<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)

Biologicals other than immunologicals

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

The scientific overview document should not exceed 30-50 pages, incl. 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).

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 guidelines. Details on the data which have not been provided by the applicant (i.e. the data gaps) should be listed (and will be 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 Annex II to Regulation (EU) 2019/6 (as amended), 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 (Art. 25 of Regulation (EU)2019/6). Any post-authorisation measure for the provision of data should be detailed in the appropriate section of the scientific overview, 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.

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.

This template is a standard document created based on the requirements set in Annex II of Regulation (EU) 2019/6 (as amended). However, because of the complexity and variability of biological non-immunological products, the final text of this scientific overview could be significantly adapted by the assessor, depending on the type of product.

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

<Product name> <presentation> contains <concentration(s)> of <active substance> and is presented in < for example packs containing 1 bottle + 1 syringe>.

If applicant is registered as an 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 19 of Regulation (EU) 2019/6 – a hybrid application.>

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

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

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

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

< 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: <quality>, <safety><and><clinical> development 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.

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(1)(c) 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.>

<Sterilisation of the active substance <name of active substance> 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.>

**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 both the active substance and 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 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.

For in vivo studies and tests the Rapporteur may comment 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 toxicity.

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

Qualitative and quantitative composition

<Rapporteur to include text>

Briefly describe the product’s pharmaceutical form and its appearance. Mention the compositions of the product, specifying the concentration/ strength/biological activity of the active substance and listing the nature and quantity of the excipients, indicating in general terms their function in the formulation .e.g. adjuvant, preservative, stabiliser, thickeners, emulsifiers, markers, flavouring or colouring agents. Comment may be necessary whether or not the use of a preservative and colorants is justified.

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

Provide details of any separately supplied or composite solvent and its composition.

Examples:

<The finished product is presented as <pharmaceutical form(s)> containing <strength(s)> of <INN> as active substance.> <The product contains <> as adjuvant.>

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

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. 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, its performance data and the adequacy of its specifications*.*

Examples:

<The primary packaging is <describe as stated in the SPC 5.4>. <The material complies with the relevant European Pharmacopoeia (Ph. Eur.) and EU requirements>. <The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.>

<A child-resistant closure is required for user safety>.

Product Development

<Rapporteur to include text>

Give a critical summary of the development of the active substance(s), e.g. why the particular substance was chosen and the proof of concept of the mechanism of action of the biological active substance. Give the rationale for combined products where there is more than one active ingredient in the final formulation.

Give a critical summary of the rationale for the development of the product and the significant process validation and developmental clinical studies and how they led to the choice of the final formulation, any adjuvant and excipients which are either critical to the development of the finished product or are “novel” should be mentioned here together with their function, the container-closure system used, the chosen manufacturing process for the product, any manufacturing, filling or stability overages, etc, and how the development studies assure the quality of the finished product.

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).

The justification for the chosen packaging should also be briefly summarised, including brief reference to compatibility studies.

Include reference here to e.g., any dosing device etc. If any device is supplied with the product brief details should be included here on its performance data*.*

Examples:

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

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

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

<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 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. demonstration of biosimilarity, in vitro comparison data, other theoretical justification.

If biosimilarity was not demonstrated between the clinical formulation and the proposed commercial formulation, mention how this was justified.

Characterisation

Elucidation of structure and other characteristic

*Comment on the characterisation of the biotechnological or biological substance (which includes the determination of physicochemical properties, biological activity, immuno-chemical properties, purity and impurities) and on the specifications established.*

*Summarise all relevant information provided on the primary, secondary and higher-order structure including post-translational (for example, glycoforms) and other modifications of the active substance.*

*Comment on the biological activity (namely the specific ability or capacity of a product to achieve a defined biological effect) and on whether it was determined or evaluated using an appropriate, reliable and qualified method. Lack of such an assay shall be justified*.

Impurities

Comment on the data provide on process-related impurities (for example, host cell proteins, host cell DNA, media residues, column leachable) and product-related impurities (for example, precursors, cleaved forms, degradation products, aggregates). Quantitative information on impurities shall be described including maximum amount for the highest dose.

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.*

*Include a brief description of the method of manufacture highlighting any critical steps and stating whether they are adequately controlled, any manufacturing overages (stating if justified or not), the reasons for inclusion and adequacy of any in-process controls, commercial batch size, etc.*

*Include a list of all the substances at the appropriate steps where they are used, including those which cannot be recovered in the course of manufacturing, the details of the blending, including an example for a representative production batch, list of in-process controls including the stage of manufacture at which they are conducted and acceptance criteria.*

*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.>

<The proposed commercial batch size <range> is <X><X – Y> <unit, e.g. kg/l/tablets>.<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>.

<An acceptable process validation protocol for future commercial scale batches was provided>.

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 (Annex II) 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 product and absence of introduction of any extraneous agent.>

Starting materials not listed in a pharmacopoeia

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 seeds, biotechnological cell constructs 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. Include details of the tests on seeds including compliance with the relevant monographs or GLs and whether any specific issues were identified. A summary of the tests conducted (e.g. for identity, extraneous agents (bacteria, mycoplasma, fungi and viruses)) should also be included. Storage conditions should be briefly indicated.

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 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 description of the starting cells or strains, the construction of the expression vector (name, origin, function of the replicon, promoter enhancer and other regulator elements), control of the sequence of DNA or RNA effectively inserted, oligonucleotide sequences of plasmid vector in cells, plasmid used for cotransfection, added or deleted genes, biological properties of the final construct and the genes expressed, copy number and genetic stability.

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 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 add product specific details here>

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 (Annex II) 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.

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. active substance content, microbiological quality, sterility). In line with the Ph. Eur. controls relevant to this section also include detoxification, physical tests, chemical tests, pH, freedom from extraneous agents (bacteria, mycoplasma, fungi and viruses) etc.

Description of a test for biological activity shall be included unless not provided and therefore its absence justified.

Upper limits, taking into account safety considerations, shall be set for the impurities.

Control tests on the finished product

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.

Upper limits, taking into account safety considerations, shall be set for the impurities.

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, pH, osmolality 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) 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) Potency

A brief description of the potency test should be provided.

A brief description of the activity test or test for quantification of the active substance or test to quantitatively measure the functionality (biological activity/functional effect) which is linked to relevant biological properties should be provided. Comment whether the above show that each batch will contain the appropriate potency to ensure its safety and efficacy. Where degradation occurs during manufacture of the finished product, the maximum acceptable levels of individual and total degradation products immediately following manufacture should be described here.

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 excipient components

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

5) 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.

6) Residual humidity (if relevant)

Each batch of lyophilised product shall be tested for residual humidity.

7) Filling volume

<Rapporteur to include text>

Examples:

<The specifications proposed for use at release and at the end of shelf-life are appropriate to control the quality of the finished product.>

<The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for <assay> <and> <impurities> testing has been presented.>

Batch-to-batch consistency

<Rapporteur to include text>

Batch analyses results from three consecutive batches of active substance and finished product 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 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 <*list tests*>.

Batch analyses results should be summarised with comment on whether they confirm consistency and uniformity of the product.

<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.>

<Batch analysis results are provided for <number+ scale> batches confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.>

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:

<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>.

<Real time stability data of <number, scale> batches of finished product for <number> months at 2-8 ºC 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 <container>.><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 potency (xx/dose) and release potency (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 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 novel , 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 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 5.22 of the dossier. In case of questions, these should be added to the LoQ section at the end of this document.*

The applicant requested the active substance, <active substance>, 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.> <as, in comparison to the known substance, {substance approved}, previously authorised in the European Union as {name of the medicinal product approved}, it is 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 quality and chemical structure.>

<could be qualified as a new active substance considering quality and chemical structure 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 quality and chemical structure.> In case this option is chosen, please add justification.

<cannot currently be designated as a new active substance, as insufficient data have been provided. The applicant is requested to update Annex 5.22 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.

Overall conclusions on quality

<Rapporteur to include text>

Summarise briefly the conclusions in respect to the compliance with requirements in accordance with the Annex to Regulation (EU) 2019/6 (as amended) highlighting the adequacy and completeness of the data provided in general (without giving details of studies), the conclusions drawn (e.g. shelf-life and storage conditions) and identifying any deficiencies. The conclusions should be taken into account in the benefit-risk assessment and the product information, as appropriate. The list of questions (day 120) or list of outstanding issues (day 180) should mirror these conclusions.

