safety assessment is needed the CVMP guideline on user safety for pharmaceutical veterinary medicinal products (EMEA/CVMP/543/03-FINAL-Rev.1) may also be helpful.

Provide an overview of the assessment of the hazard presented by the product to the users, as presented by the applicant, highlighting significant findings/shortcomings/omissions including (co)rapporteur’s conclusions.

Briefly outline any inherent toxicity (including immunological/ pharmacological effects if relevant), exposure (worst case scenarios), mention any relevant studies submitted and whether there is a risk arising.

If different exposure scenarios are to be considered, briefly describe the exposure scenarios with the conclusions on the risk characterisation (normally 1 paragraph), and discuss resulting risk management proposals, where appropriate.

If any of these issues are considered key, then it may be appropriate to describe these in a little more detail, highlighting significant findings/shortcomings/omissions and conclusions on the risk including, the MOE and consequences arising therefrom, i.e. questions to be addressed by the applicant, or consequences for marketing authorisation, e.g. appropriate user safety advice/warnings, any restrictions of use.

Unless specific warnings result from the user safety assessment, standard type warnings in the SPC usually do not need to be repeated in this document, it is sufficient to make reference in this report if sufficient warnings are included in the SPC or not. Specific warnings should comply with the ABCD format described in the CVMP guideline on user safety for pharmaceutical veterinary medicinal products (EMA/CVMP/543/03)(e.g. The warnings and safety measures are communicated via the SPC and package leaflet and should inform the user about the following aspects:

a) The concerned risk;

b) What exposure must be avoided to minimise the concerned risk;

c) How to avoid that exposure;

d) What to do in the event of exposure.

If the amount of text included in this section needs to be significant then appropriate subheadings may be included.

Examples:

<The applicant has presented a user safety risk assessment which has been conducted in accordance with CVMP guideline EMEA/CVMP/IWP/54533/2006 (and EMA/CVMP/543/03<version>).>

<The main potential routes of accidental contact with the product have been considered and it was concluded that the most likely are those of accidental self-injection and dermal and/or oral exposure.><The active substance is an inactivated protein and is not infectious>

<<Organism> is not pathogenic for humans and therefore does not pose a risk for the user>

<The excipients including adjuvants are commonly used in other vaccines and do not pose a risk for the user>

<As a result of the user safety assessment the following advice to users/warnings for the user are considered appropriate:

- This product can cause <effect>. <Personal protective equipment consisting of e.g. needle protector should be used when handling the product>. In case of accidental <exposure>, seek medical advice immediately and show the package leaflet or the label to the physician.

- This product can cause eye-irritation. Avoid contact with the eyes. Wear protective glasses. When the product comes into contact with the eyes, rinse immediately with plenty of water.

- Since the product contains mineral oil, the standard warning for mineral oil-containing vaccines is included, appropriately, in the product literature>.

<Based on the above risk assessment the CVMP concluded that the product does not pose an unacceptable risk to the user when used in accordance with the SPC.>

Study of residues

While IVMPs will normally not require studies of residues there may be a need for investigations into the effects of possible residues from adjuvants and/or preservatives. In this case it may be useful to follow the sections on MRLs and residues presented in the pharmaceuticals template (EMA/441473/2015).

In addition, if other substances used in the manufacture of the IVMP, such as formaldehyde (when used as an inactivating agent) or antibiotics used during cell culture, may be present in the final product, an evaluation of the potential levels in the final product may need to be considered. However, while trace amounts of such substances should be evaluated in order to determine that there is no safety risk, such substances are not required to be included in the SPC.

<MRLs>

<Rapporteur to include text>

For an application for a product for food producing animals the MRL status for the active substance(s) and excipients and if appropriate adjuvants, should be presented here.

EMA to include a statement regarding MRL status of excipients, if there are no concerns this will be:

Examples:

<The active substance being a principle of biological origin intended to produce active immunity is not within the scope of Regulation (EC) No 470/2009.

The excipients, including adjuvants, listed in section 2 of the SPC are either allowed substances for which Table 1 of the Annex to Commission Regulation (EU) No 37/2010 indicates that no MRLs are required or are considered as not falling within the scope of Regulation (EC) No 470/2009 when used as in this product.>

If an antimicrobial substance is used as part of the manufacturing process and is present in the final product, e.g gentamicin, a specific sentence to address the issue should be included.

<The <antimicrobial substance> used in the manufacturing process is present at low residual levels (not more than xxxx) in the finished product which is not considered to constitute a risk to the consumer>.

In case of excipients which are not included in the Annex to Regulation (EU) 37/2010 or in the out of scope list but that the rapporteur concluded that they are not pharmacologically active at the doses given to the animal, e.g phenol red, a specific sentence to address the issue should be included.

<The excipient(s) <substance(s)> which are not covered by Regulation (EU) 37/2010 are considered without pharmacological activity at the dose used in the animal (<dose>) and are therefore considered not falling within the scope of the Regulation.>

If concerns were identified by EMA during MRL validation, then rapporteur should address concerns expressed by EMA, if any, and to include text in case of information is missing.

Example:

<New> information on an excipient> or <information that was not considered before> which requires consideration regarding its MRL status, or <starting material remains in high concentration in final product>requires further information from the applicant>.

<Withdrawal period>

<Rapporteur to include text>

In most cases a zero day withdrawal period is expected, in which case this conclusion should be stated:

Example:

<The withdrawal period is set at zero days >

In those rare cases where consideration needs to be given to a withdrawal period it may be helpful to consult the scientific overview and LoQs for pharmaceuticals (EMA/441473/2015).

Interactions

<rapporteur to include text>

Describe if any claims for compatibility with any other veterinary medicinal product are proposed and include information on whether any studies to investigate interactions with any other veterinary medicinal product have been submitted. If studies have been provided, provide a description of the study and conclude on the adequacy of the data to support the safety of any proposed compatible use claim. Include information regarding the use of the product with other veterinary medicinal products and conclude how it should be correlated to the wording of Section 3.8 of the SPC and 3.9: i.e. whether the product can be mixed and administered together (e.g. in drinking water for poultry, or in the same syringe for injection) or whether the product can be not mixed but can be used concurrently, (e.g. at the same time but at different sites of injection), with another veterinary medicinal product. (Consult Guideline on the requirement for combined vaccines and associations of immunological veterinary medicinal products (EMA/CVMP/IWP/594618/2010)) Note also that data from field studies may also be relevant to comment on, e.g. if a vaccine was used under field conditions in the target species that were also vaccinated with other vaccines in accordance with standard vaccination regimes.

If the applicant has not provided data investigating interactions of the immunological veterinary medicinal product with other veterinary products propose to include a statement in Section 3.8 of the SPC that: ‘No information is available on the safety and efficacy of this vaccine when used with any other veterinary medicinal product. A decision to use this vaccine before or after any other veterinary medicinal product therefore needs to be made on a case by case basis’.

Examples

<The applicant has not provided data investigating interactions of the vaccine with any other veterinary medicinal product and therefore proposes to include a statement in Section 3.8 of the SPC that <‘No information is available on the safety and efficacy of this vaccine when used with any other veterinary medicinal product. A decision to use this vaccine before or after any other veterinary medicinal product therefore needs to be made on a case by case basis.’>

Or

<The applicant has provided data investigating interactions of the vaccine with <x> and <y> immunological products. Data provided included <> and indicated that there is <no> risk of interaction when these products are used <before>, <after>, <together>>. <The SPC has been updated accordingly>.

Clinical studies[[2]](#footnote-2)

<Rapporteur to include text>

Relevant guideline: Guideline on clinical trials with immunological veterinary medicinal products EMA/CVMP/IWP/260956/2021.

