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COMMITTEE FOR MEDICINAL PRODUCTS FOR VETERINARY USE (CVMP)

GUIDELINE FOR AN ASSESSOR PREPARING ASSESSMENT REPORTS FOR VETERINARY MEDICINAL PRODUCTS

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DATE FOR COMING INTO EFFECT	Immediately

This guideline replaces the existing guideline in Volume 7 of the Rules Governing Medicinal Products in the European Union.

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Guideline for an Assessor Preparing Assessment Reports for Veterinary Medicinal Products

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Additional Notes	This guideline is intended to provide guidance to assessors preparing assessment reports for veterinary medicinal products to ensure that there is consistency and coherence in the assessment of dossiers in the Member States of the European Union.

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Guideline for an Assessor Preparing Assessment Reports for Veterinary Medicinal Products

INTRODUCTORY NOTES

LEGAL BASIS

Directive 2001/82/EC requires that no new veterinary medicinal product may be authorised unless the applicant has demonstrated that the product fulfils the quality requirements, does not present an unacceptable risk for the consumers of food of animal origin, the users of the product, the target animals or for the environment, and will be effective with regard to the claimed indications.

According to Article 25 of Directive 2001/82/EC, it is a requirement to prepare an assessment report.

Article 25 paragraph 4 of Council Regulation 2309/93 provides for an assessment report which describes the assessment of the product and states the reasons for the conclusions.

SCOPE AND OBJECTIVES

The objective of this guideline is to ensure that such assessment reports (ARs) are consistent, clear, complete and logical.

The final decision on an application takes place after several stages in the authorisation procedure. Sequential assessment reports are prepared during the procedure. A draft AR may be generated and subsequently amended and updated in the light of new information from the applicant, oral explanations and discussions in committees. By this process the draft reports lead to the production of the final AR, which will be the document exchanged between Member States in the mutual recognition procedure and which forms part of the CVMP opinion documentation leading to a Commission Decision in the centralised procedure. Full details of the authorisation procedure for both centralised and mutual recognition applications may be found in the Notice to Applicants Volume 6A, Chapter 4 and 2 respectively.

The AR is the key document explaining why a marketing authorisation and each of the proposed indications have been approved or rejected and detailing the basis of the risk versus benefit considerations for the product. It also serves as an audit trail explaining why an authorisation has been granted or rejected and provides an explanation for the agreed contents of the final SPC, labelling and package insert. As such the report is central to the efficient operation of the centralised and mutual recognition procedures.

The AR therefore needs to include some specific features. It should be a total report, comprising a critical analysis of the application. It should be produced on the basis of a full consideration of the dossier supplied by the applicant.

In the centralised procedure, the draft AR should contain sufficient information to provide clear advice to the Committee for Veterinary Medicinal Products as to whether, on the basis of the submitted documentation and all other relevant scientific information, the product conforms to the criteria of quality, safety and efficacy established by Directive 2001/82/EC as amended and if so, under which conditions a marketing authorisation may be granted and, if not, the reasons for a negative opinion.

For the mutual recognition procedure (MRP), the AR provides the basis for mutual recognition. The report should be based on the updated dossier so that assessors from the Concerned Member State(s) (CMSs) need not carry out a full review of the dossier. The updated dossier will consist of the documentation on which the medicinal product has been authorised in the Reference Member State (RMS), taking account of the changes agreed and additional data supplied during the authorisation procedure, after authorisation (e.g. pharmacovigilance data) and any agreed variations. It may be necessary for the expert report to be updated if there have been important changes from the first submission of the dossier. Where variations have been agreed after the initial authorisation has been granted in the RMS, the AR will need to be updated before commencing a mutual recognition procedure.

STRUCTURE AND CONTENT OF THE ASSESSMENT REPORT

i) General points

As indicated above, the AR should be a critical analysis of the whole dossier, which has been updated if necessary. This dossier will include the expert reports, appropriate summaries, published and unpublished data. The Safety and Efficacy assessors should attempt to identify any published material not included in the submission but deemed relevant for the submission.

The AR for the MRP should have a reference as to whether or not the expert reports have been updated to take account of the updating of the dossier The assessor may wish to confirm that the proposed SPC and product literature corresponds to that in the RMS.

The adequacy or otherwise of the expert report should be considered and comment provided, especially in order to point out if all main points of the dossier have been covered.

The critical analysis should include comparisons, where appropriate, of the data in the dossier compared with the requirements of the Directives, the Notice to Applicants for Marketing Authorisations for Veterinary Medicinal Products in the Member States of the European Union, associated guidelines, relevant pharmacopoeial monographs and scientific knowledge. Where an applicant has provided a justification for not having carried out a test or has undertaken a different test from that specified in the directives or in guidelines the assessor should comment on the appropriateness of the approach taken.

The AR must give an indication of compliance with (or indicate deviations from) the requirements of Good Manufacturing Practice (GMP), Good Clinical Practice (GCP), and Good Laboratory Practice (GLP).

There should be appropriate cross-references to the applicant's data. Any fresh analysis of the data by the assessor should be clearly indicated as such and be accompanied by a reference to the source of the data (i.e. from which parts of the dossier it derives).

The AR should include clear conclusions and recommendations, both at the end of each Part and subsection. For draft ARs, it may be recommended that a marketing authorisation can be granted subject to the provision of further data.
For ARs for the mutual recognition procedure, where data do not comply with current guidelines and no valid justification has been provided, the assessor should indicate why the authority has considered the data acceptable or, in the case of new requirements subsequent to the initial authorisation, how the dossier has been updated.

A marketing authorisation may be granted subject to specific obligations to be fulfilled or follow-up measures to be completed by a certain date.

It should be possible to prepare the CVMP AR from the Rapporteur-Co-Rapporteur's assessment reports, and then the European Public Assessment Report (EPAR) from the CVMP AR, where appropriate. In that perspective, special attention should be paid to summaries and conclusions at the end of each subsection of Quality, Safety and Efficacy Parts of the dossier.

The INN (or where no INN exists, an appropriate name of the active substance) should be used when referring to other products/comparators, rather than the invented name of the other/comparator product, except for applications for Generic products. For Generic applications it is essential to include clear reference to the actual product. Codes should not be used to name other products.

ii) Structure

The following are considered to be the necessary elements of an assessment report.

1. The front page of an assessment report should start with a table providing basic information about the application - name of applicant, name of product, date of receipt, application number, any other relevant reference number, name of originating Member State (for MRP) and a contact name with telephone and fax numbers and email address (see Appendix IV).

2. The second page should be an index to the report.

3. There should be a brief introductory paragraph. This can cover information of a general type about the product and its history.

4. The bulk of the report needs to be laid out in sections corresponding to each part of the dossier, as required by Directive 2001/82/EC, for that type of product.

   The headings used for the sections should be those given in the relevant part of The Rules Governing Medicinal Products in the European Union, Volume 6, Notice to Applicants for Marketing Authorisation for Veterinary Medicinal Products in the Member States of the European Union. The headings and sections in the AR should appear in the same order as in the Notice to Applicants.

   Each section should be presented in three parts

   i) There should be a brief summary of the information provided in the dossier or a cross-reference given to an available summary in the dossier.
   If an assessor considers that factual data e.g. tabulated summaries provides a complete and accurate summary of the data presented then this can be incorporated into the AR.

   ii) There should then be a comparison of where the data provided do, or more particularly do not comply with the requirements of the directives and the associated guidelines, relevant pharmacopoeial monographs and scientific knowledge. A reference to the specific page numbers in the original dossier should be included where appropriate, in order to facilitate direct access to the data in the dossier.

   iii) A technical discussion followed by the opinion of the assessor on the adequacy of

the data provided or the justification for a lack of data.

5. For each subsection of the dossier (for example, stability, ecotoxicity and field trials) and the corresponding part of the AR, the assessor should provide an overall conclusions section for that part, drawing on the conclusions of each subsection, indicating any concerns.

6. Finally, there should be a section setting out the assessor(s)' general conclusions, indicating the main strengths and weaknesses of the product and/or the data provided and commenting particularly on the risks in relation to the benefits (benefit-risk section). An indication should be given as to any changes required to the SPC and product literature to ensure that, in the absence of further data, it contains only claims and recommendations for use which have been adequately supported by data and that the precautions, warnings and contra-indications are adequate. In centralised procedures, these conclusions may be used as the basis of Part V of CVMP AR and EPAR.

7. For draft ARs, for example for discussion in the procedure for a marketing authorisation according to Council Regulation 2309/93, an appendix should be attached to the back of the report listing the points for clarification and questions that the assessor(s) considers should be put to the applicant.

8. The AR(s) should be dated and the name and address of the author(s) of the report should be given.

SPECIFIC REQUIREMENTS

The following appendices provide more detailed guidance on the type of information, comments and critical assessment that would be expected in ARs.

Appendix I
Content of Assessment Reports for Veterinary Medicinal Products (excluding Immunological Products)

Part 1 – Summary of the Dossier
Part 2 – Analytical Information
Part 3 – Safety and Residues
Part 4 – Pre-clinical and clinical

Appendix II
Contents of Assessment Reports for Veterinary Immunological Products

Part I – Summary of the Dossier
Part II – Analytical Information
Part III – Safety
Part IV – Efficacy

Appendix III
Guidance Note for an Assessment Report for the Human and Environmental Risk Assessment for Veterinary Medicinal Products Containing or Consisting of a Genetically Modified Organism

Appendix IV
Standard Format for the Front Page of a Mutual Recognition Assessment Report

APPENDIX I

Content of assessment reports for Veterinary Products (excluding Immunological Products)

PART 1 – SUMMARY OF THE DOSSIER

1.A – ADMINISTRATIVE DATA

1. **Product**
   Name of Product (Invented name)
   Active Substance(s)
   Strength
   Therapeutic Class
   Pharmaceutical form
   Route of administration
   Target species

The assessor should provide the basic information from the dossier on these points to provide an easy reference in the report.

2. **Source**
   Name and address of the applicant
   Name and address of the manufacturer(s)) of the dosage form
   Name and address of the manufacturer(s) of the active substance(s)
   Sites involved in the different stages of the manufacture
   Name and address of the importer, where relevant

The assessor should make reference to the suitability of the data on the site of manufacture and any queries requiring resolution.

3. The type of marketing authorisation application should be indicated, for example, bibliographic. Reference should also be made to the legal basis of the application, for example, Well Established Use and how that was justified.

1.B – SUMMARY OF PRODUCT CHARACTERISTICS

Draft SPC
Proposed product literature

1.C – EXPERT REPORTS

Chemical, pharmaceutical and biological
Safety including operator safety and environmental safety
Residues
Preclinical and clinical

PART 2 – ANALYTICAL (PHYSICO-CHEMICAL, BIOLOGICAL AND MICROBIOLOGICAL DOCUMENTATION

It is vital that an assessor is fully cognisant of the relevant CVMP and VICH guidelines relating to the various sub-categories contained within Part II of the dossier. Copies of the most up to date versions of these guidelines are available on the relevant EMEA and VICH web sites.

This should also include the following:

- Where relevant, a discrete and clearly identified critical appraisal of the active substance manufacturer Restricted ("Closed") part of the Active Substance Master File.

- An assessment of the GMP status of the dosage form manufacturing site(s).

Where possible, the quality data should be related to the efficacy and safety of the product.

The required content of this part of the report is detailed below:

2.A – QUALITATIVE AND QUANTITATIVE PARTICULARS OF THE CONSTITUENTS

1. Formulation

A description of the pharmaceutical form together with a table of qualitative and quantitative particulars of the:

- Active substances

- Constituents of the excipients (including colouring matters, preservatives, flavourings, emulsifiers, etc.)

- Constituents of the outer covering of the medicinal product, for example, gelatine capsule.

- A statement of the function of each of the excipients

- Reference to (non-)compendial quality standards

This table should be included in the assessors' report. If there are any deficiencies with these data, for example, if the method of expression of the composition used by the applicant is not considered to be the most appropriate, this should be highlighted.

Comment should be made on any excipients, or levels thereof, included in the formulation which are considered to be atypical for the type of pharmaceutical form under consideration.