A useful final sentence (after summarising all the basic quality elements) is:

<Information on the development, manufacture and control of the active substance and the 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.>

<The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SPC. 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>.

*Plus, if Recommendations are made:*

*Note: ‘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.*

<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)

<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. 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 for a food-producing animal species and that the active substance has been assessed before by the CVMP in order to establish maximum residue limits (MRLs)or to assess the need for an MRL evaluation, or that the product is a new fixed combination product and substance x or all active substances have been assessed before in marketing authorisations in the EU, or that a product with the same active ingredient is authorised for human use, 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 <active substance>, a compound that acts <describe in very general terms the actions>>

<<Product name> is a new fixed combination for <species> containing <active substance> with <action e.g. an anthelmintic> and <active substance> with <action>>

<<active substance> is a new active substance, which has not been authorised for a veterinary medicinal product in the EU at the date of submission of the application.>

<A full safety file in accordance with Article 8(1)(b) of Regulation (EU) 2019/6 has been provided.>

*If reference is made to a previous CVMP assessment for a separate VMP (e.g. containing the same active substance), the pivotal data underlying that assessment should still be included in the dossier. Rapporteurs should not simply cross reference the previous assessment but should report/summarise the relevant studies, striving for consistent conclusions with previous reports.*

*When making reference to a study please add study number(s) if needed.*

*For all sections, if no data have been provided, the (co)rapporteur should note this and comment on why this is or is not appropriate. In the case of marketing authorisation for limited market, identify the data gaps compared to standard requirements.*

*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.*

Safety tests

<Rapporteur to include text>

*Describe the studies conducted briefly (e.g. “X male and female beagle dogs were given y mg/kg bw over z days once/twice daily by <administration route> and the controls …”).* *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.*

Pharmacodynamics

<Rapporteur to include text>

*Mechanism of action and pharmacodynamics findings relevant for the safety evaluation should be (briefly) summarised here. More detailed pharmacodynamics relevant to therapeutic effect in target species should be addressed in Part 4. Cross references may be made to studies addressed in Part 4.*

*Secondary pharmacodynamics to be considered, if relevant.*

Examples:

<See part 4.>

<Pharmacodynamics are adequately described in section 4.2 of the SPC> <Section 4.2 of the SPC should be updated to reflect….>

Pharmacokinetics

<Rapporteur to include text>

*This section should focus only on the pharmacokinetics in laboratory animals.*

*The pharmacokinetics data presented here may be related to the identification/characterisation of which substances (parent or metabolites) are responsible for pharmacodynamic/toxicological effects, to dose/effect findings in the pharmacological and toxicological studies, to the relevance for extrapolating between species, or to determine adequate exposure of test systems in case of absence of toxicity finding.*

*Repetition of more detailed descriptions of studies reported at other places in this report should be avoided; but where necessary, ensure consistency in terminology when describing, referencing and concluding on the same study.*

*Key studies should be briefly summarised (e.g. three studies were conducted to examine pharmacokinetics in rats, rabbits and dogs…) including their findings, allowing to identify which finding relates to which study and the (co)rapporteur’s conclusions drawn.*

*Significant findings as well as any shortcomings/omissions should be highlighted and justified as appropriate, and the (co)rapporteur’s conclusions drawn. Comment on whether studies were performed in compliance with GLP.*

Examples:

<<active substance> exhibits dose proportional pharmacokinetics over the range of x to y mg/kg bw.>

<Single dose administration of x to y mg/kg bw demonstrated non-linear pharmacokinetics: the increase in peak plasma concentration and AUC were <greater, lower> than proportional to the dose increase.>

<See part 4.>

<Pharmacokinetics are adequately described in section 4.3 of the SPC.><Section 4.3 of the SPC should be updated to reflect (…).>

*Include a brief summary of pharmacokinetic data relevant to user safety (i.e. dermal absorption, half-life, excretion of active substances).*

Absorption

<Rapporteur to include text>

Distribution

<Rapporteur to include text>

Metabolism

<Rapporteur to include text>

Excretion

<Rapporteur to include text>

Toxicology

<Rapporteur to include text>

*For each of the sections below, provide a brief outline of the data submitted.*

*If several studies and references have been provided, first summarise briefly how many studies were provided and separate these into pivotal and supportive.*

Example:

<One pivotal study and two supportive published repeat-dose toxicity studies were provided.>

<The active substance <active substance> was previously assessed by the CVMP in the context of the establishment of MRLs and the key findings of the toxicity studies evaluated (see European Public MRL Assessment Report (EPMAR) (EMA/MRL/ …/…) are summarised 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 drawn. Describe pivotal studies individually. The description of one study should be concise and normally not require more than 1 paragraph. Include information on applicable guidelines/deviation from guidelines: provide relevant information on study design, e.g. tested animal species, sex, number of animals, duration of treatment, reversibility period if any, administration route, examinations performed.*

*Comment on dose response, i.e. was a NOAEL established, which toxic effects and target organs were identified at higher dose levels. Comment on the biological relevance of the observed effects. Indicate if the toxicity is due to the pharmacological effect of the substance. Comment on consistency between similar studies.*

*The toxicity findings used in the user safety should be reported in this section.*

*In case of a new fixed combination product the toxicology of the product should be addressed. Where studies on the individual active substances are reported the description of the toxicology studies/findings for any new active substance (applications under article 8)should follow standard approach regarding detail, while for an active substance assessed before in the context of an existing EU marketing authorisation (applications under article 20), the description of the toxicology may be briefer.*

*For a biological veterinary medicinal product for use in a food-producing animal species, and where previously the substance has been evaluated for the establishment of MRLs, the relevant study findings of the MRL assessment as detailed in the EPMAR should be summarised briefly using key paragraphs/sentences from the EPMAR. Only new studies not available for the MRL assessment should be described in more detail.*

*As it can be expected that in general the studies comply with GLP and internationally harmonised study design (e.g. OECD) it is not necessary to state this for each individual study, but instead give a summary statement of compliance in the introduction and point out only any deviations in the description of individual studies, including a comment, as appropriate, on the reliability of the study arising therefrom and the impact on its use in the assessment.*

*In the case where a veterinary medicinal product is intended for topical use and the systemic absorption has been investigated in the target animal species, if it is proved that systemic absorption is negligible,* *the repeated dose toxicity tests, the tests for developmental toxicity and the carcinogenicity tests may be omitted, unless: (a) under the intended conditions of use, oral ingestion of the veterinary medicinal product by the animal is to be expected, or (b) under the intended conditions of use, oral exposure of the user of the veterinary medicinal product is to be expected. This should be explained in the sections below.*

Single-dose toxicity

<Rapporteur to include text>

Examples:

<Acute toxicity studies of <active substance> were carried out in <sex, strain, species> by <route>.>

<The <study was><studies were> not compliant with GLP> <OECD guideline for acute toxicity (No N)>.>

<After oral/dermal exposure in <species>, the acute toxicity of the test substance was low as no apparent toxicity was observed at up to x mg/kg bw.>

<At y mg/kg bw and higher doses, clinical signs/pathology findings included <effect>. Mortality was observed from z mg/kg bw.>

Repeat-dose toxicity

<Rapporteur to include text>

Examples:

<<active substance> was tested by <route> in <species 1> (x weeks) and <species 2> (y and z weeks).>

<In a x month oral (gavage) repeat dose toxicity study in <species>, <active substance> was administered at dose levels of 0, x, y and z mg/kg bw X times per day. At the highest dose, the <impacted parameters> were significantly increased / decreased. At the mid dose, slight effects on <impacted parameters> were also observed. The dose of x mg/kg was retained as the NOEL for this study / a NOAEL could not be established since <effect> was observed at the lowest dose tested / all dose levels.><The study did not comply with GLP standards>< was not carried out according to OECD guideline <408><409>.>

<The adverse effects on <impacted parameter> were consistent between studies.>

<These effects are probably due to the pharmacological activity>.