The purpose of the field safety studies is to demonstrate the safety of the vaccine when used in field conditions where disease, husbandry and housing conditions are similar to those as of farms within the EU for which the product is intended for use. Describe briefly the design of the studies with information on the animals used, dose tested, formulation used, duration of tests and observations. Comment on whether the site(s) chosen and the conditions of those sites were appropriate for the evaluation of the safety parameters (i.e. exposure to the disease). Comment whether animals were in the age range/class intended for treatment as indicated in the proposed SPC. Their serological status should also be mentioned, whether a negative or positive control group was included and whether treated and control animals were managed similarly. Comment on whether (a) representative batch(es) of the product (was) were used and the titre used. Comment on whether observations recorded where appropriate and if the frequency and duration of observations were adequate. Observations should cover local (i.e. size, duration and nature of any lesions at the site of injection) and systemic (i.e. pyrexia, allergic reaction, mortality, anorexia, weight gain, milk/egg production, fertility, etc.) reactions. Summarise adverse events documented and any attempts to determine causality for the adverse events. The results should be evaluated in relation to the safety of the final product under field condition when used as recommended in the proposed SPC. Copy the final, relevant conclusion(s) to the Overall conclusion on safety

If this is an application for a limited market product/exceptional circumstances, indicate where reduced data were acceptable and where not, and why.

If appropriate, pharmacovigilance data can support or replace clinical studies.

Example:

<One pivotal <one/multi> centre <non->randomised, <fully/partly/semi> <blind/open>, <placebo/positive/non->controlled> study of <x> <parallel > group design, conducted to evaluate <insert study objective/indication or part of indication> at <describe dose> in <insert species and describe disease/condition for which the animals need to be treated>. The study was conducted in <insert region>, <country> and did <not> adhere to GCP. Description of results.>

<The study was well designed and conducted and confirmed that the product is safe <insert study objective/indication or part of indication> at <describe dose> in <insert species> and describe disease/condition for which the animals need to be treated>. <Clinical investigations included <pyrexia, mortality, etc.> were carried out daily for <x > days post vaccination. Local reactions such as size, duration, nature of lesions at the site of injection were monitored and recorded for <x> days. Additional investigations included.>

<<None> or <x> animals from the ones vaccinated showed clinical signs and symptoms associated with <x> infection. <No> local reactions were recorded following vaccination.>

At the end of this section, provide an overall conclusion on the clinical trials summarising the strength of support all the studies together provided for the safety of the product, but also any major outstanding issues on these. Other concerns can be mentioned but don’t need to be specified. Flag up any major issues arising from the field studies that should also be reflected in the product information, e.g.: warnings (target animals, user, animals in contact, etc.) or other advice.

Copy the final, relevant conclusion(s) to the Overall conclusion on safety.

Example:

<<One> pivotal field study and < two> supportive published studies were provided to investigate the safety of the product for the proposed indication.>

Brief description of results

<The data show that the product is <not> safe when used at a dose of <x dose> in <target species.>>.

Alternatively provide a brief description of the pivotal study, using the study summary table below whenever suitable to ensure consistency and that key information is included in the scientific overview. Information on any deviations observed should also be included if relevant. Additionally, data on pre-exposure of the animal to the pathogen (country or rearing free of this specific pathogen), housing facilities and observed withdrawals can be mentioned if appropriate.

|  |
| --- |
| ***Reference and Study title***Include the dossier reference (study title as it appears on the front of the study summary) |
| Objectives | Specific objectives/aims of the study. |
| Study sites | Setting/location. Single/multi-centre. |
| Study design | Randomised/ blinded/ placebo or active-controlled/ superiority/ non-inferiority. |
| Compliance with regulatory guidelines  | GCP.  |
| Animals | Species, sex, genetic (if relevant) physiological status (with or without MDA, conventional/SPF, laying/broilers, fattening/piglets/sows, pregnant/non pregnant,…), age, allocation (randomly or not, how much groups, number of animals in each group, ….) |
| Eligibility criteria | Eligibility (disease status). |
| Test product | Name, active substance Which one was used – pilot batch, commercial batch,…, which titre (if not minimum, which justification is provided, Dose administered/vaccination regimen.Method of administration.  |
| Control product/ Placebo |
| Vaccination scheme |  |
| Safety end points  | State clearly the observations made were appropriate to investigate the safety of the product.  |
| Statistical method | Comment on whether the methods used were appropriate or not. which test(s) and why they were chosen, relevant parameters chosen (alpha, beta values, significance limits) |
| **Results** |
| Outcomes-Safety observations | For each investigated observation provide a summary of the results for each group, the estimated treatment effect size, P-value, and its precision (95% CI). State results in absolute numbers where possible, in addition to %. |
| Adverse events | List the adverse events and incidence rate for investigational veterinary product and control product. |
| **Discussion** |
| Discussion/conclusions further to assessment | Summarise the assessor’s interpretation of the results. This should take account of the aims of the study and address the safety of the test product.  |

Environmental risk assessment

<Rapporteur to include text>

This section should provide a brief overview of the ERA, highlighting significant findings/shortcomings/omissions. If any of the issues are considered key, then it may be appropriate to describe these in a little more detail. The ERA for an immunological must address the risks arising from each of the components of the product, not just from live organisms in vaccines.

To address the risk of live vaccinal organisms (part A below) the EMA Note for guidance on Environmental risk assessment for immunologicals veterinary medicinal products (EMEA/CVMP/074/95-Final) should be followed.

To address the risk of components other than the live vaccinal organisms (part B below), the ERA described for pharmaceutical substances outlined in CVMP/VICH guidelines (VICH guidelines GL6 and GL38 and CVMP guideline on the Environmental Impact Assessment for Veterinary Medicinal Products in support of the VICH guidelines GL6 and GL38 (EMEA/CVMP/ERA/418282/2005<version>)), is to be followed (please also see template for pharmaceutical products).

If no phase II assessment is required, the reason for this should be made clear.

<Considerations for the environmental risk assessment>

Part A. Environmental risk assessment of live vaccinal organisms:

where possible standard sentences should be used.

Examples (one or more of the following sentences might apply):

<There is no capacity of live organisms to transmit to non-target species.>

<There will not be shedding of life product (route, numbers, duration).>

<The live product cannot survive, establish and disseminate in the environment.>

<The live product is not pathogenic to other organisms.>

<The life product organisms have no potential for other effects.>

<The components (all) and/or excreted metabolites of the product are not toxic.> (see part B below)

A

1. Hazard identification

2. For products with hazards identified in point 1 above, to provide an estimate of the likelihood (probability and frequency) of hazard(s) being manifested

3. Assessment of the consequence of a hazard occurring

To complete for products with hazards identified in point 1 and 2 above

4. Assessment of the level or risk

To complete for products with hazards identified in point 1, 2 and 3 above:

Evaluation or risks associated with each of the hazards identified in point 1

B

Environmental risk assessment of components other than the live vaccinal organisms

Substances that constitute a specific risk to the environment (e.g. thiomersal) should be specifically addressed including information on the levels released in the environment

For products that enter Phase II, if the trigger for a phase II assessment is not related to the risk associated with live vaccinal organisms, then the Phase II assessment for pharmaceuticals can be considered.

<The active substance is a natural substance, the use of which will not alter the concentration or distribution of the substance in the environment.>

<The veterinary medicinal product will only be used in non-food animals.>

<The veterinary medicinal product will be used to treat a small number of animals in a flock or herd.>

<The active substance is extensively metabolised in the treated animal.>

<The active substance is completely degraded in manure/slurry/poultry litter.>

<The initial Predicted Environmental Concentration in soil (PECsoil, initial) is lower than (x) 100 µg/kg.>

<The Environmental Introduction Concentration (EIC) is lower than (x) 1 µg//l.>

If environmental risks are not as low as reasonably practicable, RMMs can be considered at this stage. If it is considered that there is insufficient knowledge to come to a satisfactory conclusion, further studies in Phase II assessment should be undertaken.

If it can be concluded that no risk for the environment is expected, the following sentence should be used:

<Based on the data provided the ERA can stop at Phase I. <Product name> is not expected to pose a risk for the environment when used according to the SPC.

<Product name> is expected to pose a negligible risk to the environment when used as recommended>>

For those ERAs where a risk to the environment cannot be excluded/ruled out the following sentence should be used followed by a short description of the reasons and the required actions:

<Based on the data provided for ERA Phase I and Phase II a risk to the aquatic and/or terrestrial environment and/or groundwater cannot be excluded when used according to the SPC.>

<The following risk mitigation measures are proposed for <Product name>:>

For those substances that are not PBT (persistent, bioaccumulative and toxic) or vPvB (very persistent, very bioaccumulative) this will not be mentioned.