2. Containers

- Description of the pack and sizes

- Qualitative composition of the containers

- Closures

- Dosing devices (supplied with the product)

For each point, after the summary of the information provided, the assessor should provide an indication of the suitability of the materials being used, with reference to the requirements of the pharmacopoeia where appropriate. In the case of dosing devices supplied with the veterinary medicinal product, the assessor should comment on the accuracy and precision of these devices in relation to their use.

Comment should be made if the pack sizes are not considered to be the most appropriate, for example, if there are considered to be an unusually high number of doses in a single pack, or if a large number of doses would be taken from a multidose vial.

3. Development pharmaceutics

- Stereochemistry of the active substance(s)
- Composition of product
- Constituents
- Containers
- Overages
- Method of manufacture, including sterilisation
- Antimicrobial preservative efficacy
- Particle size/polymorphism considerations and dissolution

For each part, after the summary of the information provided, the assessor should provide an indication of the appropriateness of the information.

If the applicant has elected to use a mixture of stereoisomers, then the assessor must comment on the relative activities of the different isomers and the applicant’s justification for selection of a mixture of stereoisomers.

Inclusion of chemical preservatives and or antimicrobial preservatives in the formulation must be supported by stability data and antimicrobial preservative efficacy data respectively. The methods used in these studies should have been validated. Comment on these aspects should be provided. If a product only meets the target B criteria of the European Pharmacopoeia for antimicrobial preservative efficacy then this should be highlighted. Comment must be given by the assessor on the supporting data, which should demonstrate that despite failure to meet the target A criteria of the European Pharmacopoeia use of the product does not pose a safety hazard to the target species.

Multi-broaching studies (bung integrity testing) should also be commented on here.

Any overages must be adequately justified and the assessor should comment on this aspect.

If the product is manufactured aseptically when terminal sterilisation would be appropriate the assessor should comment on the applicant's justification for this.

2.B – METHOD OF PREPARATION

- Flow chart of manufacture with an indication of the stages for sampling and in-process control tests
- Description of stages of manufacture, including those steps to ensure homogeneity is achieved
- Batch size (range if applicable)
- Actual manufacturing formula including mention of any substances which may disappear in the course of manufacture and any overages (which should be indicated and justified)
- Details of substances which may be used in the manufacturing process, but which are removed during production, for example, granulating and coating solvents
- Process validation study results
- Process validation scheme
- Details of sterilisation processes and/or aseptic procedures for sterile products, and validation of sterilisation processes for non-pharmacopoeial sterilisation cycles.

Comments should be made if the flow chart is not adequately clear and detailed.

The assessor should comment on whether or not sufficient details have been submitted to provide confidence that the production method will consistently result in safe and effective products, and that batch to batch consistency is achievable.

To this end the assessor needs to consider points such as whether the manufacturing method has been described in sufficient detail, and whether all the critical steps in the process have been identified and controlled.

The assessor should comment on whether the Applicant's definition of the process as being a standard or a non-standard process has been fully justified.

The assessor should indicate whether or not validation data have been provided for all the processes. For each, the degree to which the data is adequate and provides the necessary reassurances should be remarked upon. In addition if the process validation studies have not been conducted at the proposed production batch size then the relevance of these data to full scale production should be commented on by the assessor. The suitability of any proposed process validation scheme should be commented upon.

With regards to in-process tests, in the exceptional circumstances that an in-process test does not form part of the finished product specification, then the assessor should comment on the validity of the arguments provided in support of testing in-process rather than testing the finished product.

2.C – CONTROL OF STARTING MATERIALS

"Starting materials" refers to all the constituents of the medicinal product and, if necessary, of its container.

1. Starting materials

1.1 Starting materials listed in pharmacopoeias

In order of precedence, European Pharmacopoeia, Member State Pharmacopoeia, third country Pharmacopoeia.

The assessor must comment on the appropriateness of the pharmacopoeial monograph to ensure the quality of the substance, particularly for those monographs of Pharmacopoeias of third countries. If tests additional to those included in the monograph are conducted, for example, for residual solvent levels or particle size, the assessor should comment on this and on the suitability of the methods used and the limits proposed. The assessor must state how it has been confirmed that the pharmacopoeial monograph adequately controls the substance from the source(s) specified. For example, for active substances this might be done by reference to an ASMF (Active Substance Master File) or by a European Pharmacopoeia Certificate of Suitability, or by another means.

For substances of animal, plant or microbiological origin - the details on the source needs to include the species, their country of origin and the means of harvesting and collection, and the extent to which this is adequately described and specified should be mentioned. The assessor should indicate if the risks from the material are acceptable taking into account any changes to disease patterns or new knowledge on species susceptibility to infectious agents.

The applicant should have provided sufficiently precise specifications and batch analyses data (which might be in the form of Certificates of Analysis) for each starting material to enable the assessor to comment on its batch to batch consistency and the adequacy of routine testing.

The assessor should summarise the stability data presented for the active substance, with particular reference to the storage conditions (including the packaging used). Comment should then be included on any special storage precautions and whether the proposed retest period has been adequately supported.

1.2 Starting materials not in a pharmacopoeia

- Name(s), structure
- Method of synthesis, flow diagram and description
- Specification, analytical methods and their validation
- Impurities
- Batch analyses data
- Stability (including any special storage precautions and whether the proposed retest period has been adequately supported)

The assessor should comment on the suitability of the proposed specification to ensure that the batches are representative of those used in the efficacy and safety studies.

In terms of impurities, comment should be made on their levels and methods of control and whether mass balance has been achieved. The assessor should comment on the thoroughness with which the company has investigated the extent of impurities present. Comment should also be made whether

the impurity limits in the specification are considered qualified or justified in terms of safety, for example, by the toxicological studies.

Colouring matters must satisfy the requirements of Council Directive 78/25/EEC and the assessor should comment on this.

For substances of animal, plant or microbiological origin - the details on the source needs to include the species, their country of origin and the means of harvesting and collection, and the extent to which this is adequately described and specified should be mentioned. The assessor should indicate if the risks from the material are acceptable taken into account any changes to disease patterns or new knowledge on species susceptibility to infectious agents.

For materials of animal origin, the assessor should comment on the proposed measures to ensure freedom from pathogenic agents.

The applicant should have provided sufficiently precise specifications and batch analyses data (which might be in the form of Certificates of Analysis) for each starting material to enable the assessor to comment on its batch to batch consistency and the adequacy of routine testing.

If an excipient is new, this must be clearly stated, and the adequacy of the supporting data provided (as listed in the bullet points above) should be discussed in the assessment report.

The assessor should summarise the stability data presented for the active substance, with particular reference to the storage conditions (including the packaging used). Comment should then be included on any special storage precautions and whether the proposed retest period has been adequately supported.

1.3 Physico-chemical characteristics liable to affect bioavailability

If bioavailability of the active substance(s) within the product depends on specific factors, for example any of the following, then appropriate details and a discussion of their affects should be provided: crystalline form and solubility coefficients; particle size (where appropriate after pulverisation); state of solvation; oil/water partition coefficient; (possibly) pKa.

2. For source materials such as micro-organisms, tissues of either plant or animal origin, cells or fluids (including blood) of human or animal origin or biotechnological cell constructs

The assessor should comment on the origin and history of the starting materials for these, with respect to the final quality, safety and batch to batch consistency of the finished product.

For substances of animal, plant or microbiological origin - the details on the source needs to include the species, their country of origin and the means of harvesting and collection, and the extent to which this is adequately described and specified should be mentioned. The assessor should indicate if the risks from the material are acceptable taking into account any changes to disease patterns or new knowledge on species susceptibility to infectious agents.

Cell banks – confirmation should be made in the assessment report that the cell characteristics have remained unchanged at the passage level used for production and beyond.

Seed materials, cell banks, pools of serum and other material of biological origin, and when possible the source materials from which they are derived – comment should be included in the

assessment report regarding the testing performed for adventitious agents, including the validation of any further processing necessary to ensure the elimination and/or inactivation of such agents.

2.D – SPECIFIC MEASURES CONCERNING THE PREVENTION OF THE TRANSMISSION OF ANIMAL SPONGIFORM ENCEPHALOPATHIES

The assessment report should include comment regarding demonstration that the medicinal product is manufactured in accordance with the Note for Guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products.

2.E – CONTROL TESTS CARRIED OUT AT INTERMEDIATE STAGES OF THE MANUFACTURING PROCESS

For tests described under this section of the dossier, the assessor should comment on these and the way in which these intermediate tests ensure the conformity of the veterinary medicinal product. The analytical methods and their validation, including any shortcomings, should be described.

In the exceptional circumstances that an intermediate test does not form part of the finished product specification, then the assessor should comment on the validity of the arguments provided in support of testing the intermediate product rather than on the finished product.

If any intermediates are stored, the suitability of their assigned shelf-life should be commented upon.

2.F – TESTS ON THE FINISHED PRODUCT

A summary table of validated tests and acceptance criteria should be provided.

For each test the following points should be included:

- Function of test
- Brief description of test
- Release limits (and shelf-life limits if different)
- Summary of validation of test
- Frequency of non-routine tests

If the product concerned is subject to the provisions of a general monograph of the Ph.Eur., the assessor should comment on how the provisions are applicable.

For control tests conducted both at the time of manufacture and throughout the shelf-life of the product, the assessor should summarise what tests are performed, and then indicate whether or not this provides sufficient information and control.

Comment is required as to whether or not the level of detail provided for each test method is such as to allow the control laboratory to repeat the test on the product. Furthermore the adequacy of the supporting validation data for each of the non-pharmacopoeial finished product test methods should

be commented upon, which for example may include assays for the active substance, assay for the preservatives (chemical and antimicrobial), dissolution tests and sterility tests. The significance of any omissions from the validation data should be addressed by the assessor. In the case of *in vitro* tests designed to monitor the *in vivo* performance of products, the assessor should comment on the correlation studies conducted and whether or not the *in vitro* test method is sufficiently discriminating between batches with different *in vivo* performances.

If the limits for the active substance content of the finished product exceeds $\pm$5% at the time of manufacture this must be specified and the adequacy of the justification for this must be commented upon. Similarly if any of the limits (e.g. for degradation product levels, pH, etc) applied at the time of manufacture differ from those applied throughout the shelf-life of the product, the assessor should highlight this and indicate whether the stability data support this and furthermore whether this is likely to influence the safety or efficacy of the formulation. It should be mentioned whether impurity limits (with the focus on degradation products) are up to the qualification level or justified by toxicological studies.

Comment should be made on the batch analyses data provided, particularly with reference to the consistency of manufacture, and evidence that the production process is well controlled.

If it is known that a Member State has arranged for independent analysis to be performed on the product, this should be stated. If available, the name and address of the laboratory at which the sample(s) were tested should be given and a copy of the test results should be appended to the assessors report.

2.G – STABILITY TESTS

Stability of the finished product:

A summary table of results of tests (usually on at least 3 batches, although 2 batches is the minimum for existing active substances in conventional dosage forms) should be included with the following:

- Brief description
- Results with batch number, batch size, dates of manufacture and testing, and including clear reference to the length of the studies
- Parameters studied
- Test methods and, if different from those described in Section 2.E, validation studies
- Justification for the proposed shelf-life and the proposed storage conditions

The assessor should comment if the stability data presented is not relevant to the product to be marketed in any respect (e.g. differences in containers, composition, method of manufacture). It is useful to indicate if some or all of the batches studied were pilot batches.

Also, if more than one type of container is to be used, has data been provided on batches of the product stored in each container type/size? It would be helpful to indicate the extent to which the data has been updated since the original authorisation was granted by the originating Member State.

The assessor should comment on the temperature, humidity and light conditions to which the product was exposed in the stability studies, and whether or not these are in accordance with VICH Guidance.

The assessor should comment on the proposed shelf-life and storage conditions and whether they are supported by the data presented. The justification for and suitability of the proposed specifications at the end of shelf-life should also be the subject of comment. If appropriate, the maximum permitted level of degradation products should be stated. If the data have been extrapolated in order to support the proposed shelf-life this should be stated and the validity of these extrapolations should be commented upon by the assessor.

It is useful if confirmation is provided that there are for example, "….no significant changes" or alternatively that "…..observed physical and chemical changes were small, and not likely to have a significant effect on the efficacy and safety of the product when used in accordance with the directions given in the SPC". The following "standard" wording may also be used "In general, the results support the shelf-life and storage conditions as defined in the SPC."