<The <species> was the most sensitive species with a NOEL of x mg/kg bw/day in the y week study.>

Tolerance in the target species

<Rapporteur to include text>

*A brief summary shall be provided. Details of studies/reports are provided in Part 4.*

Example:

<See Part 4.>

<<Effect(s)> has/have been observed in <target species> after <duration> of <dose> via <administration route>. The details of this study as well as other details on tolerance in the target animal species are described under Part 4.>

Reproductive toxicity, including developmental toxicity

<Rapporteur to include text>

***Study of the effect on reproduction***

*Depending on the results, consider potential contraindication in breeding, pregnant or lactating animals.*

Examples:

<No studies on the effects on reproduction have been provided. This is acceptable since the product is not intended for use in breeding animals or animals intended to be used for breeding. Adequate warning is included in the SPC.>

<Reproductive safety studies were performed in line with VICH GL43.>

<In a reproduction toxicity study, rats were orally administered with <dose levels> mg/kg bw/day of <active substance> before mating, during pregnancy and lactation. Embryotoxicity was observed at maternotoxic doses only. From this study a NOEL for maternotoxicity and embryotoxicity of <NOEL> mg/kg bw/day was established.>

<<number of studies><reproductive toxicity studies were conducted in rats.> <The study N did not comply with GLP standards>< was not carried out according to OECD test guideline <No N>>. Based on the findings of these studies, <active substance> has no effect on reproductive performance at doses up to <NOEL> mg/kg bw/day. Dose of <LOEL> mg/kg bw/day was associated with effects on <implantation rate, litter size, pup weight, litter loss during lactation>.>

<Given the potential for effects on spermatogenesis, the product is contraindicated in breeding animals.>

<Based on information that <active substance> may affect neonatal development, the product is contraindicated in lactating animals.>

***Study of developmental toxicity***

<Rapporteur to include text>

*Comment on embryo/foetotoxic doses in relation with maternal toxicity.*

<For the evaluation of user safety, standard developmental toxicity testing of <active substance> was evaluated in accordance with standard tests based on established guidance (including VICH GL32 and OECD tests).>

Examples:

<Studies of embryofoetal and developmental toxicity in rats and rabbits given <dose levels> <active substance> <route> on gestation day GD7 to GD17 and GD6 to GD18, indicate a maternal NOAEL of <NOAEL rat> and <NOAEL rabbit> mg/kg bw/day, respectively, based on reduced body weight gain. The NOAEL for foetal toxicity was x mg/kg bw/day, based on <effect>.>

<After daily administration of <dose levels> mg/kg bw/day in pregnant female rats between day 7 and day 17 of gestation, there were signs of maternal toxicity in the <dose level> mg/kg bw/day group, including <effect>. Skeletal abnormalities such as <abnormality> were observed in all treated groups and appeared dose related although only significantly different from controls in the highest dose group.>

<The teratogenicity studies in rats and rabbits show no evidence of foetotoxicity or teratogenicity in rats, but for rabbits, a NOEL of x mg/kg bw/day was established, based on <teratogenic effect> in the y mg/kg bw/day group.>

<Based on information in the published literature, <active substance> is not teratogenic in the rat (substance administered from days 7 to 17 of gestation, maximum dose tested <max dose rat> mg/kg bw/day) or the rabbit (substance administered from days 6 to 23 of gestation, maximum dose tested <max dose rabbit> mg/kg bw/day).>

<Based on the above described rat and rabbit studies, <active substance> showed no potential for teratogenicity.>

<Given the teratogenic potential observed in laboratory animals, the use in pregnant bitches is contra-indicated.>

Genotoxicity

<Rapporteur to include text>

*Refer to the standard battery of genotoxicity tests where applicable. Notify when the conditions of validity of a test are not fulfilled.*

*The text can be very brief when standard tests were conducted and results were unequivocal.*

Carcinogenicity

<Rapporteur to include text>

*If carcinogenicity testing is not performed, comment on the justification provided for the absence of carcinogenicity studies.*

Examples:

<No carcinogenicity data have been provided. This is considered acceptable due to the lack of genotoxic potential, the lack of structural alerts, and the lack of findings relevant to neoplastic lesions in repeat dose toxicity studies.>

<In <strain> rats administered <active substance> at mean daily doses of x, y and z mg/kg bw/day in feed for at least 104 weeks, no evidence of carcinogenicity was found.>

<There was no evidence of carcinogenicity when <active substance> was administered in the diet for up to 24 months to rats and mice in doses up to x mg/kg bw/day.>

<In <species>, a 24-month carcinogenicity study was conducted with doses of x, y and z mg/kg bw/day (50 animals/sex/group). In <sex>, there was a statistically significant increase in the incidence of <neoplasm> at z mg/kg bw/day.>

<These findings are consistent with the preneoplastic lesions observed in the x day repeat dose toxicity study.>

<These changes are well-known effects of <class of substance> in <test species> after life-time treatment and considered not relevant to humans or <target species>.>

<The applicant justifies the absence of carcinogenicity studies based on the fact that the standard battery of studies investigating genotoxic potential were negative and the absence of pre-neoplastic lesions in the repeat dose studies. However, the longest duration of repeat dose studies presented in this dossier was 28 days. Given the absence of chronic toxicity studies, this aspect of the applicant’s justification is not accepted. The applicant is requested to provide further justification for the absence of carcinogenicity data.>

<The dietary carcinogenicity study in <species> is considered of limited value for the assessment of the carcinogenic potential of <active substance> <since the survival rate in the <dose level> group was too low, since the highest dose level did not induce significant toxicity.>

<Consequently carcinogenic effects of <active substance> at therapeutic dose levels in <species> cannot be excluded.>

Other requirements

***Special studies***

<Rapporteur to include text>

*Mention here other studies relevant to the evaluation of the safety of the product. These may include immunogenicity, immunotoxicity, skin or ocular irritation, skin sensitization, or delayed neurotoxicity.*

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

Examples:

<Dermal irritation potential of <substance, final formulation> was evaluated in an in vitro skin irritation assay/in vivo in New Zealand White rabbits. The substance was found to be non-irritant.>

<In a guinea pig study/in a local lymph node assay in mice, <active substance> tested at concentrations up to x% did not show any skin sensitisation potential.>

<No specific studies on the immunotoxicity or neurotoxicity of <active substance> were provided. This is acceptable because no indications of such effects were observed in toxicology or pharmacodynamics studies.>

<No signs of immunotoxicity and neurotoxicity were observed in repeat dose toxicity studies. Therefore, no specific studies were performed.>

Observations in humans

<Rapporteur to include text*>*

*When a medicine with the same active substance is approved for human use, specify the therapeutic dose and the known adverse effects in clinical use.*

***Development of resistance and related risk in humans***

<Rapporteur to include text>

*Delete, if not applicable.*

*Mention here data on the potential emergence of resistant bacteria or resistance determinants of relevance for human health and which are associated with the use of veterinary medicinal product. Where necessary, measures to limit resistance development from the intended use of the veterinary medicinal product shall be proposed by the applicant.*

*If necessary cross reference shall be made to Part 4, e.g. resistance data relevant for clinical use of the product in target animals.*

Excipients

<Rapporteur to include text>

*Include a comment on the safety of excipients, especially when an excipient has a known toxic effect.*

*For (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 the relevant safety data as required by the Annex II to Regulation (EU) 2019/6 (as amended), should be summarised.*

*For known excipients, i.e. included in previously authorised products, a brief text should be used.*

Example:

<Excipients of the product are currently used in veterinary medicines and do not raise any toxicological concern>

User safety

<Rapporteur to include text>

Relevant guidelines: CVMP guideline on user safety for pharmaceutical veterinary medicinal products (EMEA/CVMP/543/03-FINAL-Rev.1). The CVMP guideline on user safety for immunological veterinary medicinal products (EMEA/CVMP/IWP/54533/2006) 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 pharmacological effect if relevant), exposure (worst case scenarios), mention any relevant studies submitted and whether there is a risk arising. The toxicity findings used in the user safety should be clearly identifiable from the preceding toxicology section. Any details on the toxicity findings should be presented in the toxicology section.

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 applicants in LoQ or LoOI, 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 (EMEA/CVMP/543/03).