For those substances that are PBT or vPvB the following phrase should be applied, followed by the reason why the criteria are fulfilled:

<active substance> is considered to be (a potential) PBT (persistent, bioaccumulative and toxic) and/or vPvB (very persistent, very bioaccumulative).

For DNA plasmid vaccines, the risk of integration of the plasmid into the genome of vaccinated animals should be evaluated, in particular for food-producing species. Potential risk(s) that such immunological veterinary medicinal products might pose on human health and the environment (including plants and animals) should be discussed here.

<Environmental risk assessment for products containing or consisting of genetically modified organisms>

<Rapporteur to include text>

Delete section and title, if not applicable.

*Address compliance with Directive 2001/18/EC (Annex II), interaction with competent authorities etc.*

If applicable, the following standard sentence should be maintained:

Examples:

<The product> falls within the scope of Directive 2001/18/EC on the deliberate release into the environment of genetically modified organisms. Detailed information on the possible risks for humans and for the environment has <not> been provided.

If limited market application: If the vaccine contains a genetically modified organism (GMO) according to Directive 2001/18/EC as amended, the full set of data with regard to Directive 2001/18/EC should be provided. It is however acceptable to fulfil part of the requirements through data which has been gained with similar GMO constructs already authorised.

Text should include reflections of the following points in addition to points described in point 3.2.2 of CVMP guideline on live recombinant vector vaccines for veterinary use (EMEA/CVMP/004/04-FINAL):

Identification of the characteristics of the recipient organism which are relevant to the assessment of the GMO in question. Identification of any known risks to human health and the environment resulting from the release into the environment of the recipient non-modified organism.

Assessment of whether the genetic modification has been characterised sufficiently for the purpose of evaluating any risks to human health and the environment.

Description of the result of the genetic modification in the modified organism.

Genetic <and phenotypical> stability

Reversion to virulence

Estimation of the likelihood (probability and frequency) of recombination event between the vaccine virus strain and the field strain

Identification of any new risks to human health and the environment that may arise from the release of the GMO in question as compared to the release of the corresponding non-modified organism based on the environmental risk assessment carried out in accordance with Annex II.

A conclusion on whether the GMO in question should be placed on the market and under which conditions, should be provided. These conditions should be specified if applicable. The conclusion should clearly address the use proposed and the risk management (e.g. if appropriately reflected in the SPC). In the case that it has been concluded that the GMOs should not be placed on the market, a brief justification should be provided and should be copied in the overall conclusions.

<The proposed vaccine is compliant with Directive 2001/18/EC.>

<The applicant has <not> provided detailed information on the possible risks for humans and for the environment.>

<<x> does <not> infect humans and is restricted to the infection of <animals> of the order <e.g. Artiodactyla>.>

<The vaccine strains were generated by <e.g. two targeted deletions identical for (x) and do <not> contain any foreign sequences. <The deletions minimise the risk for reversion to virulence>.<Accordingly, reversion to virulence studies (in vivo) did not show any tendency for genetic instability or reversion>.

<The vaccine virus was <not> shed from vaccinated animals via secretion or excretion routes except in trace amounts via <e.g. milk> for a <limited> time span. <Animals> fed on this milk did <not> develop any signs of infection or antibodies against<>. Similarly, commingling of sentinels with vaccinated animals did <not> lead to seroconversion of the sentinels. Accordingly, <no> <a> biologically relevant spread of the vaccine viruses into the environment could be detected.>

<Taken together, any risk emerging from the use of the <attenuated> <vaccine> viruses is expected <not> to be negligible for humans and <e.g. low> for the environment. >

Overall conclusions on the safety documentation

<Rapporteur to include text>

Briefly summarise the conclusions for each safety section normally without repeating individual study findings, and review concerns raised in the assessment of the safety dossier to ensure these are taken into account in the benefit-risk assessment. In respect to the overdose, one and repeated dose studies, alternatively to describing the summary and conclusion in text an overview table can be presented. Include information as to whether the product might adversely affect the immune response of the target animal or of its progeny, and therefore justify the need and/or adequacy of suitable tests on the immunological functions that were carried out. If the product is a live vaccine or contains a GMO describe the additional investigations and on basis of results provided, include a conclusion on the level of risk posed by the product as per different investigations and their acceptability.

Warnings in the SPC usually do not need to be repeated in this document, it is sufficient to make reference in this report if sufficient warnings are included in the SPC or not.

At the stage of the List of questions, concerns or information gaps addressed in the List of Questions should be briefly highlighted here.

Examples:

<The applicant has provided (x) pivotal pre-clinical studies to investigate the safety of a) a (x) fold overdose, b) one dose, c) repeated administration of one dose to target animal species of the minimum recommended age using <maximum titre> via the <recommended route>. Batches used in these studies were <pilot>, <routine>.>>

<On the basis of the results it was concluded that the safety of the targeted animals when the product is administered according to the recommended schedule and via the recommended route is <not> acceptable.>

<Reproduction safety was <not> investigated. The product was found <not> to be safe when used in <pregnant> animals at <stage of gestation>, <lactating animals>, <male breeding animals>, <laying hens>. The SPC has been amended to accordingly. >

<As this is a live vaccine the applicant also conducted studies to establish the potential for spread and dissemination of the vaccine strain>. Reversion to virulence <and the recombination and the genomic re-assortment of the strain(s)> was also investigated and results showed that the potential risk is <significant> <low> and <not> <acceptable>.> <The biological properties of the vaccine strain were described adequately and found to be <not> acceptable. >

<As this product contains a GMO active substance the applicant conducted studies to investigate.>

<The product <might> <is not expected to adversely> affect the immune response of the target animals or of its progeny, and therefore <no> suitable tests on the immunological functions were carried out.>

<The applicant did not provide data on <…>. This was in accordance with <…> and was considered acceptable.>

<The data presented are considered adequate to characterise the safety profile of the vaccine <and the active substance> as acceptable.>

<A user safety assessment in line with the relevant guidance document has been presented. Based on that assessment, the potential health risk of the product to all users (adults and children) is considered low and acceptable when used in accordance with the SPC.>

<Based on the assessment presented, the product does <not> pose an unacceptable risk to the user when used in accordance with the SPC. The appropriate warnings for the user have been included in the product literature.>

<<Product name> is not expected to pose a risk for the environment when used according to the SPC.>

<<Product name> is expected to pose a negligible risk to the environment when used as recommended.>

<The worst-case scenario for user safety is <self-injection>.>. <Appropriate safety advice/warning statements are included in the SPC to mitigate the risks.> <The proposed <measures> <warnings> are not considered adequate to mitigate the risk to the user, and the applicant is requested to reconsider <packaging> <safety advice/warnings>. <The CVMP concluded that <product> is not expected to pose a risk <to the user> < to the environment> when used in accordance with the SPC.>

<A final conclusion on <user safety> <environmental safety> <safety> cannot be made until the outstanding issues are addressed.>

<An appropriate environmental risk assessment was provided. The product is not expected to pose a risk for the environment when used according to the SPC.>

If GMO product

<The vaccine virus strains were <not> shown to be genetically <and phenotypically> stable <e.g. in studies>,>, with <e.g. very low>> risk of reversion to virulence.>

<A recombination event between the vaccine virus strain and the field strain is <e.g. possible, unlikely>> <not> <leading to the generation of a recombinant virus strain.>.>

Part 4 – Efficacy documentation (pre-clinical studies and clinical trials)

General requirements

<Rapporteur to include text>

As introduction, the relevant elements pertinent to the efficacy assessment (e.g claims, vaccination scheme, minimum age, OOI, DoI) of the product under consideration should be presented, in order to understand the approach taken, without repeating the general description of the product. Reference can be made to the general description in the Introduction of the Scientific Overview document, however information on e.g. proposed indication(s), target species and dosing could be included here.

If there are several target animal species/indications/pharmaceutical forms, data for these species should always be presented in the same species/indication/pharmaceutical form order. Comment on whether there are specific Ph. Eur. monographs that the applicant needs to adhere to. Comment on batches used in the study (routine production scale or pilot) and whether the content of the doses used was the minimum recommended.

This section should refer to data for the target animal species only. If scientific advice was given, briefly outline what the advice related to. Comments whether the advice was followed or not should be made when discussing the relevant study and if not followed, explain the deviation and whether it was justified or not.