Stability of the reconstituted product, or stability of the product in use, or stability of the product incorporated into the administration vehicle (e.g. feed/water/milk), as appropriate:

The in-use specification should be summarised and its adequacy should be commented upon.

A summary table of results of tests should be included with the following:

- Brief description
- Results with batch number, batch sizes, dates of manufacture and testing
- Parameters tested
- Test methods and validation where appropriate
- Justification for the proposed shelf-life
- If appropriate, compatibility with administration devices

Similar comments apply. Again the assessor should comment on the proposed shelf-life and storage conditions on reconstitution, in-use or in the administration vehicle, as appropriate, and whether they are supported by the data presented. The assessor should ensure that the proposed shelf-life is adequately justified. If appropriate, the maximum permitted level of degradation products should be stated and comment given on their toxicological qualification.

In the case of products incorporated into feed, the assessor should comment on whether the product may be incorporated into both mash and pellets. In the case of pelleting, appropriate processing conditions should be defined in the SPC. For stability studies on pelleted feed, it is necessary to distinguish between degradation resulting from the pelleting process and that arising during subsequent storage. Where a wide range of assay results are reported for medicated feeds, the assessor must comment on the significance of this in terms of efficacy and safety. Any potential for segregation of the active substance in the medicated feed on transport should be commented upon by the assessor.

Assessor's conclusions on Quality

Since the preceding sections are largely descriptive, the assessor should present a Conclusions section here which is more focussed, with discussion indicating any important or interesting issues and any concerns over the quality of the product such as batch to batch consistency, shelf-life and stability. If there remain any concerns with respect to quality, it would be helpful if the assessor indicated if these might for example be addressed by amending the Summary of Product Characteristics.

For standard and uncontentious products the following "standard" wordings could be considered useful for this section (if appropriate): <Information on the development, manufacture and control of the active substance, and finished product have been presented in a satisfactory manner. The results of tests carried out indicate satisfactory consistency and uniformity of the important quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance.">; <The quality of the product is considered to be acceptable when used in accordance with the conditions defined in the SPC. Physicochemical and biological aspects relevant to the uniform performance of the product have been investigated and are controlled in a satisfactory manner.>

The following standard wordings could be considered useful for the Joint Rapporteur's and Co-rapporteur's assessment report on the Responses to the List of Questions: <…..There are a number of minor unresolved quality issues which have no impact on the Benefit/Risk ratio of the product. These could be considered as Follow-Up Measures and ……..>

If there are any outstanding data which need to be provided as Follow-Up Measures these should be mentioned here, with a comment if this is reflected in the SPC.

PART 3 – SAFETY AND RESIDUES DOCUMENTATION

INTRODUCTION

It is vital that an assessor is fully cognisant of the relevant legislation and guidelines relating to the various sub-categories contained within Part III of the dossier. The assessor should be aware of the legislation in Directive 2001/82/EC as amended by Directive 2004/28/EC, which is available in a consolidated Directive published on the Pharmacos website. In addition the assessor should be familiar with the relevant sections of Notice to Applicants (NTA) Volume 6B, CVMP Notes for Guidance, VICH Guidelines and OECD Guidelines. Copies of the most up to date versions of these guidelines are available on the websites for EMEA [www.emea.eu.int] and Pharmacos [www.pharmacos.eudra.org]. Details of where to get copies of OECD Guidelines are on the website [www.oecd.org].

Directive 2001/82/EC, as amended requires that no new veterinary medicinal product may be authorised unless the applicant has demonstrated that the use of the product will not present an unacceptable risk for the consumers of food of animal origin, the target animals, the environment, and users of the product.

With respect to Part 3 of the dossier, Directive 2001/82/EC, as amended requires that the safety documentation shall show:

1. the potential toxicity of the veterinary medicinal product and any dangerous or undesirable effects which may occur under the proposed conditions of use in animals; these should be evaluated in relation to the severity of the pathological condition concerned;

2. the potential harmful effects to man of residues of the veterinary medicinal product or substance in foodstuffs obtained from treated animals and what difficulties these residues may create in the industrial processing of foodstuffs.

3. the potential risks which may result from exposure of human beings to the veterinary medicinal product, for example during its administration to the animal;

4. the potential risks for the environment resulting from use of the veterinary medicinal product.

Furthermore, with respect to point 2, above, the Directive states that: *"A veterinary medicinal product may not be the subject of a marketing authorisation for the purpose of administering it to one or more food-producing species unless the pharmacologically active substances which it contains appear in Annexes I, II, or III to Regulation (EEC) No 2377/90."*

It is clear that in the case of most centralised MA applications for products intended for food producing animals, the safety data pertaining to Part 3A of the dossier will be similar or identical to those previously assessed by CVMP during the MRL application. Often the applicant for the centralised MA is the same as the MRL applicant and in such cases, the assessor should make use of the existing MRL assessment and MRL Summary Report to write the assessment report.

In the case of National MA applications (and subsequent decentralised MA applications) for products intended for food producing animals, it may also be that the applicant is the same as the

MRL applicant and in these instances the assessor should make use of the existing MRL assessment and MRL Summary Report to write the assessment report.

If, however, for those applications above, in which the applicant for the MA was **not** responsible for the MRL application the assessor may not use the data (and dossier) from the existing MRL assessment and MRL Summary Report. However, the assessor must be fully cognisant of the MRL Summary Report because it is a published document and is considered as generally available knowledge on the substance. If an applicant chooses to submit an MRL Summary Report as one of the literature references in place of conducting full toxicity studies, (in the interest of not repeating animal studies and therefore reducing the use of animals), this must be supported by an acceptable justification for the omission and it must be assessed as any other published reference.

The assessor must also be cognisant that additional safety studies may have been performed since the time of the MRL application. In such cases, where the new data indicate that the ADI or MRL are unsound or may need to be revised, the matter should be referred to the European Commission for consideration by the EMEA.

As a consequence of the use of an existing MRL assessment and MRL Summary Report, the primary focus of the assessment of the safety data in Part 3A of the dossier in relation to user safety is to assess potential risks from exposure to the product during or after its administration to the animal. The assessor should not make a new assessment of the data or make different conclusions, unless there is due concern that the MRL assessment requires re-consideration; also the assessor should not duplicate any ADI assessment conducted in the MRL assessment.

In the case of products intended for companion animals where there is an existing MRL and if the applicant is the same as the MRL applicant, the assessor should make use of the existing MRL assessment and MRL Summary Report for the pharmacological and toxicological data to write the assessment report. If the applicant for the MA was **not** responsible for the MRL application, the same advice as given above for food producing species applies

The headings used in the Assessment Report should be those given in the Notice to Applicants for Marketing Authorisation for Veterinary Medicinal Products in the Member States of the European Union, Volume 6B of the Rules Governing Medicinal products in the European Union, and they should appear in the same order. Doses in toxicity and residue studies should be given in mg/kg body weight or mg/kg body weight/day; where other units are given, these should be converted (where possible and practicable) to mg/kg bw/day).

The studies, which should conform to the requirements of CVMP guidance and recognised guidelines, should be summarised to give relevant and significant details of the guideline or protocol used, the effects and endpoints observed and compliance with Good Laboratory Practice (GLP), particularly for unpublished reports.It is recognised that for published reports and older studies, information on GLP compliance may not be available and this should be noted. If the test has been conducted according to recognised guidelines e.g. OECD (and/or in accordance with CVMP and VICH requirements) then this should be stated. Where no information on a particular aspect is provided then this should be also stated, e.g. *"No data available"*. The summaries should be presented in a tabular format where possible as indicated in the sections below.

A brief and clear conclusion on each study shall be drawn as to its validity and quality and to its contribution to the risk assessment. The conclusion should be critical and point out obvious flaws in study design or shortcomings in their conduct, including failure to comply with GLP or relevant guidelines. In addition, it is important for the assessor to conclude on the relevance of the effects observed in the study for risks to humans and the environment and on the significance of any deviations from the principles of GLP or relevant guidelines, and in particular, to the effects of any

such deviations on the integrity/validity of the data presented. The assessor should comment on the justifications submitted for deviating from recognised guidelines and also on justifications for omitting data.

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According to Directive 2001/82EC an excipient used in the pharmaceutical field for the first time shall be treated like an active substance.

With reference to point 4 above, the environmental risk assessment is addressed under Part 3A

PART 3A – SAFETY DOCUMENTATION

3.A.1 – PRECISE IDENTIFICATION OF THE PRODUCT & SUBSTANCES CONCERNED BY THE APPLICATION

An understanding of the basic physicochemical properties of the substances used in a product is useful and sometimes essential to the understanding of its biological effects, including pharmacology and toxicology, and environmental and user safety. The assessor should briefly summarise these properties as given in the Notice to Applicants (reference Part III.A.1) and this should be recorded in a tabular format

3.A.2 – RELEVANT PHARMACOLOGICAL STUDIES

Pharmacological studies are of fundamental importance in clarifying the mechanisms by which the veterinary medicinal product produces its therapeutic effects and these are reported in Part 4 of the assessment report. However, pharmacological studies may also assist in the understanding of toxicological phenomena or show pharmacological effects in the absence of toxic responses and should therefore be considered in the evaluation of user safety.

Where possible, reference should be made to existing CVMP MRL Assessment Reports[1] and MRL Summary Reports that have previously addressed pharmacological data presented under this heading; the assessor is reminded of the notes in the Introduction on the use of these reports.

3.A.2.1. Pharmacodynamics

The assessor should report on studies conducted to establish the pharmacodynamic effects and the mode of action if relevant to the evaluation of user safety. The assessor should consider studies that assist in the understanding of toxicological phenomena, and also studies that may produce pharmacological effects in the absence of a toxic response or at doses lower than those required to elicit toxicity, and studies that show secondary pharmacodynamic effects in the absence of toxicity. The assessor should summarise the details of the tests conducted, such as species and strain, routes of administration, and doses and the nature of the significant effect(s) (if any) should be described and NOEL/NOAELs identified.

There should be a brief conclusion at the end of the section highlighting any major points on pharmacodynamics and identifying the most relevant endpoint and NOEL/NOAEL in relation to user safety. The conclusion should also record if the data submitted are satisfactory and if not, should give significant deficiencies that need to be addressed.

[1] Note : the assessment reports are only available to assessors for centralised procedures.

If the same studies are included in both Part III and Part IV the assessment should be carried out only once and reference should be made to this assessment in the other part of the assessment report.

3.A.2.2. Pharmacokinetics

The assessor should report on the studies of the fate of the active substance and its metabolites in the species used in the toxicological studies submitted, covering absorption, distribution, metabolism and elimination (ADME). The assessor should comment on how the data are related to the dose/effect findings in the pharmacological and toxicological studies and if determine adequate exposure has been determined.

The pharmacokinetics of the active substance following oral exposure to residues may have been considered as part of the MRL application and the assessor should make reference to the MRL summary report. Assessment of pharmacokinetics in Part 3A should relate mainly to user exposure. Normally the data should be described in the following sequence:

– *absorption;* absorption from the gastrointestinal tract, across the skin, from the injection site, *in vitro* data. Bioavailability of the active substance. AUC measurements.

– *distribution;* data on general patterns of distribution, identification of target organ(s).

– *metabolism;* data on hydrolysis in the gastrointestinal tract, oxidation in the liver, conjugation in the liver, deconjugation in the kidney. Quantitative data on metabolites should be given where possible and a metabolic pathway diagram provided.

– *excretion;* routes of excretion including urinary; faecal, exhalation, percutaneous and in milk. Where available, data on hepato-biliary recirculation. This is often a convenient place to note clearance from plasma and organs.

If the same studies are included in both Part III and Part IV the assessment should be carried out only once and reference should be made to this assessment in the other part of the assessment report.

Bioequivalence data would usually be considered in Part 4 of the dossier.

The assessor should report on the studies of the fate of the active substance and its metabolites in the species used in the toxicological studies submitted, covering absorption, distribution, metabolism and elimination (ADME). The assessor should comment on how the data are related to the dose/effect findings in the pharmacological and toxicological studies and if determine adequate exposure has been determined.