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/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 dermal and/or oral exposure.>

<It is considered likely that adverse events will not occur as a result of dermal contact with these tablets Sensitisation and irritation studies have confirmed that the product does not cause these effects in the test animals used. This is also the case for eye irritation.>

<With regard to accidental oral exposure, the applicant has considered that ingestion of x of the largest (y mg) tablets by a small child (10 kg) should be used as a worst-case scenario. When comparing this level to the oral NOAEL, the margin of exposure is <below/above> the trigger value of 100.>

<This NOAEL has been based on a chronic dose toxicity study whereas the accidental exposure is considered a single exposure.>

<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>. Avoid direct contact with treated animals until the application area is dry. Keep children away from treated animals for at least <time period> following application of the veterinary medicinal 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.>

<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.>

<User safety warnings are adequately described in section 3.5 of the SPC.><Section 3.5 of the SPC should be updated to reflect (…).>

Environmental risk assessment

<Rapporteur to include text>

Environmental risk assessment of veterinary medicinal products not containing or consisting of genetically modified organisms

*Relevant guidelines: 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), EMA Note for guidance on Environmental risk assessment for immunologicals veterinary medicinal products (EMEA/CVMP/074/95).*

*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 more detail.*

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

If a Phase II assessment is required, the guidance/information included in the non-biologicals SO template could be used (e.g. tables to report data).

Environmental risk assessment for veterinary medicinal products containing or consisting of genetically modified organisms

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.>

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

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

If limited market application: If the product 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*
* *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.

In case a Phase II assessment is needed, the information included in the non-biologicals SO template can be used (e.g. tables to report data).

<Residue tests>

MRLs status

<Rapporteur to address concerns expressed by EMA, if any, and to include text in case of information is missing, e.g. new information on an excipient or that was not considered before which requires consideration regarding its MRL status, or starting material remains in high concentration in final product and further information from the applicant is required.>

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

<The MRL status of the constituents of <VMP> is as follows.>

<The active substance<s> in <VMP> <is an/are> allowed substance<s> currently included in table 1 of the annex to Commission Regulation (EU) No 37/2010 as follows:

| **Pharmaco-logically active substance** | **Marker residue** | **Animal species** | **MRL** | **Target tissues** | **Other provisions** | **Therapeutic classification** |
| --- | --- | --- | --- | --- | --- | --- |
|  |  |  |  |  |  |  |

For an MRL recommended by CVMP but not yet adopted by the Commission:

<On <date>, the Committee for Veterinary Medicinal Products adopted an opinion recommending the inclusion of <substance> in <species> in table 1 of the annex to Commission Regulation (EU) No 37/2010 as follows: <MRL recommendation>

<The active substance in <VMP> is a biological substance considered as not requiring an MRL evaluation as per I.6 and I.7 of Annex I to Commission Regulation (EU) No 2018/782.

<The <remaining> excipients 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.>

Depletion of residues

<Rapporteur to include text>

*State compliance with the relevant guidelines:*

* *CVMP/VICH guideline GL 48: Studies to evaluate the metabolism and residue kinetics of* veterinary *drugs in food-producing animals: marker residue depletion studies to establish product withdrawal periods.*
* CVMP/VICH guideline GL 56: Studies to evaluate the metabolism and residue kinetics of veterinary drugs in food-producing species: study design recommendations for residue studies in honey for establishing MRLs and withdrawal periods.
* CVMP/VICH guideline GL 57: Studies to evaluate the metabolism and 4 residue kinetics of veterinary drugs in food-producing 5 species: marker residue depletion studies to establish 6 product withdrawal periods in aquatic species.

*The purpose of these studies, which measure the rate at which residues deplete in the target animal after the last administration of the medicinal product, is to permit the determination of withdrawal periods.*

*Briefly describe the residue studies, including description of the formulation used, comparing this to the proposed formulation. The analytical method employed to determine the residue concentration in the different target tissues studied should be very briefly described and commented as to its validation and suitability.*

*Highlight any concerns/shortcomings/omissions and whether studies were performed in compliance with relevant guidelines (CVMP/VICH; GLP). Deviations from guidelines or other deficiencies should be critically discussed as to whether the study is acceptable.*

Examples:

<No residue studies were submitted. The omission of a residue depletion study was considered justified as no constituent of the product is subject to numerical MRLs.>

Residue analytical method

*This section applies to the analytical method used in the residue depletion studies. State compliance of the method with VICH GL 49: Studies to evaluate the metabolism and residue kinetics of veterinary drugs in food-producing animals: validation of analytical methods used in residue depletion studies.*

Withdrawal periods

<Rapporteur to include text>

Relevant guidelines:

* CVMP guideline on determination of withdrawal periods for edible tissues (EMEA/CVMP/SWP/735325/2012)
* CVMP guideline on injection site residues (EMEA/CVMP/542/2003)
* Draft CVMP reflection paper on injection-site residues: consideration for risk assessment and residue surveillance (EMA/CVMP/520190/2007-Rev.1)
* Note for guidance for the determination of withdrawal periods for milk (EMEA/CVMP/473/98)

Comment on whether or not the studies presented are sufficient to permit the determination of a withdrawal period.

Discuss the appropriate calculation method for determining the withdrawal period and provide a brief assessment of the withdrawal periods proposed by the applicant. State whether or not the proposed withdrawal period is acceptable or propose a more suitable withdrawal period.

<Conclusions on withdrawal periods are adequately reflected in section 3.12 of the SPC.><Section 3.12 of the SPC should be updated to reflect (…).>

Overall conclusions on the safety documentation: safety <and residues> tests

<Rapporteur to include text>

Briefly summarise the conclusions for each safety section normally without repeating individual study findings, such as specific NO(A)ELs, 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 toxicity studies, alternatively to describing the summary and conclusion in text, an overview table can be presented.

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

Also briefly summarise the main conclusions/concerns raised in the assessment of the residues dossier to ensure these are taken into account in the benefit-risk assessment.

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

In the case of marketing authorisation for limited market, summarise the data gaps compared to standard requirements.

Examples:

*Pharmacology:*

<Following oral administration, <active substance> absorption was fast and bioavailability was high. The active substance has low systemic clearance and distributes into tissues.>

<The lack of pharmacokinetic data in laboratory animals has not been justified and the applicant refers to summaries of data extracted from the product information for the original product authorised for human use. As no references for the individual studies are provided, the data cannot be assessed, which is not acceptable.>

<The absence of pharmacodynamic and pharmacokinetics interaction of <active substance 1> and <active substance 2> has been demonstrated. It is concluded that the combination is unlikely to change the safety of both single substances.>

*Toxicology:*

<In acute toxicity studies, the oral limit dose for lethality is greater than x mg/kg bw and the dermal limit dose is greater than y mg/kg bw in <species>.>

<In repeat dose toxicity studies, the NOEL was x mg/kg by <route> in <species>. <Effects> were observed at higher dose levels.>

<In repeat dose toxicity studies, the oral toxicity profile consists of <effect 1> identified in <species> and <effect 2> identified in <species>. The NOAEL in a <species> 90-day toxicity study is x mg/kg bw/day.>

<The main target organ in the repeat dose toxicity studies was <target organ>. Effects on <target organ> (<nature of clinical or pathological effects>) were observed at x mg/kg bw/day and above in the y week and z week oral studies.>

<The longest repeat dose toxicity studies conducted were the 4-week studies. No chronic studies were presented. The applicant will be requested to justify the absence of longer duration repeat dose toxicity studies.>

<In the absence of studies on the effects on reproduction the use of the product is contraindicated for breeding animals.>

<<active substance> has no potential for embryo/foetotoxicity or teratogenicity.>

<Reproduction toxicity was only studied in laboratory animals and not in the target species.>

<Data in rats and rabbits indicate that <active substance> is not a developmental or reproductive toxicant.>

<<active substance> is not genotoxic. Carcinogenicity studies have not been performed and are not requested.>

<The product was shown to be non-irritant to skin, a severe ocular irritant and a non-sensitizer of skin.>

<The data presented are considered adequate to characterise the toxicity profile of the active substance.>

The following optional table may be used as an alternative to text to summarise the pivotal toxicity studies and will be useful to provide an overview in particular if not many further comments or discussions are required. It might be necessary to add an overall statement following the table to present the overall conclusions on the toxicity studies. If for one or several of the studies more detailed explanations or discussions are required, e.g. in case of equivocal results (e.g. positive and negative results in genotoxicity tests) or no clear conclusions can be drawn, a summary text may be more useful than a table. The table below provides an example and can be adjusted by the assessor as necessary.