Example:

<The vaccine is intended to <claims> when administered to <target species, minimum age> from <x> of age onwards. Immunity is intended to be established <x> weeks further to a <e.g single injection> lasting for x months>.>.

<Efficacy was demonstrated in compliance with the Regulation (EU) 2019/6, and the European Pharmacopoeia (Ph. Eur.) chapter 5.2.7>. as well as <specific monograph applicable to product>.

<Scientific advice was given concerning <insert in brief terms what the advice was>,

If this is an application for a limited market product or multi-strain dossier, indicate where reduced data were acceptable and where not, and why.

Challenge model

Provide here a brief description of the challenge model i.e. origin, epidemiological relevance of the challenge strain(s), titre, route and comment whether it was appropriate for the purpose of the efficacy studies. In so far as possible, the conditions under which the challenge is carried out in the pre-clinical trials shall mimic the natural conditions for infection, for example with regard to the route of administration of the challenge. Describe here the model used and its justification and any studies or tests that have taken place to confirm its validity. If there are any concerns describe them briefly and how they may impact the outcome of the efficacy studies.

Example:

<The <X> challenge strain was used. The strain originated from <e.g an infected sheep> and was administered <intranasal> to animals as a <single> dose containing <X>ml. <One> study was conducted to validate the challenge model in <sheep>>.

<The challenge model was <not> considered adequately validated and therefore <not> appropriate for using in the efficacy trials in order to mimic the natural conditions for infection.> <As a result the following concerns are raised over some of the results seen in the pre-clinical trials :>

Efficacy parameters and tests

Provide here brief information on the efficacy parameters and the selected tests to evaluate them as chosen by the applicant; comment whether they are appropriate for this purpose if they have been adequately validated and the eligibility of the selected tests for assessment of the efficacy of the vaccine.

Example:

<The efficacy parameters as provided <e.g. in Ph. Eur.> or if not provided <as chosen by the applicant>, investigated in the efficacy studies are <e.g. the level of virus neutralising antibody titres > <viral load>. <The tests performed to evaluate them were < e.g virus neutralisation test >, < ELISA test>, <haemagglutination inhibition test >, <virus isolation> etc.>. <The parameters chosen are <not> considered appropriate for evaluating the efficacy of the product. <No> Validation results were presented and <confirm > do not confirm> and that the tests chosen are <not> adequately validated to provide reliable results. <At this stage the justification for the choosing the main efficacy parameter is not adequate and the applicant should address how it can be representative of the proposed claims>.

Efficacy documentation

Provide briefly an overview of pivotal studies conducted to support the efficacy of the product.

Example:

<X studies were conducted to investigate the efficacy of the product and included <z> pre-clinical studies and <y> clinical trials. Laboratory studies were well documented and carried out in <target animals> of the minimum age recommended for vaccination, using <pilot> <production> batches containing <Production> <pilot> batches were used in the < clinical> trials.>

Alternatively, please populate the overview table for the purpose of providing a brief overview of the amount of data i.e. list of pivotal efficacy trials.

| **Study reference** | **Study title**  | **Batch used**  |
| --- | --- | --- |
|  |  |  |

Other trials (supportive/pilot/exploratory) should only be briefly summarised, if relevant. The assessor should indicate why studies could not be considered relevant (e.g. inappropriate study design, dose, etc.).

Pre-clinical studies

<Rapporteur to include text>

Please note that guidance provided in this section is applicable for each pre-clinical trial to be described under the appropriate heading.

Provide a brief description of the efficacy trials carried out in the laboratory. These shall be controlled trials including untreated control animals. Efficacy shall be demonstrated for each category of each species recommended for vaccination, by each recommended route of administration and using the proposed schedule of administration. Any claims regarding onset and duration of protection shall be supported by data from the trials. Studies or a discussion on the influence of passive acquired and maternally derived antibodies on the efficacy of the vaccine should be included if relevant.

For each pivotal study provide a description, using the study summary table below whenever suitable to ensure consistency and that key information is included in the scientific overview. For each trial the, following details are needed:

|  |
| --- |
| ***Reference and Study title***Include the dossier reference (study title as it appears on the front of the study summary) |
| Objectives | Specific objectives/aims of the study. |
| Study design | Randomised/ blinded/ placebo or active-controlled/ superiority/ non-inferiority. |
| Compliance with regulatory guidelines  |  |
| Animals | Species, sex, physiological status (with or without MDA, conventional/SPF, laying/broilers, fattening/piglets/sows, pregnant/non pregnant,…), age, allocation (randomly or not, how much groups, number of animals in each group, ….). |
| Eligibility criteria | Eligibility (disease status). |
| Interventions: Vaccine  | Name, active substance, which one was used – pilot batch, commercial batch, …, which titre (if not minimum, which justification is provided).Nominal dose rate/regimen.Method of administration.  |
| Control product/ Placebo |
| Vaccination scheme |  |
| Challenge | (if relevant): strain, titre, route of administration,… |
| Efficacy parameters | State clearly the efficacy parameters used to investigate proposed claims.  |
| Statistical method | Which test(s) and why they were chosen, relevant parameters chosen (alpha, beta values, significance limits) |
| ***Results*** |
| Efficacy parameter  | For each efficacy parameter, please provide a summary of the results for each group, P-value, and its precision (95% CI). State results in absolute numbers where possible, in addition to %. preferably in the same order than listed above. |
| ***Discussion***(delete this section in the table if the discussion is described in textual format in the section below the table) |
| Discussion/conclusions further to assessment | Summarise the assessor’s interpretation of the results. This should take account of the aims of the study and address the efficacy and safety of the test product.  |

Alternatively provide a text description of the study commenting on the validity of the study design for investigating the proposed treatment (product and dose regimen) for the intended indication, including an evaluation of the appropriateness of the statistical methods used for each study in the sections. If the study deviates from guidance or specific Ph. Eur. monographs indicate if this is has been justified or not. Comment on the dose, number of animals (treated/vaccinates and controls) and batch used in the study and if appropriate.

Comment on the study results for the efficacy parameters and relate these results to the efficacy claims. Comment on the reliability of results in consideration of the quality of the study. Highlight clearly those outstanding issues, which are of pivotal importance for determining whether the study brings evidence for an effect that can be regarded clinically relevant (major outstanding issues). Ensure that clear information on results and conclusions are provided for each study.

Dose determination

Summarise and conclude here on the justification provided by the applicant for the recommended dose and any dose confirmation studies conducted.

<Rapporteur to include text>

Example:

<The proposed dose of <…> for <product> was established based on <the findings of a dose determination study>

Onset of immunity

<rapporteur to include text>

Provide a brief description of the pivotal study/ies investigating the onset of protection after administration of the product.

Examples:

<<x> studies were carried out in < species> < age> <in compliance with Ph. Eur. requirements> to investigate the onset of protection, <one> by <each> the recommended administration route.>

<In study <dossier reference (study title may be as short version and study number)> <x> groups of <y> animals of <age > were used. A vaccine dose of <x> <e.g log10 EID50 per dose> from <pilot> <production scale> batch, was administered to groups <x> <y> respectively by the <recommended> route. Groups <z> and <t> were unvaccinated. All of the vaccinated groups and <one > of the unvaccinated groups were challenged with virulent <x> <y> weeks after vaccination. Following challenge animals were investigated for the following clinical signs <pyrexia>, <lethargy>, etc.>.

<Results: Most of the vaccinated <animals> in groups <> and <> were found to have < neutralising antibodies> to <the product’s strain> on the day before challenge. <X> days after challenge <>% of the vaccinated animals in group <> had normal <levels of neutralising antibodies> and were considered to be <not> <protected against the challenge. Vaccinated animals <never> shed virus in their nasal secretion. There was <no> viraemia in all but <x> vaccinated animals that lasted for up to <x> days after challenge. <All> <%> of control animals had <e.g viraemia> for <x> days after challenge. They <e.g shed virus intermittently> in their <nasal secretion> from day <e.g 2 to 14>. <None> of the challenged controls were considered to be protected. <No special clinical signs were noticed except a moderate increase in temperature in <vaccinates>. <x%>of <vaccinated>, <controls> animals were pyrexic for <> days following challenge.>

<It was concluded that vaccination by the recommended route with dose <less> <more > than the minimum recommended content as in the SPC was <not> efficacious and <met> <did not meet> efficacy requirements <x> weeks post vaccination.>

Duration of immunity

Describe here briefly the design of the pivotal duration of immunity studies under laboratory conditions, with clear information about the duration of protection (interval between administration of vaccine and observed protection against challenge) and whether it is from the basic vaccination scheme or from the re-vaccination scheme.