3. A.3 – TOXICOLOGICAL STUDIES

Toxicological studies provide data on adverse effects of the substance(s) in the product and in most cases the studies would be conducted with the active substance(s), rather than the formulated product. However, some studies are required on the formulated product where user safety exposure needs to be assessed. The tests themselves should follow the relevant OECD guidelines or other recognised guidelines and any deviation should be justified.

Where possible, reference should be made to existing CVMP MRL Assessment Reports[2] and MRL Summary Reports that have previously addressed toxicological data contained under this heading; the assessor is reminded of the notes in the Introduction on the use of these reports.

The assessor should report on all the toxicological studies submitted including relevant and significant details of the guideline or protocol used, the effects and endpoints observed and compliance with Good Laboratory Practice (GLP). If studies are submitted which are not relevant to the evaluation of user safety, the assessor should note this and make no further assessment. The emphasis in the assessment report should be on summarising significant details in identifying and concluding on risks in relation to users and identifying if the data submitted are satisfactory for evaluation, rather than duplicating detailed descriptions of studies conducted that have previously been summarised in the Expert Reports and dossier.

There should be a brief conclusion at the end of each section highlighting any major points and identifying relevant endpoints and NOEL/NOAELs in relation to user safety. The conclusion should also record if the data submitted are satisfactory and if not, should give significant deficiencies that need to be addressed.

For applications for products intended for companion animals, the assessor must be fully cognisant with the Directive and relevant Articles permitting reduced data packages. The assessor should consider the acceptability of the justifications submitted for omitting data and evaluate the reduced data package commenting on any deficiencies that need to be addressed.

3.A.3.1. Single dose toxicity

Acute LD_{50} studies are not required although they may be submitted where they exist in the study archive or in published literature. For new substances modern single dose toxicity studies are required to predict the possible effects of acute over dosage in the target species, the possible effects of accidental administration to humans, and the doses that may usefully be employed in the repeat dose studies. The studies to be carried out should be selected with a view to providing information on user safety, e.g. if substantial exposure of the user of the veterinary medicinal product is anticipated, for example by inhalation or dermal contact, these routes should be studied.

If MRL assessments and MRL Summary Reports are being cross referred to, the assessor should be aware that studies relating to acute toxicity may not have been addressed during MRL applications for products intended for food producing species because acute LD_{50} toxicity studies are no longer a requirement of VICH guidelines (as adopted by CVMP) relating to consumer safety.

The assessor should summarise the studies and results should be presented in tabular form recording signs of toxicity, deaths, doses and where possible target organs and for older studies the numerical LD_{50} values.

When inhalation studies are available, results should be reported in the same way as for other routes. Attention should be paid to local pulmonary effects. Duration of exposure should be stated for inhalation studies. Studies using other routes of exposure should be considered in a similar way.

[2] Note : the assessment reports are only available to assessors for centralised procedures.

3.A.3.2. Repeated dose toxicity

Repeated-dose toxicity tests are intended to reveal any physiological and/or pathological changes induced by repeated administration of the active substance or combination of active substances under examination, and to determine how these changes are related to dosage.

Repeated dose studies involve oral administration of the test substance for periods of 90-days and chronic studies of up to one year duration. Repeated dose studies may be available in the case of products containing active substances with MRLs for food-producing animals. They may not necessarily be available for products intended exclusively for use in companion animals.

The assessor should summarise the studies, preferably in a tabular form, focusing on the significant details and findings and the overall conclusions. During the assessment of the data, the assessor should evaluate the choice of species, the method and frequency of administration and the length of the studies and include relevant details such as: species; strain; sex; dose (in mg/kg bw {/day}); vehicle (if appropriate); route; duration of dosing; and duration of any recovery period in the assessment report as appropriate.

The assessor should include in the summary any significant observations such as, information on clinical signs, blood biochemistry, behavioural changes, gross pathology, and histopathology at termination, and where relevant at interim kill or interim deaths. It may be relevant to include comments on deaths that occur, and assessors should check that there was some attempt by the sponsor or the study supervisors to determine the cause of death or more specifically, whether or not death was due to the substance or to some other cause such as accident or infection.

Target organs should be identified, any compound-related effects reported, and NOEL/NOAELs identified. They may provide early indications of long-term effects such as pre-neoplastic changes and other chronic effects. Where relevant, a mechanism for the toxic effects seen should be proposed or identified. The NOEL/NOAELs should not differ from those previously identified for studies that were assessed in the MRL application. An overall summary should be included in tabular form if not already included.

For the purposes of determining the safety of residues of veterinary drugs in food producing species, the assessor should comment on the significance of any deviation from the current CVMP-VICH requirements recommend that two 90-day repeat dose toxicity studies (using one rodent and one non-rodent species) and, usually, a chronic study in the most sensitive species,

3.A.3.3. Tolerance in the target species animal

The assessor should summarise any signs of intolerance that have been observed during studies conducted in the target species. The detailed assessment of these studies should be included in Part 4 of the assessment report and it may be appropriate to cross-refer to this assessment. The assessor should not duplicate the evaluation as this can lead to confusion if there are different interpretations and conclusions by different assessors. If the assessor comes to different conclusions these should be discussed with the other assessor and an overall conclusion reached. A cross reference should be included if there is information on studies which are relevant to the evaluation of human safety

3.A.3.4. Reproductive toxicity, including developmental toxicity

3.A.3.4.1. Studies of the effects on reproduction

The purpose of these studies is to identify possible impairment of male or female reproductive function or harmful effects on progeny resulting from the administration of the medicinal products or substance under investigation.

The assessor should summarise the studies, preferably in a tabular form focusing on the significant details and findings and the overall conclusions. The attention of the assessor is drawn to existing CVMP-VICH guidelines relating to reproductive toxicity and developmental toxicity. The assessment report should include significant observations on gonadal function, effects on the oestrous cycle, mating behaviour, conception, parturition, lactation, weaning and growth and development of the offspring, that are relevant to the conclusions on reproductive toxicity. In addition the assessor should note critical absences in these data and comment on any outstanding deficiencies that need to be addressed.. For complicated dosing regimes and multigeneration studies a generation diagram to show the dosing and fates of the F0, F1 ..Fn etc. generations can be useful and should be provided where necessary.

Details of significant adverse effects should be recorded and NOEL/NOAELs reported.

Significant effects from the reproductive studies relating to target species safety may be highlighted here and cross-referred to Part 4 of the assessment report where they should be discussed in more detail. The safety assessor should draw the attention of the veterinary/efficacy assessor to these observations.

3.A.3.4.2. Study of developmental toxicity

Studies conducted under this heading have traditionally been performed in two species (one rodent and one non-rodent); however the current CVMP-VICH guideline allows for a tiered approach that may result in reduced animal testing[3]. The assessor should comment on the suitability of the approach adopted by the applicant under this heading.

These tests should be designed to detect any adverse effects on the pregnant female and development of the embryo and foetus consequent to exposure of the female from implantation through the entire period of gestation to the day before caesarean section.

The assessor should summarise the studies, preferably in a tabular form focusing on the significant details and findings and the overall conclusions.

The assessor should include relevant data on the methodology employed, and adverse effects such as enhanced toxicity relative to that observed in non-pregnant females, maternal and embryo-fetal toxicity, embryo-fetal death, altered fetal growth and structural changes to the fetus. The periods of dosing should be reported and it should be noted if this failed to cover the period for implantation until immediately before the expected day of parturition.

The assessor should differentiate between anomalies that appear to have been induced by maternotoxic effects and true teratogenesis and a NOEL/NOAEL reported.

[3] VICH Guideline 32 on developmental toxicity testing has not yet been implemented in the EU. The implementation is postponed until appropriate changes to the Annex to Directive 2001/82/EC have been adopted.

Significant effects from the developmental toxicity studies relating to target species safety may be highlighted here and cross-referred to Part 4 of the assessment report where they should be discussed in more detail. The safety assessor should draw the attention of the veterinary/efficacy assessor to these observations.

3.A.3.5. Genotoxicity

A standard battery of *in vitro* and *in vivo* genotoxicity tests in accordance with established guidance shall usually be carried out on the active substance(s). In some cases, it may also be necessary to test one or more metabolites that occur as residues in foodstuffs.

The CVMP-VICH guideline relating to genotoxicity testing for evaluating the safety of residues of veterinary drugs in human food details the battery of *in vitro* and *in vivo* tests recommended under this heading.

Tests for genotoxic (mutagenic and clastogenic) potential are performed to reveal changes, which a substance may cause in the genetic material of cells. Any substance intended for use in veterinary medicinal products must be assessed for mutagenic properties.

The battery of mutagenicity tests detailed in the CVMP-VICH guideline would normally be expected to be provided here. The assessor should comment on the relevance of the studies selected and their state of validation whenever a less common test is employed.

The assessor should also comment on the relevance of the results of the assays and on the suitability of any statistical tests used. Results should be presented in tabular form and the assessor should report a conclusion on the mutagenicity of the substance based on the results of the studies provided and any known structure-activity relationships.

3.A.3.6. Carcinogenicity

The aim of carcinogenicity bioassays is to determine the carcinogenic potential of substances. Carcinogenicity bioassays in laboratory animals represent the most suitable experimental approach to explore the carcinogenic potential of a substance. If appropriate, the study of carcinogenicity may be combined with long-term toxicity studies. The harmonised CVMP-VICH guidelines require that carcinogenicity bioassays are necessary for substances that are suspected to have carcinogenic potential*:*

- where structure-activity relationships indicate a close chemical analogy with known carcinogens;
- where findings in toxicity studies have identified potentially pre-neoplastic lesions or are indicative of neoplasia.
- where genotoxicity testing produced results indicating a possibility of carcinogenic effects;

The assessor should summarise the studies, preferably in a tabular form focusing on the significant details and findings and the overall conclusions. The assessor should comment upon the significance of any omission to submit carcinogenicity bioassays, and the justification for this approach by the applicant.

3.A.4 – STUDIES OF OTHER EFFECTS

3.A.4.1. Special studies

These tests are required to address the effects observed during repeated dose studies in animals which may include changes indicative of immunotoxicity, neurotoxicity, endocrine dysfunction, etc, and further testing may be required, e.g. sensitisation studies, delayed neurotoxicity tests, mechanistic studies etc.

Other tests such as those for inhalational exposure, skin/eye irritation and skin sensitisation may be chosen because of potential for user exposure. Studies on the active substance should only be included in this section and those on the formulated product should be included below in 3.A.4.4.

The assessor should summarise the studies, preferably in a tabular form focusing on the significant details and findings and the overall conclusions. The assessor should comment upon the significance of studies submitted and the justification for this approach by the applicant.

3.A.4.2. Observations in humans

For novel active ingredients there may be no data available following human exposure and this should be stated in the report. For new veterinary medicines with active substances that have been/are used in other applications such as human medicine, there may be human data available.

The assessor should comment on the relevance of the data for user safety assessment The assessor should summarise the data in a tabular form recording effects observed (including adverse reactions), the number of patients or volunteers and the doses used. If the substance(s) are no longer used as medicinal products for human therapy, the reasons should be stated. The assessor should report an overall conclusion of the relevance of the human data for the evaluation of user safety.

3.A.4.3. Microbiological studies

These studies investigate the microbiological risk presented by residues of anti-microbial compounds for the human intestinal flora. In certain cases, it may be necessary to carry out tests to determine whether microbiologically active residues may interfere in technological processes in the industrial processing of foodstuff.

Any data submitted on the effects of residues on the human gut flora and microorganisms used in food processing, submitted as part of the MRL procedure should be briefly summarised at this point.

The assessor should summarise the data, preferably in a tabular form focusing on the significant details and findings and the overall conclusions. The assessor should report if there is no microbiological activity and therefore no data to evaluate.

3.A.4.4. Studies on metabolites, impurities, other substances and formulation

Where studies have been carried out on a metabolite, an excipient or degradation product these should be addressed in a similar method and in the same order as the active substance and where more than one substance has been identified, each one should be dealt with in turn.

Studies on the formulation such as those for inhalation exposure, skin/eye irritation and skin sensitisation that have been conducted to assess potential for user exposure to the formulated product (as opposed to the active substance) should be included in this section.

The assessor should summarise the studies, preferably in a tabular form focusing on the significant details and findings and the overall conclusions. The assessor should comment upon the significance of studies submitted and the justification for this approach by the applicant.