<Overview of toxicity findings:

| **Results of pivotal toxicity studies** |
| --- |
| **Study type** | **Tested species/test system** | **Result**<result of pivotal study, e.g. NO(A)EL, LOEL, other findings, or summary/ range of results, e.g. if several single dose tox studies> | **Comments**<e.g. uncertainties, deficiencies, duration where relevant>  |
| Single toxicity |  |  |  |
| Repeat dose toxicity |  |  |  |
| Reproduction toxicity |  |  |  |
| Developmental toxicity |  |  |  |
| Genotoxicity |  |  |  |
| Carcinogenicity |  |  |  |
| Other requirements |  |  |  |

>

*User safety:*

<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.>

<The worst-case scenario for user safety is <self-injection> <ingestion of x tablets by a child>, with an estimated margin of exposure of <MOE value>. 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.>

*Environmental risk assessment:*

<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.>

*<Residues tests:>*

<In a non-radiolabelled residue depletion study in <species>, <marker> concentrations were highest in <tissues 1 and 2> at all slaughter days, and significantly lower in <tissues 3 and 4>. Residue concentrations at the injection site were below LOQ in all samples at <day x> for the first time.>

<Based on the marker residue data and the MRLs established by the CVMP, withdrawal periods for edible tissues of <length of withdrawal period 1> for <species 1> and <length of withdrawal period 2> for <species 2> were calculated.>

<A final conclusion on the withdrawal period for <tissues> cannot be made until the outstanding issues are addressed.>

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

Part 4 – Efficacy

*Pre-clinical studies*

As introduction, the relevant elements pertinent to the efficacy assessment of the product under consideration in the target species 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; 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/form order. Add subheadings, as needed.

Overview tables may be used for the purpose of providing a brief overview of the amount of data provided, using the format presented. The pre-clinical table is intended to provide an overview of dose determination/justification/confirmation studies. In addition, a summary of each pivotal field study is useful to present the study in a consistent way. Other studies than the pivotal studies (or other key studies) should only be briefly noted as summary text.

This section should refer to data for the target animal species only.

Examples:

<Product name> is <add a general description of the formulation, active ingredients and their pharmaceutical classification>. <Product name> is intended for use in <add the target species and very general indication *>.* The proposed dose is <add a description of the dose and route of administration>*.*

<active substance> is a new active substance, which has not been authorised for a veterinary medicinal product in the EU at the date of submission of the application.>

Any omission of data should be justified.

If reference is made to a previous CVMP assessment for a separate VMP (eg, containing the same active substance), the pivotal data underlying that assessment should still be included in the dossier. Rapporteurs should not simply cross reference the previous assessment but should report/summarise the relevant studies, striving for conclusions consistent with previous reports.

Examples:

<The application makes reference to the dossier / studies and previous assessment of the CVMP in the context of <the marketing authorisation application for <name of the product> <and the conclusions drawn regarding <endpoint, specific study><supplemented by relevant scientific literature / proprietary studies>. ><, in which it was concluded that…<e.g. X is of low toxicity/ quickly absorbed/metabolised via liver> This approach was agreed by the CVMP in a scientific advice prior to submission of the dossier>>.

Pharmacology

Pharmacodynamics

<Rapporteur to include text>

Describe briefly only the most important studies (design and results) in necessary detail, with specific focus on any new active substance, and relation to the intended use in the target species. Validity of study design/models should be commented on as this affects the reliability of the study results. Provide a short and clear conclusion on what relevant evidence the study provided.

Summarise the mode of action, as known, and the main pharmacodynamic effects of the active substance as well as secondary effects (if any) **with relevance to the target species only**. Do not repeat information already included in part 3 (cross-references preferred). Only specific information for target animals should be added here (unless already assessed in part 3). In case of a fixed combination product, potential interactions between the active substances should be considered.

The section should allow conclusions on intended and unintended effects on the target animal and/or other animals in contact.

Only data of relevance for the application should be detailed here. Indicate the extent of data i.e. how many studies or publications were provided, identify the extent of relevant data. Only briefly acknowledge less relevant studies, and state why they are of limited value for the assessment of the dossier (e.g. inappropriate study design, old data, non-relevant animal species, routes of administration etc.)

In the end of the section, summarise the extent of evidence provided, briefly conclude on the total evidence provided and the main characteristics, comment on the strength of evidence. Highlight clearly any outstanding issues and whether these are major concerns, or include a clear statement that the pharmacodynamic properties of the substance/product have been demonstrated and that no outstanding issues.

Examples:

<A total of one laboratory study and 13 published papers were provided to describe the pharmacodynamic action/mode of action of the active substance. Of these data, the laboratory study and 4 papers were of central relevance for the dossier.>

<In addition to a number of references from published literature, the applicant also provided a pilot study investigating the effect of <active substance> in <target species> at a dose of xxx using a well-established/validated/experimental model of <…>. Treatment with <active substance> showed…>

<Based on the data provided, <active substance > has been shown to <summarise those observations concerning mode of action that are relevant for the indication or for target animal safety>. However, <the experimental model was not validated; only very young animals were tested; …> and only limited conclusion can therefore be drawn to the clinical relevance/suitable dose/target population.>

*If all relevant information is already described in part 3, cross-reference can be made to part 3.*<See part 3>

Indicate if accurate and sufficient information is included in section 4 of the SPC.

Examples
<Pharmacodynamics are adequately described in section 4.1 of the SPC><Section 4.1 of the SPC should be updated to reflect….>

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

Pharmacokinetics

<Rapporteur to include text>

Information in this section should be relevant to dose finding, efficacy, and duration of effect in the target species. Do not repeat information already included in part 3 on other species, but make cross-reference to part 3, if needed.

<See part 3.>

Reference can be made to the CVMP Guideline for the conduct of pharmacokinetic studies in target animal species (EMEA/CVMP/133/99-FINAL).

The pharmacokinetic properties of the active substance should be presented with special focus on the kinetic profile of the final formulation when administered at relevant/proposed doses by the proposed administration route to the target animal species. When appropriate, describe the kinetic profile in relation to the time to onset and duration of the drug effect in order to assess the justification for the chosen start dose (range), dose interval and/or dose adjustments. Possible pharmacokinetic interactions with other drugs should be indicated. Briefly describe the source and quality of the data (e.g. peer reviewed literature or GLP- or GCP-compliant studies), and the study design of the most important (pivotal) study. Non-pivotal (corroborative, supportive) studies should be summarised very briefly to understand the extent of data in the dossier and to understand why they were not considered of highest importance. Tables summarising the most relevant results may be used instead of a narrative description, if this is easier to read.

Compare kinetics between target species, if applicable.

If scientific advice was given, conclude whether the advice was followed or not. If not, explain the deviation and whether it was justified or not.

Example:

<Scientific advice was given concerning <insert in brief terms what the advice was>, which was <not> followed in the approach/study design. <The deviation from the advice was <not> justified and therefore the study <explain the impact on the results and the reliability/relevance of the results.>

Provide a succinct conclusion, summarising the main strengths and weaknesses of the pharmacokinetic data and concluding on the most relevant parameters with reference to the source study. Make note of any remaining major or other outstanding concerns. Indicate if accurate and sufficient information is included in section 5.2 of the SPC.

Example:

<Pharmacokinetics are adequately described in section 4.3 of the SPC><Section 4.3 of the SPC should be updated to reflect….>

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

<Biosimilarity >

<Rapporteur to include text>

Delete section and title, if not applicable.

The purpose of the studies provided to support biosimilarity should be clearly stated and the design of the study briefly summarised (e.g. cross-over/parallel design, group allocations, choice and number of animals, etc.). State if appropriate statistical analyses were employed, i.e. confirm if the statistics used to demonstrate biosimilarity are appropriate.

If scientific advice was given, conclude whether the advice was followed or not. If not, explain the deviation and whether it was justified or not.

Example:

<Scientific advice was given concerning <insert in brief terms what the advice was>, which was <not> followed in the approach/study design.> <The deviation from the advice was <not> justified and therefore the study <explain the impact on the results and the reliability/relevance of the results>.>

<Justification of fixed combination>

<Rapporteur to include text>

Delete section and title, if not applicable

The rationale for the combination provided by the applicant should be presented. A lack of justification/rationale should be highlighted. Add here briefly whether the data support the rationale or not.