Describe how protection has been investigated, i.e. based on challenge or on surrogate to protection (serology correlated to protection).

Comment on whether it covers the active or passive immunity or both, basic dose tested, the batches used (pilot, routine), duration of the tests, conditions, etc. The validity of the study model should be commented upon and the results evaluated in relation to the recommended use of the final product.

Duration of immunity allows either to justify the vaccination scheme (in particular the time of booster); if no booster vaccination is foreseen, it should normally cover the period at risk; any deviation to this should be commented by rapporteur.

<Rapporteur to include text>

Examples:

<The efficacy of the proposed re-vaccination scheme/booster dose, if one is proposed, should be supported. If the scheme for revaccination differs to that of primary vaccination (i.e. a single dose for yearly revaccination, compared to a two-dose basic vaccination scheme), the ability of the booster dose to protect until the subsequent booster should be demonstrated. A conclusion on whether the proposed basic vaccination scheme and subsequent revaccination schedule is adequately supported should be commented on by the rapporteur.>

For duration of immunity studies under field conditions, the relevant study should be described under the section for clinical studies. Relevant EMA note for guidance on duration of protection achieved by veterinary vaccines (EMEA/CVMP/682/99) should be taken into consideration.

Examples:

<<Two> studies were carried out in <x day old > <species> to investigate the duration of immunity, by <each> recommended administration route:

In study < include the dossier reference. (study title as it appears on the front of the study summary) > <one> group of <x> and one group of <y> of <x> <one x-day-> old animals> were used. A vaccine dose of <x log10 EID50> < per dose> from a <pilot> <routine> batch was administered to group 1 by the < recommended >route. <Groups <3> and <4> were unvaccinated>. Animals in groups <1, 2 and 3> were challenged with virulent <x> strain, <x> weeks after vaccination.

Results : <> days after challenge <x>% of the vaccinated animals in group <> and <>% of the animals in group <> had <normal> <significantly raised> <levels of VN> >and were considered to be <not to be> protected against the challenge. <None of the challenged controls in group <3> were considered to be e.g. protected>.

Conclusion: In this study <x> weeks post vaccination, which is the claimed duration of immunity, <significant> <some> <no> difference in protection was demonstrated between vaccinated groups and controls, supporting <not supporting> sufficiently the proposed duration of immunity. Duration of immunity was <not> investigated in MDA-positive <animals>. >

Maternally derived antibodies (MDA)

<rapporteur to include text>

If vaccination is recommended in animals at an age at which maternally acquired immunity may still be present and may interfere with active immunity development, describe here any studies performed to determine whether or not such interference occurs. If interference occurs comment on how it is addressed by the applicant. Comment whether, batches containing the minimum active content were used and if not the justification. Relevant guidance can be found in the reflection paper on the demonstration of a possible impact of maternally derived antibodies on vaccine efficacy in young animals (EMA/CVMP/IWP/439467/2007). Describe here any data presented from scientific publications or from clinical trials relevant to MDA interference investigations.

Conclude whether the SPC should be amended.

Example:

<<x> studies were carried out in MDA-positive <animals> to investigate the < dose response> <onset of protection>, by <the recommended > administration route:

In study <name of the study> <x> groups of animals (<species> < age)> were used. From those <x> groups included <x> MDA positive animals (<species>, <age)>). Vaccine doses of <x> log10 EID50 per dose were administered to groups <> respectively by <recommended> < route>. Groups <y and z> were unvaccinated. <All> of the vaccinated groups and one of the unvaccinated groups (group y) were challenged with virulent <challenge strain> <x> weeks after vaccination. <x> days after challenge <>% of the vaccinated animals in groups <> and <none> of the controls had <normal /high / levels of virus neutralising antibodies> and were considered to be <not be> protected against the challenge. <None of the challenged controls in group <4> were considered to be protected>. <All> of the non-vaccinated, non-challenged animals <in group 5> showed <normal> <levels of virus neutralising antibodies>.

<It was concluded that vaccination by the recommended route with doses of the minimum content recommended in the SPC were efficacious and met the Ph. Eur. efficacy standard including MDA positive animals>.>

Interactions

It should be documented whether interactions with other vaccines that may be used concomitantly have been investigated if applicable. The efficacy aspects of any studies presented in support of compatibility claims should be summarised and concluded on. The rapporteur should conclude on the acceptability of any proposed compatible use claims. It should be noted that this will also involve assessment of whether the efficacy of the (authorised) product for which compatibility is claimed is affected by concurrent or simultaneous use with the IVMP under evaluation.

Clinical trials

<Rapporteur to include text>

Relevant guideline: Guideline on clinical trials with immunological veterinary medicinal products EMA/CVMP/IWP/260956/2021.

In general, pre-clinical studies shall be supported by trials carried out in field conditions. When pre-clinical studies fully support the claims made in the summary of product characteristics, trials carried out in field conditions are not required. Unless justified, results from pre-clinical trials shall be supplemented with data from clinical trials. In cases where pre-clinical trials cannot be supportive of efficacy, the performance of clinical trials alone may be acceptable.

If data from clinical efficacy trials are not provided, please include the justification given by the applicant and conclude whether or not it is acceptable.

If clinical efficacy trials are provided, state here the pivotal trials only. Indicate the location (e.g. Member States), briefly summarise the protocol and the outcome. The same level of information as for laboratory studies is necessary in this section.

If applicable, include separate paragraphs for different indications, target species, species subcategory and/or pharmaceutical forms, and follow the same order of species/indications/formulations throughout the section. Use subheadings if it facilitates reading.

Provide a brief description of the pivotal study, using the study summary table below whenever suitable to ensure consistency and that key information is included in the scientific overview.

|  |
| --- |
| ***Reference and Study title***Include the dossier reference (study title as it appears on the front of the study summary) |
| Objectives | Specific objectives/aims of the study. |
| Study design | Randomised/ blinded/ placebo or active-controlled/ superiority/ non-inferiority. |
| Study sites | Setting/location. Single/multi-centre. |
| Compliance with regulatory guidelines  | GCP.  |
| Animals | Study population: number of study animals, species, age, sex, physiological status (with or without MDA, conventional/SPF, laying/broilers, fattening/piglets/sows, pregnant/non pregnant,…), age, allocation (randomly or not, how much groups, number of animals in each group, disease condition, high number of animals excluded or lost to follow up during the study, ….) |
| Eligibility criteria | Eligibility (disease status). |
| Interventions: Vaccine  | Name, active substance, Which one was used – pilot batch, commercial batch,…, which titre (if not minimum, which justification is provided. Nominal dose rate/regimen.Method of administration.  |
| Control product/ Placebo |
| Vaccination scheme |  |
| Challenge | (if relevant): strain, titre, route of administration,… |
| Efficacy parameters | State clearly the efficacy parameters used to investigate proposed claims.  |
| Statistical method |  Which test(s) and why they were chosen, relevant parameters chosen (alpha, beta values, significance limits. |
| ***Results*** |
| Efficacy parameters  | For each efficacy parameter, please provide a summary of the results for each group, P-value, and its precision (95% CI). State results in absolute numbers where possible, in addition to %. preferably in the same order than listed above. |
| ***Discussion***(delete this section in the table if the discussion is described in textual format in the section below the table) |
| Discussion/conclusions further to assessment | Summarise the assessor’s interpretation of the results. This should take account of the aims of the study and address the efficacy and safety of the test product.  |

Modifications to the study summary table above may be required depending on the type of product and study design.

If the same study design was used in several field studies (e.g. studies investigating different parasites for the same target species), this should be clearly stated; it is not necessary to repeat this information for each study.

Add information on major deviations from the study protocol.

Introduce the results of the efficacy parameters, as applicable to support proposed claims.

Evidence (or lack) of significant interactions with concomitantly administered products should be reported.