3.A.5. – USER SAFETY

This section should include a discussion of the effects found in the preceding sections and relate this to the type and extent of human exposure to the product with a view to formulating appropriate user warnings. An assessment of the hazard presented by the product should incorporate the following aspects:

3.A.5.1. An appraisal of the inherent toxicity or other harmful effects such as flammability of the active substance or other components, including, as appropriate, studies on:

– skin irritation;

– eye irritation;

– skin sensitisation;

– percutaneous toxicity;

– inhalation toxicity;

– known adverse reactions to similar products.

Relevant information in the dossier in relation to user safety may include physicochemical properties of the formulation, pharmacokinetics, single dose toxicity and reproductive toxicity. One or more of the above additional studies may be required, depending on the toxicity of the compound and the type of exposure. The results of these studies should be critically appraised by the assessor, who should also comment on the results of the tests to specific user groups e.g. women of child-bearing age or pregnant women, individuals known to be sensitive to beta-lactam antibiotics.

3.A.5.2. An appraisal of the exposure of the user, or others who may come into contact with the product:

– route and degree of exposure, e.g. inhalation of vapours, aerosols, sprays and dusts (including particle size analysis and dust generation in use); skin contact (including splashing and handling animals after application); ingestion (including accidental/deliberate misuse); and accidental self-injection

– frequency of use and volume used

– identification of the end user, e.g., vet, farmer, animal owner

User safety relates to persons treating the animals and those handling the products and treated animals. Some veterinary medicinal products such as tablets and capsules, offer very little opportunity for user contamination, while others may offer much greater scope. The assessor

should comment on the likelihood of exposure, and on the likely degree and extent of exposure and relate this to the toxicity of the drug. Worst case exposure calculations may be helpful in assessing the potential risk.

The assessor should bear in mind the likely frequency, duration and extent of exposure bearing in mind that a product intended for occasional use (e.g. by a pet-owner) will not represent the same degree of risk as a product intended for frequent use on a large number of animals (e.g. by a farmer or veterinarian). However, some products intended for single use may represent a significant user hazard, e.g. injectable barbiturates and some morphinoids. Any risks from accidental ingestion or injection should also be considered.

3.A.5.3. Conclusions including risk management proposals, including the following, where appropriate:

– contra-indications and safety warning phrases

– handling techniques

– other methods of controlling user exposure e.g. engineering methods such as dust, vapour or gas extraction and packaging (appropriate pack sizes/special closures).

– recommended protective clothing (type and appropriateness)

– action to be taken in the event of accidental exposure

– advice to doctors

– Occupational Exposure Limits (OELs) – if these have been set

– sufficient information for the end-user to perform a risk assessment, if applicable.

The assessor should critically review any proposed methods of limiting user exposure and any safety recommendations and warnings proposed for the SPC.

3.A.6 – ENVIRONMENTAL RISK ASSESSMENT

Studies on ecotoxicity are designed to investigate the effects of a product (active substance, residues, effluents and leachates) on the environment, and to propose measures, which may be taken to reduce the risks. The assessment should be conducted in two phases, as described in the Annex to Council Directive 2001/82/EC:

3.A.6.1. Phase I assessment:

– assessment of potential exposure of the environment, to the product, its active substances or relevant metabolites;

3.A.6.2. Phase II assessment:

– if necessary, having regard to the extent of exposure of the product to the environment, and the available information about the physical/chemical, pharmacological and/or toxicological properties of the compound. Further specific investigation may be required of the effects of the drug and its metabolites on particular ecosystems, if necessary for the specific use of the product, including the following, if appropriate:

– fate and degradation in soil

– fate or behaviour in water or air

– effects on aquatic organisms

– accumulation in organisms

– effects on other non-target organisms

3.A.6.3. If necessary, appropriate instructions for risk management should be included in the SPC.

The studies should be carried out in accordance with current CVMP guidelines, Annex V of Directive 67/548/EEC, as amended, or, where studies are not covered by these, in accordance with other internationally agreed guidelines e.g. OECD guidelines.

Assessor's conclusions on the Safety Documentation and overall conclusions and recommendation for User Safety and Environmental Safety.

Here, the overall toxicology for the product should be discussed in relation to user safety and environmental safety. This section should briefly summarise the effects noted, the major shortcomings in the studies and the overall conclusions on toxicity, and conclude whether the studies are satisfactory to make a full risk assessment or identify any outstanding deficiencies that have to be addressed before further assessment can be made.

The overall conclusions on the safety file should be presented under separate headings for user safety and environmental safety. Any assessment conducted by other international bodies such as JECFA or JMPR should be reported. If the active substance(s) in the product have been entered into the annexes of Regulation (EEC) No 2377/90, the Annex entry should be reported under consumer safety, where appropriate.

PART 3.B – RESIDUES DOCUMENTATION

General

For coherence, it is recommended that the assessor should report the information for different species in the same order throughout each section, particularly if several species are involved.

3.B.1 – PRECISE IDENTIFICATION OF THE PRODUCT CONCERNED BY THE APPLICATION

- A detailed identification of the veterinary medicinal product(s) used in the testing and conditions of use relevant to residues studies should be summarised here, preferably in tabular form. This section should include the following data: formulation, detailing active ingredients and excipients that may affect theresidues profile
- the presence of other active ingredients which might affect the behaviour of the ingredient under examination (particularly if this is likely to be a common combination)
- indicated species with contraindications, recommended dose and maximum dose and duration of treatment
- Information on the extent and type of usage is desirable (e.g. restricted to specific geographical region or Member State or areas of Member States),- given on an individual animal basis or herd basis etc
- purity
- batch identification of batch used in relation to final product
- relationship to the final product
- specific activity, radio-purity and position of labelled substances

3.B.2 – RESIDUE STUDIES

The assessor should make relevant cross-reference to existing CVMP MRL Assessment Reports[4] and MRL Summary Reports that have previously addressed residues data presented under this heading; the assessor is reminded of the notes in the Introduction on the use of these reports.

3.B.2.1. Pharmacokinetics

This section should deal with conventional pharmacokinetic investigations in the target animal and the assessor should cross-refer to Part 4.1.A.2. where it is assessed and reported in detail. In most cases the same study is submitted in both sections, but the assessor should note that a summary of the study is sufficient for this section and the assessor should assess the study accordingly with cross reference to Part 4 of the assessment report. Cross-reference may also be made to laboratory animal pharmacokinetics in Part 3A where this (or a comparative critique) would be helpful. The assessor should note that although residues studies are specialised forms of pharmacokinetic studies, these should not be included in this section but be summarised in the appropriate section below.

Knowledge of the absorption, distribution, excretion and biotransformation in each target species is often valuable and sometimes essential in interpreting the data derived from the residues studies in the target animal. Examples of how the information might be helpful are given below:

[4] Note : the MRL assessment reports are only available to assessors for centralised procedures.

– *absorption;* will reveal whether residues studies are even necessary (i.e. negligible absorption) when given by a particular route of administration. Data on systemic absorption at the injection site should be summarised.

– *distribution;* will provide information on general distribution and particularly on target organs for residues of the drug.

– *metabolism;* metabolite profile and, more specifically, data on the formation of metabolites shown to be toxic in laboratory species. Similarly, data on the detoxification of toxic agents (parent and metabolites). Where possible, details of the kinetics involved should be provided as well as quantitative data on metabolites. A metabolic pathway diagram should be included.

- *excretion;* data on clearance kinetics, especially from plasma and target tissues, routes of excretion and the presence of hepato-biliary recirculation and hence re-emergence of drug into plasma and redistribution to tissues. The data may provide other data relevant to residues e.g. if excretion in milk or eggs is significant.

As the pharmacodynamics in the target animal can affect the pharmacokinetics of a drug and hence the residues profile, if this is the case, these effects should be summarised here and cross-referenced to Part 4.1.A.1. Where possible, comparisons should be made with the results in laboratory species summarised in Part 1, particularly if these confirm a general phenomena i.e. a specific pharmacodynamic effect. The implications (if any) for pharmacokinetic behaviour should be discussed.

In addition, there should be discussions on the influence of the route of administration on the metabolic profile, and on the degree and type of binding to the constituents of biological systems, the degree of bioavailability and on the significance of these findings.

There should be a brief summary of the pharmacodynamics and pharmacokinetics, highlighting the points relevant to residues.

3.B.2.2. Depletion of residues

The purposes 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.

Residues depletion studies may be of two distinct types: total residues studies which usually employ radiolabel techniques (radiometric or "hot" studies) and those which use chemical or microbiological methodologies ("cold" studies). The latter are normally employed once the residues profile has been elucidated, usually by the initial use of radiolabelled techniques.

Radiolabel techniques provide information on depletion of total residues, amounts of parent drug and key metabolites in selected tissues and amounts of bound residues, and they assist in selecting the marker tissue and marker metabolite. Using these data in conjunction with the results of cold studies, information can be obtained on levels of the marker residue in marker tissues, residues of interest in selected tissues and fluids, and on the time after treatment for residues to be non-detectable.

The residues studies should be described here, and the assessor should comment on any edible tissue omitted from the study, on any metabolite which has been ignored, on the effects of route of

administration (particularly on the effects of depot and other slow release formulations) and multidosing regimes, injection site residues (including if known, the effects of lesions - inflammation and fibrosis, induced by the injection), on whether the animals were previously medicated (and the significance if known), on the health status of the animals and its significance, and on any discrepancies between residues studies and results of pharmacology studies in target animals and laboratory species.

The rate of residues depletion involves a number of variables including the formulation, the route of administration, the frequency of dosing, the size of the dose, the age of the animal, the health status of the animal and other medication, etc. The following should be included:

– species, breed (and strain), sex, age and weight

– dose regimens

– dose formulations

- route of administration

– total numbers of animals used and numbers per slaughter time

– tissues examined (including injection site, milk, eggs, honey as appropriate)

– slaughter schedule

– sampling protocol

- analytical method (radiolabel, chemical, microbiological)

– compliance with GLP

– where applicable, studies on bound residues

– where necessary, justification for choices made e.g. of a particular analytical method, the nature and reasons for the choice of any marker residue and a discussion on the type, degree and relevance of bound residues should be discussed

- residues depletion curve

- statistical analysis of the results.

3.B.2.3. MRLs

This section should record the MRLs set, or Annex II classification, of the active ingredient(s) and list the MRL status of the excipients. It is useful to state the rationale for the establishment of the MRLs as recorded in the MRL Summary Report recommendations.

The assessor should include the following:

– the Community MRLs (µg/kg commodity), or Annex II entry, established according to Council Regulation (EEC) No. 2377/90 and published in the Official Journal of the European Communities

– the Conclusions and Recommendations from the MRL Summary Report

– substance to which the MRLs refer (parent and/or metabolites)

– food commodities involved

– list of the MRL status of all excipients.

3.B.2.4. Withdrawal Periods

The assessor should conduct the evaluation of the withdrawal period in accordance with the recommended CVMP Guidance and report any deviations from this guidance and the justifications for this.

The assessor should note that whereas the MRL is specific to a substance, the withdrawal period pertains to a given formulation or product, at a given dose by a specified route in a specified species. Alteration of any of these factors is expected to change the withdrawal period required to meet the MRL and ensure that the ADI is not exceeded. This can lead to misunderstandings and the following should noted:

- The withdrawal period should be set to ensure that the **MRL** is not exceeded.
- For a veterinary medicinal product the withdrawal period is normally determined by depletion of residues at or below the MRL in all the animals at the serial slaughter time points of interest (or milk sample or eggs etc.).

The assessor should review these aspects and examine whether the sponsor has demonstrated that compliance with the proposed withdrawal period will result in residues at or below the MRL(s); any statistical methods or models used should be commented on. Withdrawal periods should, wherever possible, be calculated using the statistical methodology recommended by the CVMP.

3.B.3 – ANALYTICAL METHODS FOR THE DETECTION OF RESIDUES

The assessor should report on the analytical method(s) used in the residues depletion study (studies) and its(their) validation. This should be addressed as follows

3.B.3.1. Description of the method

The method submitted should be in an internationally recognised format (e.g. ISO 78/2), and the assessor should comment on any significant departures from this.

