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Guideline on the principles for preparing assessment reports for veterinary medicinal products

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This guideline replaces the CVMP Guideline for an assessor preparing assessment reports for veterinary medicinal products (EMEA/CVMP/115769/2005).

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Executive summary

This guideline provides guidance on the principles for the preparation of assessment reports by regulatory authorities for applications relating to veterinary medicinal products in the European Union.

It is aimed at assessors and replaces the previous CVMP Guideline for an assessor preparing assessment reports for veterinary medicinal products (EMEA/CVMP/115769/2005).

This guidance is aimed to be applicable to all veterinary medicinal products, regardless of authorisation route or type of application, and will be complemented by templates for assessment reports for CVMP procedures.

1. Introduction (background)

This guideline is intended to provide general guidance to assessors[1] preparing assessment reports regarding procedures for veterinary medicinal products in the European Union. It is developed to replace the existing guideline, taking into account developments in the concerned field of assessments.

2. Scope

The scope of this document is to provide general guidance to assessors preparing assessment reports regarding procedures for veterinary medicinal products to facilitate consistency and coherence in the assessment of dossiers in the European Union, independent of the application procedure.

This guidance applies for pharmaceutical and immunological as well as novel therapy veterinary medicinal products. The main principles are aimed to be applicable for all types of applications and procedures, however are explained at the example of marketing authorisation applications. Additional advice is given, as appropriate, for other procedures.

The guideline will be complemented by templates for assessment reports for CVMP procedures, which provide specific advice on the expected details of the different sections of the reports. These templates can be used, as considered appropriate, also by Member States in mutual recognition or decentralised procedures.

3. Legal basis

Directive 2001/82/EC of the European Parliament and of the Council 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 and must demonstrate that potential risks are outweighed by the benefits, considering, where appropriate risk mitigation measures.

The data required and requirements for the assessment vary depending of the type of application and legal basis, e.g. full application (Art 12(3) of Directive 2001/82/EC), applications for a generic (Art 13(1)), hybrid applications (Art 13(3)), applications for a well-established use product (Art 13a), a fixed combination (Art 13b), or informed consent application (Art 13c), extensions and variations (Regulation (EC) 1234/2008), or whether it concerns an MRL application (Regulation (EC) 470/2009). Referrals (Article 33(4), 34 or 35 of Directive 2001/82/EC) deal with specified aspects of (a) marketing authorisation(s).

[1] For CVMP procedures: “assessor” means also “rapporteur” or “co-rapporteur”

CVMP assessment reports shall be published following finalisation of the procedure by the appropriate legal act after deleting information of a commercially confidential nature:

- Marketing authorisations: In accordance with Article 25(4) of Directive 2001/82/EC or Article 38(3) of Regulation 726/2004 assessment reports shall be drawn up, which shall be published following the granting of the marketing authorisation. The EMA also publishes assessment reports in case of the refusal or the withdrawal of the marketing authorisation application.
- Establishment of MRLs: the opinion (to which the European Public MRL assessment report is annexed) shall be published (Article 12 of Regulation (EC) No 470/2009).

Reports summarising the assessments for marketing authorisations are published by the EMA or Member States depending of the authorisation procedure and assessments on the establishment of MRLs and for referrals are published by the EMA

4. General principles for preparing an assessment report (example of a marketing authorisation application)

The final scientific conclusion on an application is taken after several stages of the data review in the authorisation procedure. Sequential assessment reports are prepared during the procedure or an initial assessment report may be generated and subsequently amended and updated in the light of discussions in the responsible fora (CVMP, CMDv), new information/clarifications received from the applicant/marketing authorisation holder[2] in response to the List of Questions (LoQ), List of Outstanding Issues (LoOI) or oral explanations. By this process the draft report(s) lead to the production of a final assessment report, which forms part of the CVMP opinion documentation leading to a Commission Decision in the centralised procedure or which will be the document exchanged between Member States in the mutual recognition procedure or the decentralised procedure.

The assessment report 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 benefit-risk 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 Summary of Product Characteristics (SPC), labelling and package insert. As such the report is central to the efficient operation of the centralised, mutual recognition and decentralised procedures, whether it concerns an initial application or an extension or variation.