Comment on the validity of the study design for investigating the proposed claims (product and dose regimen) for the intended indication, including an evaluation of the appropriateness of the statistical methods used. Indicate if the study complies with the VICH GCP-Guideline (and other specific guidelines, such as the Guideline on clinical trials with immunological veterinary medicinal products EMA/CVMP/IWP/260956/2021

or not. If the study deviates from guidance, indicate if this has been justified or not and can be accepted.

Comment if there was sufficient exposure to the field pathogen(s) or whether a natural disease outbreak occurred during the field trial, to enable conclusions to be drawn regarding efficacy under field conditions. Comment on the study results for the efficacy parameters (size of treatment effect and confidence interval) and relate these results to the primary objective. Comment on the reliability of results in consideration of the quality of the study. Highlight clearly those outstanding issues, which are of pivotal importance for determining whether the study brings evidence for an effect that can be regarded clinically relevant (major outstanding issues). Ensure that clear information on results and conclusions are included.

Conclude briefly on the study by indicating whether it fulfilled its objectives, at least the primary objective, and whether the study therefore provides solid/partial/strong/weak/no evidence for the effectiveness of the product (in line with relevant guidelines for the indication, where available). Indicate the impact of the results on the SPC.>

Examples:

<One pivotal <one/multi>centre <non->randomised, <fully/partly/semi> <blind/open>, <placebo/positive/non->controlled study of X <parallel/ > group design, conducted to evaluate <insert study objective/indication or part of indication> at <describe dose> in <insert species and describe disease/condition for which the animals need to be treated>. The study was conducted in <insert region>, country and did <not> adhere to GCP.>

Description of results

<Results showed that in all groups vaccinated with the product <% >protection against the natural challenge at <x> weeks was obtained whereas <X% > <100%> of controls were found to be unprotected following challenge.>

<The study was well designed and conducted and confirmed that the product is effective <insert study objective/indication or part of indication> at <describe dose> in <insert species and describe disease/condition for which the animals need to be treated>.>

At the end of this section, provide an overall conclusion on the field trials summarising the strength of support all the studies together provide for the proposed indication, but also any major outstanding issues on these. Other concerns can be mentioned but don’t need to be specified. Flag up any major issues arising from the field studies that should also be reflected in the product information,

Copy the final, relevant conclusion(s) to the Overall conclusion on efficacy.

If this is an application for a limited market product/exceptional circumstances, indicate where reduced data were acceptable and where not, and why.

<<One> pivotal field study and < two> supportive published studies were provided to investigate the efficacy of the product for the proposed indication in the field.>

Brief description of results

<The data showed that the product is effective for <insert the acceptable indication> at a dose of <dose> in <target species>. The data do not support the proposed indication for <insert rejected indication>.>

Overall conclusion on efficacy

<Rapporteur to include text>

<Briefly summarise the findings conclusions/outcome of each efficacy section under the appropriate headings, highlighting the main findings/concerns raised in the assessment of the efficacy dossier to ensure these are taken into account in the benefit-risk assessment.

A clear conclusion should be drawn on the data presented, indicating both the main strengths and the weaknesses of the dossier, and which claims have been supported by data.

If outstanding concerns remain, major concerns should be indicated and need for additional data briefly noted (explanations should be in the section where the insufficient study is described). Other concerns can be mentioned but don’t need to be specified. This information should be taken into account for the benefit-risk assessment.

If it is possible to address the objections by risk management measures (e.g. amending the SPC), this must be stated (e.g., rewording of indication, addition of contra-indications or special precautions for use).>

Examples:

<The dose of <xx> was established based on a number of dose finding studies <range: >, and supported by the onset of immunity studie(s).>

<The results from <two>laboratory and <x> field trials show that the product is effective for <indications> at the proposed dose of [insert dose] in [target species]. <However, deficiencies in the study design and analyses preclude any final conclusion on the proposed indication for [insert rejected indication]>

<Onset and duration of immunity were similar with a vaccine at <e.g 103 and 104 > TCID50/dose except for the<e.g. prevention of leukopenia> for which the <higher> dose was more effective. Results supported a primo-vaccination at <x > months of age with<x TCID50/>dose. The onset of immunity was investigated in <x-months-old > <animals>. This was considered acceptable. The annual re-vaccination scheme was supported by <>.

<MDA did <not> interfere with vaccination>.

<X> clinical studies were undertaken in <x herds>. These clinical studies did <not> provide acceptable support over the efficacy of the vaccine. >

<In conclusion, the product has been shown to be efficacious for <active> <passive> immunisation of <target species> from <minimum age> to <claim>.>

<The product has been shown to have an onset of immunity x weeks after vaccination, which was demonstrated in <animals of minimum recommended age> and duration of immunity of <x> months.>

Part 5 – Benefit-risk assessment

Introduction

For preparing the benefit-risk assessment the CVMP recommendation on the evaluation of the benefit-risk balance of veterinary medicinal products (EMEA/CVMP/248499/2007) should be taken into account.

Provide brief summary of the main characteristic of the product including product name, active ingredient(s), formulation(s), intended use and target species, proposed withdrawal period.

Include a brief description of the mode of action, immunological properties and the confirmed dose.

Add information on the basis for the application, e.g. new active component, limited market product, application under exceptional circumstances.

*For applications submitted according to Article 23 (limited markets) the benefit/risk assessment should clearly state why the availability of the product outweighs the risk inherent in the fact that certain safety or efficacy documentation has not be provided. This is also valid for applications submitted according to Article 25 (exceptional circumstances) but also including lack of quality documentation.*

<Rapporteur to include text>

Examples:

<Product name> is a<n> <presentation> containing <active substance>. <The active substance is innovative/known>.

<The active substance, <vaccine common name>, is <mode of action/class of substance>. <The product is intended for use in <species> for < indication(s)>. The <proposed><effective> dose of <insert dose, route of administration, and vaccination scheme/dosing frequency> <remains to be confirmed><has been confirmed>

<Product name> provides a new treatment principle/ is innovative because...>.

<The application has been submitted in accordance with Article <Article no> of Regulation (EU) 2019/6 <(full application, abridged application (< hybrid, for combination veterinary medicinal products, informed consent, based on bibliographic data, for limited markets, in exceptional circumstances>).>

*If limited market (Art. 23)*<The application was submitted under Article 23 of Regulation (EU) 2019/6 (limited markets). Reduced data requirements therefore apply and have been considered in the assessment. These reductions relate to <safety><efficacy>>.

*If exceptional circumstances (Art. 25)*The application was submitted under Article 25 of Regulation (EU) 2019/6 (exceptional circumstances). Reduced data requirements therefore apply and have been considered in the assessment. These reductions relate to <quality><safety><efficacy>.

Benefit assessment

Direct benefit

<Rapporteur to include text>

Summarise very briefly the outcome of the evaluation regarding the claimed benefits/indications of the product, on the basis of objectives and endpoints in clinical GCP trials, or laboratory trials or other studies/publications where justified, as applicable. These could relate to:

* Direct benefits such as disease prevention, clinical or subclinical disease treatment, prevention or reduction of infection, mortality or clinical signs and/or lesions of the disease/disease complex,
* Improvement of the clinical condition, or
* Reduction of the risks of excretion and transmission of a disease (horizontal, vertical) to other animals.

The summary on direct benefits should be linked to the intended use of the product and should address:

The indication(s) including effective dose/vaccination scheme/route of administration, and how it has been demonstrated (demonstrated in (a) pre-clinical/clinical study/studies without repeating details or study findings.

Deficiencies in the demonstration of the efficacy should also be briefly summarised here (e.g. study deficiencies, lack of statistical support and/or questionable clinical relevance for the proposed claims, dose, target species/subpopulation).

Main benefits should also include e.g. control of an enzootic zoonotic disease, reduction of the risk of transmission to man.

Deficiencies identified and conclusions must be consistent with the List of questions (D120)/List of outstanding Issues (D180)/ final conclusions on the application (D210), dependant of the stage of the assessment.

Examples:

<The <proposed> benefit of <Product name> is its efficacy in <proposed indication, which was <investigated><established> in <a large number of> well designed <pre-clinical and/or clinical> studies conducted to an acceptable standard. <However, concerns remain about < (e.g. the correct dose/efficacy a certain target population(s)…)>, which currently preclude firm conclusions.>

<Well designed clinical trials conducted in accordance with GCP demonstrated that the product is efficacious in <demonstrated indication>.