3.B.3.2. Validation of the method

The assessor should comment on whether the method is fully validated in terms of specificity, accuracy (including sensitivity), precision, limits of detection and quantification, practicability and applicability, susceptibility to interference, and storage stability of the samples – as elaborated in Volume 8 of the Notice to Applicants.

Assessor's conclusions on the Residues Documentation and overall conclusions for Consumer Safety

The discussion should highlight the problems encountered including flaws in the studies e.g. failure to comply with GLP and the validity of the residues studies in light of the considerations on the analytical method. Other points for inclusion are the adequacy of the design, conduct and analysis

of the residue studies as well as the implications of bound residues, bioavailability, restrictions on the analytical methods, injection site residues,
It should be considered whether the withdrawal period has been properly derived and whether any statistical manipulations of the data (e.g. consideration of outliers) have been justified. Any deviations from the guidelines on the establishment of the withdrawal periods should also be justified.

Additional points which might be discussed here and conclusions drawn about them are: the usefulness of bioequivalence data when considering other species, problems with the assay e.g. loss of the radiolabelled part of the molecule, and justification for not doing residue studies in one or more of the indicated species or by all routes of administration or dosage regimens due to pharmacokinetic considerations.

Attention should be drawn to where the assessor's conclusions differ from those of the sponsor or the writer of the expert report (if not the sponsor).

PART 4 – PRECLINICAL AND CLINICAL DOCUMENTATION

It is vital that an assessor is fully cognisant of the relevant CVMP and VICH guidelines relating to the various sub-categories contained within Part IV of the dossier. Copies of the most up to date versions of these guidelines are available on the websites for EMEA [www.emea.eu.int], Pharmacos [www.pharmacos.eudra.org] and VICH [www.VICH.eudra.org].

In the following text, specific guidance is given on the type of information, comments, and critical assessment that would be expected in the assessment report for clinical efficacy. General guidance is provided in the introductory notes to which the reader is also referred.

When drawing up the clinical efficacy assessment report, the assessor should consider the following:

4.1 Preclinical Studies

In case of a fixed combination product, justification should be provided by the Applicant for the combination. If there are several target animal species data for these species should always be presented in the same species order.

4.1.A Pharmacology

A.1 Pharmacodynamics

The mode of action of the active substance should be described, if it is known. In respect to antibacterial or antiparasitic products, the assessor should outline how the active substance acts on target pathogens. In this respect, it should be stated when the pathogens were isolated and tested for sensitivity, which animal tissues were used for isolating the pathogens, and what the country of origin was.

The way the active substance affects body organs and organ systems should be described in relation to the desired therapeutic effect of the product and its therapeutic index.

Pharmacodynamic data should have been utilised when selecting doses for dose determination studies.

In case of a fixed combination product, it should be considered how, if at all, the active substances interact and checked if the dossier complies with relevant guidance on fixed combination products.

A.2 Pharmacokinetics

The pharmacokinetic properties of the active compound should be presented with special focus on the kinetic profile of the final formulation when administered at relevant doses to the target animal species. The objective is to support studies on clinical efficacy, tolerance in the treated animal and safety for the consumer.

The magnitude and the time course of the systemic exposure should be discussed. Different factors that influence the kinetic profile should be identified. When appropriate, the assessor should

evaluate 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 and/or dose interval.

The variability in pharmacokinetic pattern should be assessed. For drugs with a large variability in systemic exposure, the clinical relevance of the variability should be discussed. When appropriate, the assessor should evaluate the justification for the use of flexible dosing or dose titration.

Any recorded differences between groups of patients in the magnitude or the time course of the systemic exposure should be discussed and the applicant's proposals for SPC texts should be justified. Differences between groups could be due to disease status (e.g. renal failure), feeding status (fed/not fed) or physiological characteristics (age, weight, breed etc).

Possible pharmacokinetic interactions with other drugs should be discussed.

If the applicant presents data on the pharmacokinetic/pharmacodynamic relationship for the active compound, these data should be discussed in relation to the dose finding section of the dossier.

The assessor should consider if the laboratory methods used for analytical purposes and the validation of these methods are acceptable. The assessor should be particularly attentive to the statistical analyses employed, especially when assessing bioequivalence studies. Where data have not been analysed statistically, the study report should state this and the lack of statistical analysis should be duly reported.

In the case where bioequivalence studies are presented, the assessor should describe the design of the study (cross-over/parallel). In particular, the assessor should determine if the number of animals, the method for assigning animals to treatment groups, and the choice of animals, in terms of breed, age, and physiological status, were appropriate. He or she should assess if the reference product was suitable for demonstrating bioequivalence and check if the washout period between the initial administration of the product and cross-over was sufficient. Where appropriate, reference to the guideline on bioequivalence for veterinary medicinal products should be made. The assessor should pay particular attention to the statistics used to demonstrate bioequivalence.

The assessor should review the text proposed in the SPC to see if it is, not only correct, but relatively comprehensible.

The assessor should provide an overall conclusion on the pharmacology section, indicating the main strengths and weaknesses of the scientific data and arguments presented. If there remain outstanding concerns, these should also be indicated.

4.1.B Tolerance

The assessor should describe the tolerance profile of the product. The assessor should review all constituents of the product (both active substances and excipients) and evaluate systemic and local tolerance. He or she should be particularly vigilant where a number of different formulations have been used in the tolerance studies. It should be determined if the differences are significant and what their impact is on the conclusions.

The assessor should use, as a basis for the assessment report, the guidelines on target animal tolerance, Evaluation of the Safety of Veterinary Medicinal Products for the Target Animals (TAS). The local tolerance should be assessed for parenteral formulations, intramammary products, and formulations for external use. Where repeated dose treatment is indicated, the assessor should discuss if the dossier adequately supports such a recommendation.

The assessor will make a short comment on each tolerance study presented and provide a short abstract of each pivotal study. He or she should highlight the quality and relevance of each study and comment on whether the study has been conducted in accordance with Good Laboratory Practice. Where studies on laboratory animals have been conducted in support of demonstrating tolerance in the target species, the assessor should discuss if the model can be considered as appropriate.

The assessor should pay attention to the doses that were tested. Where it was possible to establish a margin of safety, the assessor is asked to evaluate the margin of safety. The assessor should make explicit reference to the warning statements proposed in the SPC including those in relation to use in pregnant or lactating animals.

The assessor should provide an overall conclusion on the tolerance in the target species section, indicating major strengths and weaknesses of the data presented. If there remain outstanding concerns, these should also be indicated.

It may be of interest for the assessor to compare the tolerance profile established from specific tolerance studies to the knowledge gathered on tolerance from the rest of the clinical trials. The assessor should also consider that tolerance is relative, and therefore he or she should consider 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.

4.1.C Resistance

This chapter applies to antimicrobial and antiparasitic products as well as to anticancer products.

The assessor should discuss how pathogens become resistant against the active substance and explain if and how resistant pathogens impact on the clinical efficacy of the product.

In the case of antimicrobials, the assessor should make reference, where appropriate, to the relevant guidelines, such as VICH GL 27. As indicated earlier in the Pharmacodynamics section, resistance issues are to be discussed in relation to the target pathogens, but they also arise for other bacteria. The assessor should clearly differentiate between resistance issues pertaining to target pathogens, to non-target pathogens nevertheless likely to be encountered in the treated animal and having a direct potential consequence on the animal's health, and to those bacteria that are part of the commensal flora potentially having an impact on consumer health. Usually, a meaningful discussion on resistance issues is present as part of, or in addition to; the expert report and consists of reference to the scientific literature. The assessor should pay particular attention to current MIC data on pertinent_pathogens and commensal organisms and put it into context vis-à-vis the latest information on resistance mechanisms. Where appropriate, the assessor should provide an overall conclusion on this subsection, clearly indicating any concerns that exist or may arise related to the risk of increasing resistance.

Conclusions on preclinical studies

The assessor should summarise the findings of the preclinical section and provide conclusions. Any differences in opinion between the assessor and the applicant should be highlighted. Major shortcomings should be indicated and need for new studies explained.

4.2 Clinical Trials

The assessor should highlight the quality and relevance of each study and comment on if the study has been conducted in accordance with GCP.

The assessor should review the categories of target animal species for which the product is indicated and evaluate if possible interactions have been assessed.

If there are several target animal species data for these species should always be presented in the same species order. Also if there are several indications or routes of administration for each target species these should be presented in the same order under each title.

4.2.1 Laboratory trials

Dose-determination studies

For each study a summary of the study should be provided including details on animals, test and control products, challenge, treatment, observation times and efficacy criteria. Results should be summarised. Tables of most relevant study results should be included. Validity of study models should be commented and results evaluated in relation to the recommended use of the final product.

Dose-confirmation studies

For each study a summary of the study should be provided as for dose-determination studies. Pivotal studies should be indicated. Results should be summarised. Tables of the most relevant study results should be included. Validity of study models should be commented on and results evaluated in relation to the recommended use of the final product.

4.2.2 Field trials

For each study deemed relevant, a short abstract should be provided, summarising the study protocol and results. For each study, the assessor should also determine if the trial design, method of randomisation, inclusion/exclusion criteria, statistical method, and end points used for efficacy testing can be considered suitable. The assessor should focus on the efficacy parameters that were employed, the scoring system, and the characteristics of the group of animals used in the studies when compared to the target population. The assessor should consider each use indicated in the SPC and identify the number of animals treated with the test product and with the control product. He or she should then say if the control products and the statistics used to evaluate the results were suitable. He or she should look carefully at test product formulation, dosage, and route of administration used in each study and compare them to those proposed for authorisation.

Tables of most relevant study results should be included. The assessor should assess each study to establish whether or not the indications claimed in the SPC are well demonstrated in each target species and whether or not the exclusion/inclusion criteria used in the clinical trials are reflected in the claimed indications, contra-indications, and precautions. Where a scientific guideline is available, especially if from CVMP or VICH, the assessor should comment if the application complies or not to the recommendations of the guideline. 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.

The assessor should provide an overall conclusion on the clinical section, indicating the main strengths and weakness of the data presented. If outstanding concerns remain, these should be indicated.

In the conclusions the assessor should address whether or not the clinical trials are sufficient to categorise the risk benefit ratio of the product. In performing the risk benefit analysis, the assessor should compare the product to appropriate recognised therapy and state if the effective dosage has been accurately defined and if the dosage regime is validated.

Assessor's conclusions on Efficacy

The assessor should draw a conclusion on the clinical data presented and indicate which claims and recommendations for use in the SPC and product literature have been supported by data. Any differences in opinion between the assessor and the applicant should be highlighted. The assessor should clearly formulate any objections to the granting of authorisation. If it is possible to address the objections by amending the SPC, this must be stated (*e.g.*, rewording of indication, addition of contra-indications or special precautions for use…).

APPENDIX II

Content of assessment reports for Veterinary Immunological Products

In this appendix, texts in bold are headings and key points, taken from the requirements in Title II of Directive 2001/82/EC as amended and the corresponding sections of the Notice to Applicants.

PART I – SUMMARY OF THE DOSSIER

I.A – ADMINISTRATIVE DATA

1. **Product**
   Name of Product
   Active Substance(s)
   Strength
   Pharmaceutical form
   Route of administration
   Target species

The assessor should provide the basic information from the dossier on these points to provide an easy reference in the report.

2. **Source**
   Name and address of the applicant
   Name and address of the manufacturers
   Sites involved in the different stages of the manufacture
   Name and address of the importer, where relevant

The assessor should make reference to the suitability of the data on the site of manufacture and any queries requiring resolution.

3. The type of marketing authorisation application should be indicated. Reference should also be made to the legal basis of the application, for example, Well Established Use and how that was justified.

I.B – SUMMARY OF PRODUCT CHARACTERISTICS

Draft SPC
Proposed product literature

I.C – EXPERT REPORTS

Analytical (Quality)
Safety
Efficacy

PART 2 – ANALYTICAL INFORMATION

2.A – QUALITATIVE AND QUANTITATIVE PARTICULARS

1. Table of qualitative and quantitative particulars

Active substances
Constituents of the adjuvant
Constituents of the excipient
Constituents of the diluent

The assessor should include an extract from the table giving the substances and the quantity of each. There should be mention of any deficiencies if the data provided do not conform to the layout required by the Notice to Applicants or there are difficulties of interpretation of the methods of expressing the quantities, for example.