The assessment report therefore needs to be a comprehensive report, containing a critical analysis of the entirety of data available. Assessment reports should be written in a clear language and in a logical manner, providing a complete overview of the data available, providing the adequate detail for the assessment, describing the strengths and weaknesses of the data provided and the overall application leading to the overall conclusions and benefit-risk assessment.

The details of the assessment in the different reports and stages of the procedure vary.

Example of initial marketing authorisation at CVMP:

A fairly detailed report is prepared initially by the rapporteur (rapporteur's assessment report), which contains details on the studies provided, including descriptions of the studies and results, e.g. in tables. This report may be 50 – 100 pages long or occasionally even more, dependant on the amount of data to be assessed.

[2] The term "applicant" as used in this guideline also includes marketing authorisation holders when they are applicants for post-authorisation applications and procedures, e.g. extensions, variations, renewals or annual reassessments

In addition a more summarised report is prepared (for initial marketing authorisations called the Scientific Overview (SO)). The SO contains all key issues of the assessment and becomes at the end of the procedure the CVMP assessment report. It is a concise report and should be written in a clear language.

The studies provided should be individually summarised; however these summaries can be short and follow the style as used for MRL summary reports/EPMARs. The level of detail may depend e.g. on the complexity of the study or whether the study design or results require a more detailed analysis and discussion. The SO is updated during the assessment procedure considering the discussions within the CVMP and further information/clarifications provided by the applicant. It is the basis for the CVMP assessment report, which will ultimately be published (with commercially confidential data removed) as part of the set of documents called European Public Assessment Report (EPAR).

An appropriate neutral and objective tone of commenting is required, because documents are released to applicants or possibly other parties in potential future access to document requests.

The legal basis for the marketing authorisation application should be stated in the introduction section of the assessment report, because the data requirements are dependent on the legal basis.

The consequences of the specific legal basis as to the data requirements and conclusions in particular regarding safety and efficacy should be briefly stated at the beginning of the relevant sections of the assessment report.

For generic applications (Article 13(1) as well as applications under Articles 13(3) or 13(4) of Directive 2001/82/EC) clear reference to the actual reference product should be made.

5. Preparing the assessment report for an initial marketing authorisation

5.1. Prior to starting the data assessment

First, the assessors should familiarise themselves with the applicant's proposed SPC and the composition of the product.

Based on the above, assessors should ensure that they are fully conversant with:

- the relevant part of Annex I to Directive 2001/82/EC as amended (Directive 2009/9/EC) (http://ec.europa.eu/health/files/eudralex/vol-5/dir_2009_9/dir_2009_9_en.pdf)
- the Notice to Applicants (Volume 6 of the Rules governing medicinal products in the EU) (http://ec.europa.eu/health/documents/eudralex/vol-6/index_en.htm)
- relevant CVMP and CVMP/VICH guidelines (http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000173.jsp&mid=WC0b01ac058002d89a)
- relevant European Pharmacopoeia (Ph. Eur.) monographs (https://www.edqm.eu/en/european-pharmacopoeia-8th-edition-1563.html)

Assessors should ensure that they understand:

- the legal basis (Article 12(3), Article 13(1), 13(3), 13a, 13b, 13c or 13d of Directive 2001/82/EC)
- MUMS/limited market classification, if applicable
- application under exceptional circumstances, if applicable

etc. and the consequences arising from the specific situation for the data requirements and assessment for the application under consideration.

For centralised procedures, assessors should understand the purpose of the various assessment documents (rapporteur's assessment report), scientific overview and benefit-risk assessment (SO), List of Questions (LoQ), List of Outstanding Issues (LoOI), etc.

Assessors should refer to any scientific advice the CVMP has given relevant to this product or any relevant regulatory advice given by the EMA and/or CVMP and comment whether the advice was followed or not. It is expected that applicants will make reference to the scientific advice or other relevant advice given by CVMP and/or EMA in their application. In addition, for centralised applications the EMA will highlight this to the rapporteurs/assessors when sending the AR templates.