<Well designed <pre-clinical> studies <conducted in accordance with GLP> demonstrated that the product is efficacious in <demonstrated indication>.

<<Product name> has been shown to be of value in the treatment of <disease>, which causes ….>

<The onset of immunity is…>

<The duration of protection is …>

<The level of protection in a herd has been shown to be x %.>

<The cure rate is … >

<The benefit for the animal is … >

<The product has been shown to alter the physiological function of the target animal by …>

<Control of a zoonotic agent can be obtained by use of this product as it …>

<The product provides a reliable diagnostic tool by …>

<However, the efficacy in <special patient group, proposed indication> is not documented.>

<Efficacy was not established for the proposed indication <insert unsubstantiated (rejected) proposed indication >>.

Additional benefits

<Rapporteur to include text>

These benefits should be reported separately, but would generally only be considered central to the overall assessment of the benefit-risk balance where the direct benefits are adequately established first i.e. the product must have shown a positive benefit-risk balance based on the direct benefits before additional benefits would be taken into account.

Briefly summarise the additional benefits, i.e. the benefits not directly linked to the indication of the product. These can be general benefits for the veterinarian, the farmer, the user, or relate to particular properties of the product such as ease of administration (e.g. needle-free injection).

Other additional benefits should also be mentioned here, e.g. improved treatment options, e.g. if provided by a novel treatment, use of marker vaccines, reduction of antimicrobial treatment or reduction of the risk of transmission to humans or animal free antigen production.

Only information in regard to the proposed use of the product should be added, but not commercial benefits for the farmer or comparative cost-effectiveness of a veterinary medicinal product.

Examples:

<<Product name> is easy to apply by the veterinarian/owner …>

<<Product name> reduces the need for antimicrobial treatment … / reduces the field contamination …>

<<Product name> increases the range of available treatment possibilities … / provides a new treatment possibility for a limited market …>

Risk assessment

<Rapporteur to include text>

Summarise very briefly the conclusions of the evaluation of the (potential) risks, as detailed in parts 2, 3 or 4, highlighting any deficiencies in the dossier that lead to uncertainties and/or contribute to a risk.

Deficiencies identified and conclusions must be consistent with the List of questions (D120)/List of outstanding Issues (D180)/ final conclusions on the application (D210), dependant of the stage of the assessment.

Main potential risks:

* Quality: adequacy of quality and any potential risks should be addressed e.g. storage conditions…/in-use shelf-life if they constitute a concern
* Safety:
* Risks for the target animal (very brief highlighting of adverse reactions- seriousness and frequency, lack of efficacy in certain groups, under certain conditions).
* Risks for the user:
* Risks for the environment:
* Risks for the consumer:
* Specific potential risks according to product type and application, e.g.:
* genetic <and phenotypical> stability (GMO)
* unintended spread of vaccine strain
* reversion to virulence
* likelihood of recombination event between the vaccine virus strain and the field strain (GMO)
* unknown areas related to the product (e.g. additional risks in old animals, repeated treatment often necessary but not investigated)
* impact on monitoring disease programs
* emergence of antimicrobial resistance (e.g. use of antibiotic-based selection markers/resistance genes, use of antibiotics during production)

Reference to the SPC recommendation in this section are meant as recommended use considering application route, dosage, vaccination scheme as used as parameters in the risk assessment, including standard safety advice, e.g. standard storage conditions, washing hands after treatment or contact, or standard waste removal advice. It is considered important to stress that the conclusions apply to assessment based on the recommended use.

Example:

*Quality*

<Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use>. <However, there remain …… questions regarding …..>

*Safety*

<Measures to manage the risks identified below are included in the risk management section.>

*Risks for the target animal*

Considering that safety is relative, a conclusion should be included on how the specific safety profile of the product fits into the larger context of the use of the product and the benefits of such use.

<Concerns have been raised for <….briefly summarise points of concern related to safety in the target species>. No final conclusion can be drawn on safety in the target species until those issues have been satisfactorily addressed.>

<Administration of <Product name> in accordance with SPC recommendations is generally well tolerated.> <The main reported adverse reactions include <….>>. <The potential for mild and transient adverse effects such as <effects> cannot be excluded.>

The safety of <vaccine common name> in <target species> <sensitive sub-species or breed> was confirmed in a <…> study. <Effects> were observed in some animals administered <substance> at the maximum recommended treatment dose. However, the effects were mild and transient.>

<List/summary of adverse effects or reactions related to target animal safety> have been observed in <description of animals affected>. Specific <measures><advice to veterinarians> are necessary to address this risk to <description of animals concerned>.

*Risk for the user*

<A number of concerns have been raised in relation to <….points of concern>. No final conclusion can be drawn on user safety until those issues have been satisfactorily addressed.>

<The CVMP concluded that user safety for this product is acceptable when used according to the SPC recommendations.><Standard safety advice is included in the SPC>.

*Risk for the environment*

<Concerns have been raised for <….briefly summarise points of concern related to environmental risk assessment>. No final conclusion can be drawn on risks to the environment until those issues have been satisfactorily addressed.>

<Product name> is not expected to pose a risk for the environment when used according to the SPC recommendations><Standard advice on waste disposal is included in the SPC>.

<Product name> can pose a risk to <describe scenario>, <Specific measures are necessary to mitigate the risk.>

*Risk for the consumer:*

<Concerns have been raised for <….briefly summarise points of concern related to consumer safety. No final conclusion can be drawn on consumer safety until those issues have been satisfactorily addressed.>

*Special risks*

Lack of efficacy of <substance> in the treatment of <indication> in <species> has been reported <outside Europe>.

<Concerns have been raised for <….briefly summarise points of concern related to any other safety issue>. No final overall conclusion can be drawn on safety until those issues have been satisfactorily addressed.>

Risk management or mitigation measures

<Rapporteur to include text>

When a risk is identified, provide proposals for risk management and explain risk mitigation options (e.g. that appropriate text has been included in the SPC or the product has been contraindicated for …), and residual risk.

Example:

<Risk management or mitigation measures will be considered pending additional information from the applicant.>

<Appropriate information has been included in the SPC to inform on the potential risks of this product relevant to the target animal, user, environment <and consumer> and to provide advice on how to prevent or reduce these risks.>

Summarise and conclude here the most significant risks identified (e.g. serious, frequent) and how it is foreseen these are handled through risk management measures. Add information on the management/mitigation of specific risks, if needed (e.g. SPC warnings, limitations in use, contraindications, specific administration device or protective clothing, specific conditions).

Examples:

*User safety*

<User safety risks have been identified. These risks have been addressed by the safety warnings in the SPC.>

*Environmental safety*

*<Consumer safety>*

*<Antimicrobial resistance* (e.g. use of antibiotic-based selection markers/resistance genes, use of antibiotics during production)>

Conditions or restrictions as regards the supply or safe and effective use of the VMP concerned, including the classification (prescription status)

Reg (EU) 2019/6, Art 33 states: The competent authority or the Agency, as applicable, examining the application in accordance with Article 28, shall prepare, respectively, an assessment report or an opinion. In case of a favourable assessment, that assessment report or opinion shall include … b) details of any conditions or restrictions to be imposed as regards the supply or safe and effective use of the veterinary medicinal product concerned, including the classification of a veterinary medicinal product in accordance with Article 34[…]. High-level restrictions and conditions would also be included in SPC section 3.11 (see annotated QRD template v.9) and more product-specific elements could be included in Annex II.

Add a brief statement on the prescription status and the rationale of the classification

Example:

<The veterinary medicinal product is subject to a veterinary prescription.>

<The veterinary medicinal product is not subject to a veterinary prescription, because <add an explanation>

<Post-authorisation measures> *Delete, if not applicable*

Any post-authorisation measure identified needs to be well motivated in the CVMP assessment report; notably the need for it should be explained in the context of a positive benefit-risk balance.

**For Pharmacovigilance:**Add information on any post-authorisation measure in accordance with Article 76(3) as far as it is part of risk management (for example specific pharmacovigilance/surveillance activities that deviate from ‘standard’ pharmacovigilance requirements; any need for post-authorisation surveillance study).