2. Containers

Nature of the materials
Qualitative composition of the containers
Closures

For each part, after the summary of the information provided, the assessor should provide an indication of the suitability of the materials being used, with reference to the requirements of the pharmacopoeia.

3. Development pharmaceutics

Composition (qualitative and quantitative)
Containers
Overage
Preservative efficacy

For each part, after the summary of the information provided, the assessor should provide an indication of the appropriateness of what has been provided.

For overages, this should include reference to volumes for liquid preparations and potency or titre overages linked to differences between release and end of shelf life titres or potencies where this is required because of a decrease during storage.

In the case of multidose containers, information must have been provided on any preservative included in the product or a justification given for a lack of a preservative. The assessor should comment on whether or not the efficacy of any preservative has been demonstrated using a validated method in accordance with the guidelines on *Inclusion of Antimicrobial Preservatives in Immunological Veterinary Medicinal Products*.

The recommendations for in use shelf life should be based on the data generated and provided and the assessor should comment on how well the data support the proposals.

2.B – METHOD OF PREPARATION

This chapter deals with the blending of the different components, from the active substances once obtained, to the finished product as mentioned in the SPC.

Flow chart of manufacture and description of stages of manufacture, from the active substances to the finished product.

Comment should be made if the flow chart is not adequately clear and detailed. The assessor should comment on whether or not sufficient detail has been provided to give confidence that the blending is such that there can be production of safe, effective and stable product and batch to batch consistency is achievable.

To this end the assessor needs to consider points such as has the blending method been described in sufficient detail and with sufficiently tight specifications? If there are wide limits set have these been justified to give reassurance that it does not potentially compromise batch to batch consistency?

2.C – STARTING MATERIALS

1. Listed in a Pharmacopoeia

Substance

European (or other) Pharmacopoeia monograph title

In order of precedence, European Pharmacopoeia, Member State Pharmacopoeia. The assessor must comment on the appropriateness of the monograph and the corresponding certificates of control.

2. Not listed in a Pharmacopoeia

a) Biological origin

Substance
Source
Passage history, preparation, testing and storage of master and working seeds
Function
Identification
Processing, testing and limits of acceptability
Genetic engineering details

i) Seed materials

The isolation and passage history of the Master Seeds should have been provided. Any lack of information should be mentioned.

The tests for extraneous agents should have been carried out at the right stages of preparation and at the passage levels set out in the guidelines and the assessor should provide a comparison of what has been done with what is required. The range of tests should reflect the risks of contamination of

the materials from pathogens of the species of origin and the risks for the target species. The technical discussion and opinion of the assessor should indicate the acceptability or otherwise of the risks of contamination.

If GMOs are involved, further appropriate information is necessary, such as :

- origin and history of all starting materials used for the GMO construction (ie parental organisms, donor organisms, …),
- description and genetic engineering of all intermediates (ie, plasmids, bacteria used for amplification,…),
- description of the construction of the recombinant organism or description of the deletion method,
- control of homogeneity of the recombinant organism
- control of expression for recombinant organisms, or lack of expression for deleted organisms
- control of genetic stability of the recombinant organisms.

For applications for mutual recognition, according to Directive 2001/82/EC, any tests for purity required by the guidelines or new pharmacopoeial monographs which had not been carried out at the time of initial authorisation should have been undertaken and the results included in the up-dated dossier. The completeness of the testing that has been carried out and any omissions should be mentioned by the assessor.

ii) Other substances of animal origin

The applicant should have provided details on the source including the animal species. The extent to which this is adequately described and specified should be mentioned.

The sterilisation processes and the controls applied to these substances should be described, especially with regard to extraneous agents. The validation data of the methods used should be provided.

For mutual recognition procedure applications, the assessor should indicate if any changes have been made to the specifications since initial authorisation, such as changes to the source, additional extraneous agents inactivation kinetic studies or testing requirements to reflect changes in disease patterns in the species of origin of the material.

The assessor should indicate if the risk from the materials is acceptable taking into account any recent changes to disease patterns or new knowledge on species susceptibility of infectious agents.

b) Non-biological origin

An internal monograph is required for each substance, specifying :
Name of the substance
Function
Identification
Purity
Storage
Testing and limits of acceptability

For all substances, the applicant should have provided sufficiently precise specifications such as suppliers' specifications and certificates of analysis for each substance to indicate the extent to which the substance can be relied on to have batch to batch consistency. The assessor should comment on the extent to which this has been done and particularly mention any omissions and the extent to which this is a cause for concern.

Colouring matters must satisfy the requirements of Council Directive 78/25/EEC and the assessor must comment if this requirement is not met. The adequacy of the routine tests conducted on each batch of starting materials should be described by the assessor.

The sterilization processes and the controls applied to these substances should be described, especially with regard to extraneous agents. The validations should be provided.

c) Media

Each medium has to be taken as a whole. **An internal monograph is required, specifying :**

Composition (qualitative and quantitative)
Preparation
Storage
Testing and limits of acceptability

The sterilisation processes and the controls applied to these media should be described, especially with regard to extraneous agents. The validation data should be provided.

3. Production

Flow chart of manufacture with indication of stages for in-process testing
Description of stages of manufacture
Table of blending details
Validation study results

Comment should be made if the flow chart is not adequately clear and detailed. The assessor should comment on whether or not sufficient detail has been provided to give confidence that the method of production is such that there can be production of safe, effective and stable product and batch to batch consistency is achievable.

To this end the assessor needs to consider points such as has the manufacturing method been described in sufficient detail and with sufficiently tight specifications? If there are wide limits set (e.g. incubate for between 2 and 6 days) have these been justified to give reassurance that it does not potentially compromise batch to batch consistency?

Comment should be made on the adequacy of the information on any purification procedures applied to the harvest. If more than one method may be used to purify the antigen for example filtration or centrifugation does the dossier contain a satisfactory description and validation data on both methods to show they provide satisfactory equivalent effects?

Has sufficient information been provided on the processes and equipment used to allow assessment of the risk from these? For example, if the harvest is filtered, information is required on the filters used and how they are sterilised. Has the risk been minimised to an acceptable level?

Comment should be made on the suitability of the table of blending for the provision of the necessary information.

The assessor should indicate whether or not validation data have been provided for all the processes such as inactivation and any quantified purification steps. For each, the degree to which the data are adequate and provide the necessary reassurances of effectiveness should be remarked upon. For example, for the inactivation kinetics data to be relevant to the inactivation processes used during manufacture, it can be provided from a study carried out in the laboratory with conditions that mimic manufacture and the inactivation procedure used. It is not acceptable, however, if harvested antigen normally has a titre much higher than that used in the inactivation kinetics studies. Another point that should have been addressed, if relevant, is the inhibitory effect of residual inactivant, i.e. has the applicant shown that the sensitivity of the detection system is affected by the presence of this or addressed this point if it is. The inactivation data must provide data to show that the required 33% safety margin is used in production.

2.D – SPECIFIC TSE MEASURES

For each raw material of ruminant origin, either an EDQM certificate should be provided, or a scientific dossier addressing the following points:

- Nomenclature (exact composition of the raw material and/or the way it is obtained).
- Applicant's Declarations (indicating that the description of the manufacturing process is accurate, insures traceability, is reproducible, and that the Company is certified to be in compliance with ISO and/or HACCP and/or GMP rules).
- Origin of raw materials (definitive list of sourcing countries with the corresponding GRB-level of classification). Additional points should be taken into consideration:
  - are animals from which the raw material is derived fit for human consumption?
  - are carcasses of all TSE infected animals destroyed?
  - are slaughterhouses from which these tissues are coming authorised to slaughter animals for human consumption?
  - is pithing authorised in the countries of origin of these tissues?
  - are animals excluded when born from BSE discarded cows?
  - is feeding to ruminants of mammalian protein banned?
- Type of tissue used (definitive list of tissues used, description of how Specified Risk Materials are excluded from sourcing).
- Complete description of the manufacturing process. Any process which is able to reduce infectivity should be highlighted and supported by scientific data. The cleaning of all the material necessary to these manufacturing processes should be described.
- Cross-contamination (equipment specifically dedicated to the manufacturing, list of other raw materials of animal origin handled on the site and, if so, which precautions are taken to avoid cross-contaminations, measures taken to avoid cross contaminations in the slaughterhouses supplying the raw material(s).
- Traceability (if the manufacturer of the raw material is not GMP, a complete description of the traceability system should be provided, showing that the system allows identification of all the raw materials (tissues, animal origin, geographical origin,…) and equipment used to manufacture each batch of finished product, once the manufacturing process is finished. All relevant SOPs must be provided.
- Auditing system (if the manufacturer of the raw material is not GMP, a complete description of the auditing system should be provided, with all relevant SOPs).
- an expert report has to be provided.

2.E – IN-PROCESS CONTROL TESTS AND II F CONTROL TESTS ON THE FINISHED PRODUCT

For each test:

Timing/frequency
Function
Brief description
Limits of acceptance
Results of 3 batches
Annex with details of the test and validation details

For both control tests during production and on the finished product the assessor should summarise what tests are being done, and at what stage.

The technical discussion should indicate whether or not the testing is providing sufficient information and controls to ensure that it should be possible to detect any batch that is not as safe or efficacious as the ones which have been used for the safety and efficacy studies. It should also be demonstrated that the test is able to detect sub-potent batches. As part of this, for inactivated vaccines in particular, the assessor should comment on the extent to which the potency test has been satisfactorily validated. The sensitivity, repeatability and reproducibility of the test should have been investigated. The setting of the pass level and limits of acceptance for the test must also have been investigated and limits proposed which reflect the data presented on batches used in safety and efficacy studies. The extent to which the company has carried out the necessary work and the degree to which the proposals are in accordance with the data presented in this section and elsewhere in the dossier should be indicated in the report.

Comment is required as to whether or not the level of detail provided for each test method is such as to allow the control laboratory to repeat the test on the product.

For mutual recognition procedure applications, the dossier should have been updated as required to indicate that the testing is in conformity with current requirements of guidelines and pharmacopoeial monographs.

It is a requirement to include in the dossier the results of the control tests for three batches. These should be presented in the format of the batch protocol of results to be used in the future for submission of batch results to the authorities. They should be in conformity with the standard format and with the level of detail now required for batch protocols for the EC. The assessor should indicate whether or not the proposed protocols are acceptable.

2.F – STABILITY

1. Stability of the finished product

Summary table of results of tests on at least 3 batches
For each test:
Brief description (testing to be done as in II.E)
Results with batch number, date of manufacture, date of testing
Justification for the proposed shelf life

The assessor should compare the information presented with the requirements and, in the technical discussion, comment if the stability data presented is not relevant to the product to be marketed in

any way (e.g. differences in containers, composition, method of manufacture). It is useful to indicate if some or all of the batches studied were pilot batches. Also, if more than one type of container and/or closure is to be used, has data been provided on three batches stored in each type?

For mutual recognition procedure applications, it would be helpful to indicate the extent to which the data has been updated since the original authorisation was granted by the Reference Member State.

The assessor should indicate the shelf life that it is considered is supported by the data presented and indicate, if appropriate, what the associated loss of titre or potency could be. From this a release titre should be proposed (i.e. minimum titre plus loss on storage). It should be mentioned if this is in agreement with the shelf life claimed and release titre proposed by the applicant.

2. Stability of the reconstituted product

Similar comments apply. Again, the assessor should indicate the shelf life on reconstitution that would be supported by the data presented and indicate, if appropriate, what the associated loss of titre or potency could be. From this the release titre can be proposed to accommodate this (i.e. minimum titre plus loss on storage after reconstitution).

The assessor should check if the Applicant has correctly calculated and commented on the total overage above minimum release titre, which would be required, in order to establish the in-use stability, if relevant.

Assessor's conclusions on Quality

As indicated in the introduction to these guidelines, the assessor should then present a conclusions section, indicating any concerns over the quality of the product such as batch to batch consistency, or need for updating of the extraneous agents testing in the light of changes to disease patterns.

PART 3 – SAFETY

3.A – INTRODUCTION

Indication of tests carried out
Justification of any omissions
Evaluation of risk to non-target species, if applicable

After the summary of this information, the assessor may wish to comment on the validity of the points made if this is not discussed elsewhere.