If a pre-submission meeting has been held, the assessors should refer to the minutes of such meeting to see if any points emerged that might impact on the assessment (scientific or regulatory).

5.2. Preparing the detailed assessment report (for centralised procedures: the Rapporteur's Assessment Report)

Following an introductory section (see templates) the bulk of the report should be laid out in sections corresponding to each part of the dossier, as required by Annex I to Directive 2001/82/EC, for that type of product. The report concludes with a benefit-risk evaluation and overall conclusions regarding the marketing authorisation.

The Rapporteur's Assessment Report is aimed to undertake an in depth consideration and critical review of the application. It should not be a direct copy of the applicant's dossier, or of the applicant's detailed and critical summaries, with e.g. only brief statements if a study or approach is acceptable.

The Rapporteur's Assessment Report should include the assessor's/(co)rapporteur's own critical review of the applicant's data, summarising the key elements and findings of the studies provided, as well as the assessor's/(co)rapporteur's own conclusions regarding the validity of the study methods and results and the use of the findings for the assessment, and benefit-risk balance. In case the applicant proposes an approach deviating from a standard approach or CVMP guidance, this should be critically discussed and the assessor's/(co)rapporteur's own conclusions clearly drawn.

Each study should be described in a concise and clear manner, including key elements how it was conducted to judge the appropriateness of the study design. The assessor should also summarise the findings of the study. If an assessor considers that factual data (e.g. tabulated summaries of data or studies included the dossier) provide a complete and accurate overview, then this can be incorporated into the assessment report. Whenever text or data are directly copied from the applicant's dossier or expert's critical summary, this should be clearly identified and followed by the assessor's comment.

The assessment report should give an indication of compliance with, or indicate deviations from, the relevant requirements of Good Manufacturing Practice (GMP), Good Clinical Practice (GCP), and Good Laboratory Practice (GLP), the compliance with the requirements of Annex I to Directive 2001/82/EC and CVMP or VICH/ICH guidelines, or Ph. Eur. monographs, as appropriate.

Assessors should check whether parts of the dossier outside their area of review include data that are relevant for their assessment, or liaise with their appropriate colleagues to identify such data/information (e.g. pharmacokinetics might be addressed in the safety, residue and efficacy parts of the dossier, or palatability/dose/incorporation rates might be addressed under quality and efficacy). In case the same data/information is referred to or is relevant for several parts of the assessment, care should be taken for consistency in description/assessment and cross references be made.

It is recommended to review, where possible, SPCs and assessment reports for similar, already approved products, as this will be helpful to achieve consistency in assessment approach, as far as appropriate for the actual application under consideration.

Where information relevant for an assessment, which is not included in the dossier, is available to the assessor, this information can be considered in the assessment (this relates in particular to published studies on safety or efficacy). Data from another dossier must not be used in the assessment to e.g. complement gaps in the dossier, because dossier data are the property of the applicant.

Clear conclusions should be drawn on each study detailing what the study did show and did not show (e.g. stability was proven/could not be established, the proposed shelf-life can be supported/cannot be supported; a NO(A)EL can be established and the NO(A)EL be stated/the study does not allow the establishment of a NO(A)EL; the study supports the proposed indication/does not support the indication).

The critical analysis should include comparisons, where appropriate, of the data in the dossier compared with the requirements of Annex I, the Notice to Applicants (Volume 6), relevant guidelines, relevant Ph. Eur. 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 directive or guidelines, the assessor should comment on the appropriateness of the approach taken and the validity of the results obtained.

It is recommended that the summary of a study/design, findings and conclusions are written in such a way that it can be used without major modification for the SO.

For each subsection of the dossier (for example, stability, environmental risk assessment or clinical (field) trials) and at the end of each part of the dossier the assessor should write higher level overall conclusions drawing together the assessment of all the studies in this part and highlight what has been acceptably shown and what is missing in relation to the regulatory requirements.

Deficiencies or questions for clarification identified in the individual studies or subsections should be mirrored in the conclusions / overall conclusions for each part, as well as the benefit-risk assessment and List of Questions or list of outstanding issues.