The **assessment** of the acceptance of the combination should be assessed in the relevant section (e.g. pharmacodynamics, pharmacokinetics, clinical studies, dose confirmation etc.), and should take into account potential interactions between the active substances. Check that the dossier complies with relevant guidance on fixed combination products (CVMP guideline on pharmaceutical fixed combination products (EMEA/CVMP/83804/2005) and Q&A documents (EMA/CVMP/EWP/325284/2011)). Copy the final, relevant conclusion(s) to the Overall conclusion on efficacy. The section on benefit-risk balance should also address if the fixed combination is justified or not.>

Examples:

<Product name> is a fixed combination of <active substance>.

<A satisfactory justification for the combination product, in accordance with the CVMP Guideline on pharmaceutical fixed combination products (EMEA/[CVMP](https://www.ema.europa.eu/en/glossary/cvmp)/83804/2005) was provided. The principal advantage claimed for the combination is that it broadens the spectrum of activity for simultaneous treatment and/or prevention of several parasitic infections. However, <…>.>

<The rationale for the fixed combination for the treatment of heart failure is based on pharmacological grounds (both substances act on the RAAS, but at different levels), and in clinical terms in that it is proposed that benazepril and spironolactone have an additive effect in reducing the risk of cardiac mortality in dogs with congestive heart failure.>

<Development of resistance and related risks in animals>

<Rapporteur to include text>

Delete section and title, if not applicable.

Address the anticipated impact of resistance development in view of the effective use of the product in the target species, taking into account the posology. If a CVMP working party was involved in the assessment, this should be stated. The impact of resistance development in humans should not be addressed here, but in Part 3 only.

Resistance issues are to be summarised in relation to the target pathogens, and other pathogens, if relevant. Pay particular attention to current MIC data on pertinent pathogens and information on resistance mechanisms. The speed and degree to which resistance has developed, and its geographic distribution, should be mentioned. Any concerns that exist or may arise related to the risk of increasing resistance should be provided in the conclusion to this section.

Indicate the source reference for the information. In case specific studies have been conducted, describe the design and results of the most relevant studies briefly.

In the end of the section, summarise the extent of evidence provided, briefly conclude on the evidence provided, comment on the strength of evidence. Highlight clearly any outstanding issues and whether these are major or minor or include a clear statement that the development of resistance against the substance/product has been sufficiently investigated and that no outstanding issues remain.

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

If data on resistance development are required but were not submitted, indicate whether their absence is justified/acceptable or not.>

Examples:

<active substance> is a new chemical entity which has not been used in veterinary medicine before. The risk of resistance development with regard to the use of this product <can therefore currently not be assessed><is currently not expected to pose a risk to the population.> <Based on the resistance mechanisms, the product may cause a risk……>

If scientific advice was given, clarify whether the advice was followed or not. If not, explain the deviation and whether it was justified or not.>

Examples:

<Scientific advice was given concerning <insert in brief terms what the advice was>, which was <not> followed in the approach/study design. <The deviation from the advice was <not> justified and therefore the study <explain the impact on the results and the reliability/relevance of the results.>

Describe if prudent use warnings as outlined in relevant CVMP guidance documents (e.g. SPC guidelines for antimicrobials or antiparasitics) have been followed and implemented in the SPC, but it is not necessary to repeat them here. Only further warnings or precautions (not included in a CVMP document) should be listed here.

Dose determination and confirmation

<Rapporteur to include text>

Summarise the data and conclude here on the justification provided by the applicant for the recommended dose, dosing interval, duration of the treatment. The assessment should clearly indicate how the applicant has justified the proposed dose, and if this approach and the data provided are acceptable

If a table is used to provide a brief overview of the amount of data provided (e.g. dose determination/justification/confirmation studies), please use the format given below:

Examples:

<Summary table for study/ies <insert study title

| **Study reference** | **Full study title** | **Results** |
| --- | --- | --- |
|  |  |  |

>

If the same study design was used in several dose determination/ confirmation studies, this should be clearly stated and the study design only described in one place (it is not necessary to repeat this information for each study).

Where dose determination is based on studies conducted under field conditions, relevant information shall be provided as outlined under clinical studies.

Example:

<The <proposed dose of <…>> <dosing interval><duration of treatment><re-treatment> for <product name> was established based on <the findings of a dose determination study><studies described in the target species in published literature><practical experience><extrapolations from already authorised indications>.>

If scientific advice was given, clarify whether the advice was followed or not. If not, explain the deviation and whether it was justified or not.

Example:

<Scientific advice was given concerning <insert in brief terms what the advice was>, which was <not> followed in the approach/study design. <The deviation from the advice was <not> justified and therefore the study <explain the impact on the results and the reliability/relevance of the results.>.>

<In support of the proposed dose, the applicant presented a series of PK/PD model simulations analysing data from several studies in healthy cats.>

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

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

Tolerance in the target animal species

<Rapporteur to include text>

Target animal tolerance is usually based on a pivotal target animal safety (TAS) study, supported by other pre-clinical data including reproductive data, field safety data and bibliographic references. Briefly introduce the data package, and the type of relevant studies (e.g. pivotal TAS, exploratory toxicity, supportive TAS, pilot dose finding etc.)

Describe TAS in the following order: Pivotal and other TAS studies (study results and design), TAS observations from other studies: pre-clinical, clinical and other studies, if applicable. For the other studies, only the TAS-relevant results should be summarised, i.e. the study design should otherwise be described in the relevant section.

Examples:

<One pivotal <GLP-compliant> study and two supportive published studies were provided to investigate target animal safety of the product, in addition to the safety data obtained from <the clinical safety and efficacy trial(s)>.>

If a table is used to provide a brief overview of the most important data to support target animal safety (e.g. pivotal target animal safety study/studies and clinical field studies), please use the following format.

*Examples:*

<Summary table for study/ies <insert study title

| **Study reference** | **Full study title** | **Results** |
| --- | --- | --- |
|  |  |  |

>

The study design and results of the pivotal TAS study should be briefly described. As applicable for the product type, the principles outlined in the VICH GL 43: Target Animal Safety for Veterinary Pharmaceutical Products (TAS) and/or VICH GL 44: Veterinary live and inactivated Vaccines (TAS) might apply, and any deviations of the TAS study from these guideline relevant for the assessment, should be indicated. Other studies of relevance should only be (briefly) described in this section, if not included elsewhere in the dossier, e.g. tolerance testing in the clinical field studies should be described in part 4B.

The following details should be considered and described, as relevant: the doses that were tested in relation to the recommended treatment dose; the duration of the studies and the characteristics of the animals used (age, sex etc); any observed local or systemic adverse events (clinical signs, frequency, severity); a characterisation of the toxicity and margin of safety (if possible).

Where reference is made to studies in species other than the target species (e.g. for reproductive toxicity), a comment should be included on the relevance of extrapolating data from this species to the target animal.

Once all studies – pivotal and supportive – have been considered to the necessary extent, an overall conclusion on the target animal safety section should be made including a statement of the extent of data provided overall (number of pivotal/supportive studies), the strength of evidence that the studies demonstrate on safety that should be reflected in the product information, or monitored. Outstanding issues should be summarised – whether these are major objections or minor issues - and how they should be addressed. Weaknesses of the data should be addressed.

Example:

<It is concluded that the product is in general well-tolerated at the recommended dose. However, <…>. <In conclusion, clinically relevant effects of … cannot be excluded, and <…>.>

<The results from the pivotal TAS study were also reflected in the pre-clinical and clinical studies, where the main adverse reactions reported were vomitus, and inappetence, and local reactions at the injection site.> < In addition to the adverse reactions observed in the target animals safety study, a number of animals in the pivotal field study (add study number) also showed gastro-intestinal signs (vomiting, diarrhoea, inappetence).>

If relevant, tolerance of the product in certain sub-groups of target animals should be described (e.g. very young or old, animals with pre-existing conditions, pregnant or lactating animals, animals-in-contact, etc.).

Example:

<Tolerance in cats with impaired hepatic and renal function has not been demonstrated>.

The assessor should check the SPC and indicate if relevant adverse reactions following the correct use (section 4.6) or overdose (section 4.10) are correctly listed. Likewise, the assessor should indicate any warning statements proposed in the SPC, advising if these can be considered to satisfactorily mitigate risks that might be associated with use of the product in the target species or specific sub-populations (e.g. pregnant or lactating animals, juveniles).