Compliance or lack of compliance with GLP and the availability of certificates in an annex should be remarked upon here.

3.C – LABORATORY TESTS

The assessor should summarise the data available. It may be useful to provide this information in a table.

It is particularly important in these sections to provide a comparison of what tests have been carried out with the requirements of the Directives, guidelines and pharmacopoeial monographs. Again this information may be presented in tabular form, if possible.

Headings giving the key points from the Directive and Notice to Applicants are listed below. As part of the technical discussion the assessor should comment on the extent to which the relevant points such as those listed under the following headings have been satisfactorily addressed, taking into account that the work should have been done with product of the maximum potency and minimum degree of attenuation for the trials to be done as stated in chapters C1 to C5.

1. Safety of administration of one dose

Each recommended dose (at maximum or near maximum titres)

Each recommended route (or the most sensitive one)

Each intended species and category of animal (or the most sensitive one) including minimum age

Observe for at least 14 days for systemic and local reactions and until reactions no longer expected

Results of local and general reactions, especially those in line with the target disease.

PMs and histological examination carried out if appropriate

2. Safety of one administration of an overdose

Each recommended route (or the most sensitive one)

Animals of the most sensitive categories of the target species (including pregnant animals if not contra-indicated for use in pregnant animals)

Observation for at least 14 days for at least systemic and local reactions Results of temperature and performance measurements

3. Safety of the repeated administration of one dose

If appropriate

Using the recommended route (or the most sensitive one)

Animals of the most sensitive categories of the target species

Observe for at least 14 days for at least systemic and local reactions

Studies on the effects of repeated administration should have been carried out by the applicant when the product is recommended for use on a number of occasions or some characteristic of the product is likely to lead to sensitisation of the recipient (e.g. contains albumin or likely to contain endotoxin). The assessor should comment on the suitability of the studies or the justification for not having conducted these studies.

4. Examination of reproductive performance

If appropriate and may be part of (1), (2) or (3).

Each recommended route (or the most sensitive one)

In mammals, reproductive performance of males, non-pregnant and pregnant females, effects on the progeny and teratogenicity and abortifacient effects, as appropriate. In avians, laying performances, quality of eggs and hatching.

These studies are more likely to have been appropriate and performed when the product under report is a live vaccine but the effect of local or systemic reactions from inactivated or live vaccines may need to be considered (e.g. painful injection site may affect willingness to mate). The assessor should comment on the suitability of the studies or the justification for not having conducted these studies.

5. Examination of immunological functions

Where may be adverse effect on vaccinate or progeny

6. Special requirements for live vaccines

a) Spread of the vaccine strain

Recommended route most likely to result in spread

To target non-vaccinated

To non-target, susceptible

b) Dissemination in the vaccinated animal

Test faeces, urine, milk, eggs, oral nasal and other secretions.

If appropriate, dissemination in the body especially predilection sites - must do for zoonotic live vaccines for food producing animals

c) Reversion to virulence of attenuated vaccines

Least attenuated passage between master seed and final product used for the initial passage

Administered by the recommended route most likely to lead to reversion

At least 5 further serial passages in target species (in-vitro amplification may be considered to obtain sufficient virus for passaging).

In the technical discussion, the assessor should remark on the suitability of the study which has been performed bearing in mind the characteristics of the organism. The following points should be considered

i) Has the study been repeated if the organism could not be recovered after less than 5 further serial passages had been carried out?

ii) Has a sufficient number of passages (not less than 6) been carried out bearing in mind the risks?

iii) Was sufficient virus available in the last passage to carry out a valid comparison of the pathogenicity of the first and last passages?

iv) Were the observation periods of the animals in the first and last passages long enough?

d) Biological properties of the vaccine strain

Other tests if necessary e.g. neurotropism

e) Recombination or genomic reassortment of strains

Discuss probability of this with field or other strains

7. Study of residues

Consider the possibility of residues of the adjuvant or preservative and test ifnecessary

Consider the possibility of residues of live zoonotic organisms at the injection site

Propose withdrawal period and discuss adequacy

8. Interactions

Any known interactions with other products
If there is a claim in the SPC to associate different vaccines, all data about safety and efficacy of the association(s) should be provided.

3.D – FIELD STUDIES

Results in support of laboratory studies

The extent to which the data support the data from the laboratory studies should be remarked upon in the assessment report. The safety criteria might be different from those used in the laboratory studies, ie condemnation rates in slaughterhouse, weight at slaughter, egg production, food consumption, …

3.E – ECOTOXICITY

Compulsory Phase I assessment

If potential exposure, evaluation of potential ecotoxicity

Phase II – if necessary

If relevant, evaluation of potential human safety concerns.

If the product contains GMOs, all relevant information as laid down in Directive 2001/18/EC "on the deliberate release into the environment of genetically modified organisms and repealing Council Directive 90/220/EEC" needs to be provided.

Results of studies

The assessor should comment on the adequacy of the risk assessment presented taking into account the target species, proposed pattern of use, method of administration including likely extent of product entering the environment directly, possible excretion of product metabolites and persistence of these, disposal of waste.

Assessor's conclusions on Safety

The assessor should then present a conclusions section, indicating which recommendations on the SPC and product literature have been supported by data e.g. the target species covered, what is the minimum age, which recommended routes and with what product (i.e. maximum potency or titre and minimum degree of attenuation or passage level). What if any suitable warnings need to be added to the SPC and product literature to reflect side effects observed, risks to non-target species including the operator and other humans and ecotoxicity risks.

PART 4 - EFFICACY

4.A – INTRODUCTION

Indication of tests carried out

Justification of any omissions

After the summary of this information, the assessor may wish to comment on the validity of the points made if this is not discussed elsewhere.

4.B – GENERAL REQUIREMENTS

The assessor should summarise the data available.

The trials should be done with vaccine batches containing a minimum or near the minimum titres for each active substance. It is important to provide a comparison of what data has been provided and what would be required to support the recommendations for use and the claims being made for the product. The technical discussion should include comment on the extent to which the relevant points such as those listed under the following headings have been satisfactorily addressed, taking into account that the work should have been done with product of the minimum potency and maximum degree of attenuation.

Data required from laboratory and field trials on -

Each category of each target species

Each recommended route of administration (or the most sensitive one)

Proposed schedule of administration, including revaccination.

Effect of passively acquired and maternally derived antibodies

Claims regarding onset and duration of protection

Each component

Data should be available to support the claims being made. For example, if the applicant claims that the product protects against infection, the tests carried out must have included study of the recovery of organisms from vaccinates and controls and a reduction in the number of organisms recovered must have been demonstrated. Claims of protection against, say, respiratory signs and abortion must have been supported by data from studies of the decrease in the incidence of both symptoms in vaccinated animals post-challenge.

4.C – LABORATORY TRIALS

Well controlled challenge studies required

Immune mechanism established if possible

The assessor should comment on the extent to which the relevant parameters have been studied and mention should be made of any omissions such as lack of information on duration of immunity. Any weaknesses in the work should be mentioned.

4.D – FIELD TRIALS

Results in support of laboratory studies

Reference should be made of the extent to which the studies have been controlled, the types of controls used and whether or not a natural challenge occurred on one or more sites.
The extent to which the data support the data from the laboratory studies should be remarked upon.
The efficacy criteria might be different from those used in the laboratory studies, ie condemnation rates in slaughterhouse, weight at slaughter, egg production, food consumption, …

If relevant, the use of the vaccine in contaminated areas should be considered.

Assessor's conclusions on Efficacy

The assessor should then present a conclusions section, indicating which claims and recommendations for use in the SPC and product literature have been supported by data e.g. the degree of protection afforded in which target species by which recommended routes and with what product (i.e. minimum potency or titre and maximum degree of attenuation or passage level). Have the direct stated or implied claims (by reference to the revaccination schedule) for duration of immunity been supported by data?

Assessor's overall conclusions

See introduction to these guidelines

APPENDIX III

Assessment report for the human and environmental risk assessment for veterinary medicinal products containing or consisting of a genetically modified organism
Centralised Applications only

This section of the Assessment Report is required for products containing or consisting of a genetically modified organism capable of replication or transferring genetic material in accordance with Article 28 of Council Regulation (No) 2309/93. The objective is to document the assessment of the data provided on the product with regard to the risks to human health and the environment from the proposed use of the product in the EU, and present the conclusions.

The structure and content should follow that described in the introduction to these guidelines and the evaluation is included in the Rapporteur's assessment report. There should be a reference on the extent to which the applicant has provided the necessary data, which are as follows:

1. A copy of any written consent(s) for previous releases (for research and development purposes);

2. The relevant data required by Annex III of Directive 2001/18/EC of the European Parliament and of the Council (as also indicated in the Notice to Applicants);

3. An environmental risk assessment (see guidelines in Notice to Applicants).

These data should have been provided in a physically separate part of the dossier (Part IIH).

The assessor should provide a brief summary of the information presented, with references to page numbers of the dossier.

The assessor should then comment on whether or not the data submitted by the applicant satisfactorily provides the necessary information and gives a suitable basis for conducting the environmental risk assessment.

Any reports of expected or unexpected adverse effects encountered when the product was released during experimental studies should be highlighted.

Comments should be provided on the adequacy of the environmental risk assessment carried out by the applicant. For example, for both the risk to humans and the environment, it should be stated if the applicant:

- as identified the hazards;
- assessed the likelihood that the hazard will occur;
- assessed the exposure to the hazard;
- assessed the consequences of the exposure;
- reached a conclusion on the level of risk;

- made proposals to minimise the risk;
- made conclusions that can be considered valid.

Finally, the question whether the level of risk can be considered acceptable should be answered.

- is the level of risk considered acceptable?

The conclusions reached after necessary consultations of the bodies set up by the Community or the Member States in accordance with Directive 2001/18/EC should be included.

Reference may usefully be made to the EMEA SOP-V-4012.

Assessor's conclusions

The assessor should provide an overall conclusions section on the acceptability of the risks to human health and the environment from the proposed use of the product throughout the EU, taking account of the steps taken to minimise any risks.

APPENDIX IV

Standard format for the front page of a Mutual Recognition assessment report

PRODUCT DETAILS	
Name of Product	
Active Substance(s)	
Target Species	
APPLICATION(S) DETAILS	
Name and Address of Applicant	
Phone Number	
Fax Number	
E-mail address	
Date of Receipt of Request for Assessment Report	
Reference Number of Application	
Date of 'Clock' start	
REFERENCE MEMBER STATE DETAILS	
Member State Responsible for Preparing the Assessment Report	
Date of Preparation	
Reference Number in the Originating Member State (e.g. Marketing Authorisation Number)	
Date Product First Authorised in the Reference Member State	
CONTACT WITH THE REFERENCE MEMBER STATE	
Contact Name	
Address	
Phone number	
Fax number	
E-mail address	
RECOMMENDATION	

APPENDIX V

Glossary of Terms

Abbreviation	Meaning	
ADI	acceptable daily intake	
AR	Assessment Report	
ASMF	Active Substance Master File	= EDMF
AUC	area under the curve	
Cmax	maximum concentration	
CMS	Concerned Member State	in Mutual Recognition Procedure
CVMP	Committee for Veterinary Medicinal Products	
EC	European Community	
EDMF	European Drug Master File	= ASMF
EPAR	European Public Assessment Report	
EU	European Union	
GC-MS	Gas chromatography – mass spectrometry	
GCP	Good Clinical Practice	
GL	Guideline	
GLP	Good Laboratory Practice	
GMO	Genetically Modified Organism	
GMP	Good Manufacturing Practice	
HPLC	High performance liquid chromatography	
INN	International Non-proprietary Name	
MA	Marketing Authorisation	
MIC	Minimum Inhibitory Concentration	
MRL	Maximum Residue Limit	
MRP	Mutual Recognition Procedure	
NOEL	No-observed effect level	
OECD	Organisation for Economic Co-operation and Development	
Ph.Eur	European Pharmacopoeia	
RMS	Reference Member State	in Mutual Recognition Procedure
SOP	Standard Operating Procedure	
SPC	Summary of Product Characteristics	
Tmax	Time to maximum concentration	

VICH	International Co-operation on Harmonisation of Technical Requirements for Registration of Veterinary Products	
WHO	World Health Organisation	