**For Exceptional circumstances:**
In case post-authorisation measures for Annex II of the Opinion in relation to the marketing authorisation under exceptional circumstances have been identified, outstanding data that are considered ‘key’ to the benefit-risk balance may be requested as a post-authorisation ‘specific obligation’ of the marketing authorisation*.*

***For Novel therapies (Annex II of Reg (EU) 2019/6, section V.1.1.6):****In case of any data gaps or uncertainties at the time of product authorisation for novel therapies, post-authorisation measures or studies may be requested.*

Evaluation of the benefit-risk balance

<Rapporteur to include text>

At the time of submission, the applicant applied for the following indication:"<indication> List the initially proposed indications in full."

The following text is to be used when there are major/other concerns that have an impact of the benefit-risk balance, normally after the first assessment phase at day 120 when a list of questions is agreed, and often still after the second assessment phase at day 180 (list of outstanding issues), as in those cases no conclusion on the benefit-risk balance can be drawn.>

<In the presence of (major/other) concerns, no conclusions can currently be taken on the benefit-risk balance of the application.>

<The overall benefit-risk evaluation for the product <is><remains> inconclusive.>

<Based on the data presented to date, the overall benefit-risk balance is considered positive.>

<Based on the data presented to date, the overall benefit-risk balance is considered negative.>

<There remain concerns on list in general terms the major outstanding concerns that would make the application non-acceptable. Therefore, the CVMP considered that the data available would not allow the Committee to conclude on a positive benefit-risk balance.>

To be used when there are no major/other concerns that have an impact of the benefit-risk balance.

<The product has been shown to be efficacious for <indication …>

<Information on development, manufacture and control of the active substance and finished product has been presented and lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use. It is well tolerated by the target animals and presents an acceptable risk <for users and the environment>< for users, the environment and consumers,> when used as recommended. Appropriate precautionary measures<, including withdrawal period,> have been included in the SPC and other product information.>

*If limited market (Art 23) or exceptional circumstances (Art 25)*
As the application was submitted under Article <23,25>, certain pivotal data on <xxx> were not included in the dossier. However, the CVMP considered that the overall benefit of the availability of the veterinary medicinal product would outweigh the risk of absence of these data, also taking into consideration the risk management measures addressed above.

The product information has been reviewed and
In the case of major issues with the PI: <changes are considered necessary. Comments on the SPC and product literature are included in <the LoQ and/or> a separate document (“comments on the product literature”).>
In the case of minor issues with the PI: <is generally considered to be acceptable, provided that some issues are resolved, as outlined in the “comments on the product literature” document.>
If ok: <is considered to be satisfactory and in line with the assessment.>

Conclusion[[3]](#footnote-3)

Based on the original <and complementary> data presented on quality, safety and efficacy, the Committee for Veterinary Medicinal Products (CVMP) considers that the application for <Product name>.

At the stages of List of Questions and List of Outstanding Issues, where no conclusion on the benefit-risk balance can be drawn due to concerns/outstanding information for the marketing authorisation and where post-authorisation measures have been proposed.

<could be approvable provided that satisfactory answers are given to the "other concerns" as detailed in the list of questions. Failure to resolve these concerns may render the application unapprovable. No final conclusions can currently be taken on the benefit-risk balance of the application.>

<is not approvable at the present time since "major objections" have currently been identified which preclude a recommendation for marketing authorisation. The details of these major objections are provided in the list of questions. Major objections are critical points requiring resolution before recommendation for a marketing authorisation. Failure to resolve these major objections will render the application not approvable. No conclusions can currently be taken on the benefit-risk balance of the application. >

<In addition, satisfactory answers must be given to the "other concerns" as detailed in the list of questions.>

<Furthermore, the answers to questions raised may affect the final product information and/or other post-authorisation measures for the marketing authorisation.>

At opinion stage; positive opinion:

<is approvable since these data satisfy the requirements for an authorisation set out in the legislation (Regulation (EU) 2019/6).

The CVMP considers that the benefit-risk balance is positive and, therefore, recommends the granting of the marketing authorisation for the above mentioned veterinary medicinal product.>

At opinion stage; negative opinion:

< not approvable since the data on <quality, target animal safety, user safety, environment, consumer safety, efficacy*>* remain inconclusive. Therefore the data do not satisfy the requirements for an authorisation set out in the legislation (Regulation (EU) 2019/6).

<The CVMP considers <by majority decision> that the benefit-risk balance is negative and, therefore, recommends the refusal of the granting of the marketing authorisation for the above mentioned veterinary medicinal product.>

Evaluation of new active substance status (section to be deleted if not applicable)

In addition, based on the review of data on the quality, <safety> <and> <efficacy>-related properties of the active substance <active substance>, the CVMP considers that

For situations where further information should be provided by the applicant

<further evidence should be provided by the applicant to substantiate the claim that <active substance> is to be qualified as a new active substance. Satisfactory answers must be given to the concerns as detailed in the List of Questions.>

<no conclusions can currently be taken on the new active substance status. The applicant is requested to update Annex 5.21 of the dossier and provide evidence and justification that the active substance is new.>

For situations where no further information should be provided and where the applicant claimed that the active substance is novel to veterinary medicines

<< active substance> is <not> to be qualified as a new active substance considering <considerations>.>

List of questions

Please insert your questions numbered under the appropriate headings as indicated below, clearly separated in ‘major objections’ and ‘other concerns’.)

The draft list of questions should be inserted by the rapporteur’s team, critiqued by the co-rapporteur and then adopted by CVMP at day 120 of the procedure.

Post day 121 the preceding scientific overview (Scientific discussion and benefit-risk assessment) should be updated by the rapporteur and co-rapporteur to take account of the assessment of the answers to the list of questions. A brief summary of the assessment of the answers to individual questions could be inserted below, along with any outstanding issues remaining to be clarified (either at an oral explanation, in a List of outstanding Issues or as post-authorisation measures).

Questions should be numbered sequentially. Questions should be short and precise. Avoid long introductions.

The following issues and questions need to be addressed in writing.

Part 1

1.A Comments on administrative particulars

Summary of the Pharmacovigilance System Master File

<The summary of the pharmacovigilance system master file as described by the applicant has the following deficiencies:>

Manufacturing authorisations and inspection issues

GMP inspection(s)

For routine GMP inspections

<A request for GMP inspection has been adopted for the following site(s) in order to verify the GMP compliance status. The outcome of this/these inspection(s) is required for the Committee to complete its examination of the application and will be needed by Day 181.>

And/or

For triggered GMP inspections

<A request for GMP inspection has been adopted for the following site(s) in order to provide further product specific information. The outcome of this/these inspection(s) is required for the Committee during its examination of the application and will be needed by Day 121.>

GCP inspection(s)

*For routine GCP inspections*

<A request for GCP inspection has been adopted for the following clinical study(ies) <enter study number(s)>. The outcome of this inspection and the satisfactory responses to its findings are an integral part of this procedure and will be needed by Day 181.>

*And/or*

*For triggered GCP inspections*

<A request for GCP inspection has been adopted for the following clinical study(ies) <enter study number(s)>. The outcome of this inspection and the satisfactory responses to its findings are part of the responses to the LoQ and will be needed by Day 121.>

Major objections

1. <Question>
2. <Question>

Other concerns

Part 2

(questions for Parts 2, 3 and 4 should be numbered **sequentially)**

2.A.1 <Title>

1. <Question>
2. <Question>

2.A.2 <Title>

1. <Question>
2. <Question>

Part 3

3.A.1 <Title>

*e.g. safety of one dose, examination of reproductive performance, safety clinical trials, etc*

1. <Question>
2. <Question>

Part 4

4.A.1 <Title>

*e.g. pre-clinical studies (duration of immunity), efficacy clinical studies*

1. <Question>
2. <Question>
1. The Scientific Overview document will be updated by the rapporteur and co-rapporteur during the assessment process (e.g. following responses to a list of questions or list of outstanding issues), thus facilitating an easier review by CVMP members and is the basis for the CVMP assessment report, which will be published within the EPAR with the confidential information deleted following the Commission Decision on the marketing authorisation. [↑](#footnote-ref-1)
2. If relevant for safety [↑](#footnote-ref-2)
3. It is important that questions are categorised separately as “major objections” and “other concerns” to ensure that applicants have a clear understanding of the implications of such categorisation when preparing their responses. [↑](#footnote-ref-3)