Example:

<The SPC and product information contains adequate warnings about the observed adverse effects and their frequency>

However, the target animal tolerance section should focus on describing the safety characteristics of the product. How potential risks are handled through risk management measures and to what extent they can be regarded as “sufficient” should be summarised in the benefit risk section (part 5) where the risks are put in relation to the benefits to create a complete picture. The most significant reactions should be discussed and risk management measures identified.

If scientific advice was given, clarify whether the advice was followed or not. If not, explain the deviation and whether it was justified or not.

Example:

<Scientific advice was given concerning <insert in brief terms what the advice was>, which was <not> followed in the approach/study design. <The deviation from the advice was <not> justified and therefore the study <explain the impact on the results and the reliability/relevance of the results>.>

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

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

Clinical trials

<Rapporteur to include text>

State here the pivotal (most important and relevant) trials only. If a table is used to provide a brief overview of the amount of data provided, use the following format:

*Examples:*

<Summary table for study/ies <insert study title

| **Study reference** | **Full study title** | **Results** |
| --- | --- | --- |
|  |  |  |

>

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.).

If applicable, include separate paragraphs for different indications, target species 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. If no table is used, the study design and results of the pivotal study should be briefly described*:*

Example:
<One pivotal <one/multi>centre <non->randomized, <fully/partly/semi> <blind/open>, <placebo/positive/non->controlled study (add study number) of X <parallel/cross-over> 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.>

<Summary table for the pivotal study <insert study title:

|  |
| --- |
| ***Reference and Study title***Include the dossier reference. Study title as it appears on the front of the study summary. Enter all the data manually, i.e. don’t copy-paste the applicant’s data, tables or graphs, as this will interfere with the formatting. |
| 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.  |
| Interventions: Test product | *Name, active substance* *Nominal dose rate/regimen.*Method of administration.  |
| Control product/ Placebo |
| Animals | Number, species, sex, age. |
| Eligibility criteria | Eligibility (disease status). |
| Outcomes/endpoints | State clearly the primary and secondary endpoints.  |
| Statistical method | Methods used to compare primary and secondary outcomes, including margin for non-inferiority trials.  |
| Method | Details of any other methodology not addressed above, e.g. schedule of events. |
| ***Results***  |
| Outcomes for endpoints | For each primary and secondary outcome, 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 %. Discussion of the results should be done in the section/text below. |
| Adverse events | List the adverse events and incidence rate for investigational veterinary product and control product.  |
| ***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. Information is necessary with regard e.g. to the objectives, study design, sites (country(ies)), study population (number of study animals, age, sex, disease condition, high number of animals excluded or lost to follow up during the study etc, as relevant, as indicated in the study summary table), investigational and control treatments, primary and secondary endpoints, and statistical methods used to evaluate the results for the primary and secondary endpoint. 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 primary variable, for the ITT and PP population as applicable.

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 treatment (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, if applicable such as VICH anthelmintic or CVMP NSAID GLs), or not. If the study deviates from guidance, indicate if this is has been justified or not. If the applicant has justified not having carried out a test or having undertaken a different test from that specified in the guidelines, the assessor should comment if the justification is deemed acceptable. If scientific advice was given, clarify whether the advice was followed or not. If not, explain the deviation and whether it was justified or not.

Comment on the study results for the primary variable (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. Describe in less detail the results for the secondary variables. 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). Comment on the adverse reactions, causality assessment provided by the applicant, and the identification of any potentially vulnerable sub-populations. Ensure that clear information/conclusions are included here as clinical tolerance will also be considered in the TAS section.

*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). Also summarise the main issues on clinical safety. Indicate the impact of the results on the SPC*.>

*Examples:*

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

<The pivotal 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 and tolerance, 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 efficacy.

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

Brief description of results.

*Examples:*

<The data show 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>.>

<Other studies>

<Rapporteur to include text; Delete section if not applicable>

*Dose determination and/or confirmation studies conducted under field conditions should be described in the relevant section in part 4A.*

*Depending on the product, there might be other pivotal observations addressed in several parts of the dossier, e.g. palatability studies for oral products or mixing instruction (check for observations made in quality part), or the impact of swimming/shampooing for topically applied products (check for observations made in the safety part). Mention such studies in the most appropriate section with a clear heading to facilitate locating the information.*

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

Overall conclusions on efficacy

<Rapporteur to include text>

Briefly summarise the findings conclusions/outcome of each pre-clinical and clinical 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 clinical 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…).

In the case of marketing authorisation for limited market, summarise the data gaps compared to standard requirements.

Examples:

*Pharmacology*

*Pharmacodynamics* results of tests demonstrating the pharmacodynamic mechanisms underlying the therapeutic effect

<The in vitro activity of Y was determined in a very low number of target pathogens, and comprehensive conclusions on the susceptibility and resistance development of the target pathogens to <active substance> cannot be drawn>

<The mode of action has been sufficiently described. The main effects of X are vascular, i.e. it acts primarily as a peripheral arterial vasodilator and as result lowers blood pressure.>

*Pharmacokinetics* results of test the main pharmacokinetic profile

<The pharmacodynamic and pharmacokinetic characteristics of <active substance ><Product name> are generally well documented and have been satisfactorily evaluated in <target species>.>

<Absolute oral bioavailability was approximately < insert value& unit > with a mean Tmax of < insert value& unit >. Systemic clearance was <insert value> and volume of distribution was < insert value& unit >, with an elimination half-life of <insert value& unit>. The primary elimination route is <insert elimination route>.>

*<Justification of the fixed combination>*

<A satisfactory justification for the combination product, in accordance with the CVMP Guideline on pharmaceutical fixed combination products (EMEA/[CVMP](https://www.ema.europa.eu/en/glossary/cvmp)/83804/2005) was provided. The principal advantage claimed for the combination is...>

*<Development of resistance and related risks to animals>*

<The risk of resistance development seems unlikely and not highly critical for a product used in individual companion animals>

<active substance>is a new chemical entity which has not been used in veterinary medicine before. The risk of resistance development with regard to the use of this product is currently not expected to pose a risk to the population.>

*Dose determination and confirmation* results of tests to determine and confirm the dose (including dose interval, duration of treatment and any re-treatment interval)

<Dose justification was based on PK/PD calculations; however, the data were not fully conclusive, and questions have been raised.>

<The dose of <xx> was established based on a number of dose finding studies <range: >, and supported by two dose confirmation studies performed under experimental conditions.>

*Tolerance in the target animal species*

<In the TAS study, Y was well-tolerated in doses up to 3x the recommended dose. In higher doses, gastrointestinal signs were noted in most animals. GIT signs were also reported in the clinical studies at the recommended dose in a few animals…>

<Field studies confirmed that X was well-tolerated at the recommended dose of …>

*Clinical trials*

<The results from two clinical 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].>

<Others (specify, e.g. palatability, efficacy after swimming/shampooing)>:

<Dogs should not be allowed to swim in surface waters for <insert value & unit> after treatment.> <Avoid frequent swimming or shampooing of the animal because the maintenance of effectiveness of the product in these cases has not been tested.>

<The product is considered palatable i.e. it is accepted voluntarily by [species]. Voluntary acceptance of the product has been observed in > [70]/[80]% of <occasions in> [species] studied.>

Part 5 – Benefit-risk assessment

*When 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.*

Introduction

Provide brief summary of product name, active substance(s), formulation(s), intended use and target species, proposed withdrawal period.

Include a brief description of the mode of action and the confirmed dose; check consistency with the product description in the beginning (section 1 – introduction).

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

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.

Examples:

<Product name> is a<n> <presentation> containing <active substance><a fixed combination of X active substances: INN or common names of active substances>. <The active substance is innovative/well-known.> <The combination is considered a new fixed combination of active substances previously authorised within EU.>

<The active substance, <active substance>, 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>.>

<The dossier has been submitted in line with the requirements for submissions under Article 31 of Regulation (EC) No 726/2004 of 31 March 2004.>

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

<The application has been submitted in accordance with Article <Article> of Regulation EU 2019/6 <(full application, abridged application (<hybrid, fixed combination, informed consent, subject to 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,*
* *Improvement of the clinical condition,*
* *Improvement of the physiological status of the animal, or*
* *Reduction of the risks of transmission of a disease to other animals.*

The summary on benefits should address:

The indication(s) including effective dose/route of administration, and how it has been demonstrated (demonstrated in (a) pre-clinical/clinical study) 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.

Benefits for a zootechnical product could be appropriate alteration of physiology or disease status to derive a desired zootechnical benefit e.g. oestrus synchronisation, elimination or reduction of a specific microorganism).

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 <laboratory and/or field> 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 <agreeable indication>.

<Well designed <laboratory> studies <conducted in accordance with GLP> demonstrated that the product is efficacious in <agreeable indication>.

<The cure rate is … >

<The benefit for the treated animal is … / >

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

<The product provides a reliable diagnostic tool by …>

If there remain open issues:

<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. palatability, long lasting effect) resulting in improved compliance.

Other additional benefits should also be mentioned here, e.g. improved treatment options, e.g. if provided by a novel treatment, or reduction of the risk of transmission to humans.

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 produc.

Examples:

<Product name> <has a long-lasting effect ….><reduces the need for antimicrobial treatment ….> <reduces the field contamination ….>.>

<Product name> <increases the range of available treatment possibilities for <….>><provides a new treatment possibility for a minor species ….>, <provides a treatment possibility for <indication>, which is an indication classified as limited market.>

<Product name> is easy to apply by the owner …/facilitates increased administration compliance as it …>.

<The product increases the range of available treatment possibilities against <indication>.>

<The fixed combination facilitates dog handling by reducing the total number of tablets to be given.>

<The product is easy to apply by the owner as it is given once as opposed to other treatments available for this condition which require recurrent injections.>

<An additional benefit of the product is the low number of doses (two) of a medicine that is to be administered to an infected and probably painful dog’s ear, as compared to more commonly available daily applications.>

<The product is administered intravenously and is of value in the treatment of dehydrated patients as it would be standard practice to place an intravenous fluid line to these animals. Additionally, the most common adverse event shown with subcutaneous administration (pain at injection site) is avoided by the administration of the product intravenously.>

<Where the product reduces the incidence of clinical mastitis it can be expected that the product may reduce the need for antimicrobial treatment.>

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

- Any other specific potential risks, according to product type and application

Reference to the SPC recommendation in this section are meant as recommended use considering application route, dosage, frequency and duration of treatment 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 usee.

*Quality*

Examples:

<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*

Examples:

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

*Risks for the target animal*

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

Examples:

<Concerns have been raised for <….briefly summarise points of concern related to target animal safety>. No final conclusion can be drawn on target animal safety 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 <active substance> in <species> <sensitive sub-species or breed> was confirmed in a <…> study. <Effects> were observed in some animals administered <substance> at x mg/kg bw (Yx 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*

Examples:

<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>.

<<Product name> can pose a risk to <specify user group, e.g. children coming into contact with the animal shortly after treatment> and specific measures are necessary to mitigate the risk.>

*Risk for the environment*

Examples:

<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 < specify environmental compartment, e.g. surface water or sediment> <describe scenario, e.g. in case of direct excretion of <active substance> into waterbodies.> <Specific measures are necessary to mitigate the risk.>

*Risk for the consumer*

< Based on the data provided and taking into account a sufficient safety span, a withdrawal period of <x> days was considered acceptable for the use of <Product name> in <target species>.

0 days withdrawal period: If MRL values are established:

<No residues above the MRLs were detected <in target tissues> following treatment and the withdrawal period is set at 0 days <for <food commodity >.

0 days withdrawal period: If “No MRL required”:

<The residue studies available did not show residues of concern in the target tissues following treatment and the withdrawal period is set at 0 days <for <food commodity>.>

<Product name> is not expected to pose a risk to the consumer of <foodstuffs> <meat> <milk> <eggs><honey> derived from treated animals when <Product name> is used according to the <proposed> SPC recommendations. <The withdrawal period established to ensure depletion of residues below the MRLs is <…> days.

<Concerns have been raised for <….briefly summarise points of concern related to consumer safety, e.g. the residue studies available do not allow to establish a safe withdrawal period or inadequate data to conclude on the consumer safety of a new excipient.>. No final conclusion can be drawn on consumer safety until those issues have been satisfactorily addressed.>

*<Resistance>*

Examples:

Lack of efficacy of <active substance> in the treatment of <indication> in <target species> has been reported <outside Europe>. <Concerns have been raised relating to the potential for resistance emergence.>

<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.>

<With respect to antimicrobial resistance, there is no evidence that use of the product has resulted in reduced susceptibility of the target pathogen to <active substance>.

*<Special risks>*

Delete if not needed

<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, 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. 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).

Examples:

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

<Appropriate information has been included in the SPC and other product information 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.>

<The withdrawal period is set at <0> days <for <food commodity>>.

<Fixed combination product: To manage the risk of over-treatment, the product should only be used in animals whose clinical signs are successfully controlled by the administration of the same doses of the individual components given concurrently.>

*User safety*

<User safety risks have been identified, mainly the risks associated with exposure in children. These risks are mitigated by the presentation of the product in a child-resistant packaging.>

<User safety risks have been identified, mainly concerning the risks associated with exposure of reproductive organs. These risks have been addressed by the safety warnings in the SPC.>

*Environmental safety*

<<active substance> is very toxic to dung fauna and aquatic organisms and may accumulate in sediments.

The risk to aquatic ecosystems and dung fauna can be reduced by avoiding too frequent and repeated use of <active substance> (and products of the same anthelmintic class) in <species>.

The risk to aquatic ecosystems will be reduced by keeping treated cattle away from water bodies for <x weeks> after treatment.

*<Consumer safety>*

In case of products for use in Equidae and no MRLs have been established for horse milk.

<Since an MRL for milk has not been established in horses, the product is not authorised for use in horses producing milk for human consumption.>

*<Resistance*>

Prudent use advice as recommended in the revised CVMP guideline on the SPC for antimicrobial products (EMEA/CVMP/SAGAM/383441/2005) should be included, as appropriate, and any specific risk management recommendations for the antimicrobial product under consideration)>

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 safety study).*

Example:

<In accordance with Article 76(3), a non-interventional study to evaluate the occurrence of neurological and ophthalmic adverse events (to be coded using the relevant VEDDRA terminology) in dogs treated with <Product>. The protocol should be submitted to the Committee for review and comments promptly, and no later than 3 months after the Commission Decision granting the marketing authorisation, in order to allow for the study to be conducted in the stipulated period. The due date is <dd Month yyyy>.>

*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.*

Example:

<In accordance with Article 26, …>.

*Novel therapies (Annex II of Reg (EU) 2019/6 (as amended), 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.*

<In accordance with Annex II of Reg (EU) 2019/6 (as amended), section V.1.1.6, …>.

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."

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 these indications, and the CVMP accepted the indications as proposed by the applicant. (*if all the indications are accepted*)>

Or

<The product has been shown to be efficacious for xxx <if not all the indications are acceptable, list here only those (in general terms) that are acceptable>*,* and the CVMP agreed to the following indication(s): <List the agreed indications as outlined in section 3.2 of the SPC>.

<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.>

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 deemed negative.>

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

<<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.>

*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[[2]](#footnote-2)

Evaluation of benefit-risk balance of the product.

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.>

<In addition, the CVMP has recommended conditions for marketing authorisation and product information.>

<Furthermore, the answers to questions raised may affect the final product information and/or other conditions 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) No 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 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) No 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 quality and chemical structure>.>

For situations where no further information should be provided and where the applicant claimed that the compound is a new active substance in comparison to a known substance previously authorised as a medicinal product in the European Union.

<<active substance> in comparison to the known <substance approved> is <not> to be qualified as a new active substance as it <differs><does not differ> significantly in properties with regard to <safety> <and> <efficacy> from the previously authorised substance.>

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. 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:>

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.>

1.B Comments on SPC and labelling

The applicant is asked to revise the SPC and labelling in the light of the answers to questions from CVMP.

<SPC questions are detailed as annotations to the SPC located in a separate document.>

*Questions should be numbered sequentially. Please, use the following headings to indicate ‘major objections’ and/or ‘other concerns’:*

Major objections

Part <no> <title>

*<e.g. Toxicology, User safety, Environmental risk assessment, Residues,…>*

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>

2.C.1 Active substance

1. <Question>
2. <Question>

Part 3

<Title>

1. <Question>
2. <Question>

Part 4

<Title>

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. 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-2)