In the “Overall conclusions” section at the end of each main section (i.e. Quality, Safety, Efficacy) the conclusions in respect to the compliance with requirements in accordance with Annex I of Directive 2001/82/EC should be summarised highlighting for each major heading the adequacy and completeness of the data provided and conclusions drawn (in general without giving details on studies) and identifying any deficiencies. The conclusions should be taken into account in the benefit-risk assessment or the comments on the SPC, as appropriate. The list of questions (day 120) should mirror these conclusions.

The assessment should be written to allow a clear link between the conclusions on the data provided and benefit-risk assessment and any conditions of the marketing authorisation, including the SPC.

The final section should set out the benefit-risk evaluation and overall 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. The benefit-risk evaluation should present a concise and clear overview of the decision-making process leading to the conclusion recommending whether to grant the marketing authorisation for the product, including any specific conditions that should apply e.g. limitations, restrictions. The assessor should avoid repeating details or specific references described previously in the assessment report, but should draw on the most important factors from the assessment report that are relevant to provide a critical overview of the product on which a conclusion can be drawn in a clear and logical manner.

5.3. Preparing the Summary Assessment (for centralised procedures: Scientific Overview)

As described before the SO is a concise report, which contains all key issues of the assessment, which is aimed at those CVMP members who may not be in the position to read the rapporteur's assessment report in its entirety, and becomes at the end of the procedure the CVMP assessment report. This is why it is a highly critical document to be drafted with due consideration.

The SO should include all the key features of the product, highlight any concerns about the data and/or the product, and lead in to the benefit-risk assessment. As in the detailed assessment report the deficiencies or questions for clarification identified in the individual studies or subsections should be mirrored in the conclusions / overall conclusions for each part, as well as the benefit-risk assessment and LoQ.

It is recommended to prepare the SO in parallel to or directly following the Rapporteur's Assessment Report, and using the assessor's description of the study design, the study findings as well as the assessor's own conclusions as the basis of the relevant text for the SO.

In the "Conclusions" section at the end of each main section (i.e. Quality, Safety, Efficacy) the conclusions in respect to the compliance with requirements in accordance with Annex I of Directive 2001/82/EC should be summarised highlighting for each major heading the adequacy and completeness of the data provided and conclusions drawn (in general without giving details on studies) and identifying any deficiencies. The conclusions should be taken into account in the benefit-risk assessment or the comments on the SPC, as appropriate. The list of questions (day 120) should mirror these conclusions.

When preparing the SO in the initial assessment phase the list of proposed questions should be appended.

The SO is updated at key stages of the assessment, in particular following the assessment of the response to the LoQ and LoOIs, by the assessor, and should reflect exactly the up-to-date knowledge on the data and conclusions taking into account supplementary information and explanations received, and highlight any remaining questions and concerns. The Rapporteur's initial AR is not updated following the assessment of the answers to the List of Questions.

5.4. Preparing the List of Questions and List of Outstanding Issues

The LoQ is intended to list all outstanding issues identified following the initial assessment of the application. The LoQ adopted by the CVMP at day 120 is the consolidated list based on the assessments by the rapporteur and co-rapporteur, and considering comments from remaining CVMP members and the discussions by the Committee.

The issues identified can be 'other concerns' if the product could be approvable provided satisfactory answers are given to these points or can be 'major objections' that would prevent approval of the marketing authorisation, or of a part of the proposed indication, at the present time.

In drafting the LoQ the assessor should take care that the issues raised follow clearly from the assessment of the related part of the dossier or data submitted, and that the deficiencies or questions are clearly described in the rapporteur's assessment report and SO. Also the conclusions on each part of the dossier on both the AR and SO should indicate these deficiencies. The outstanding issues/questions should be points necessary for concluding on the compliance with the quality, safety and efficacy requirements and for granting the marketing authorisation or addressing points where the proposals of the applicant cannot be followed on the basis of the data provided.

When updating the SO following comments the LoQ needs to be brought in line with any amendment of the assessment, and vice-versa.

Following the assessment of the response to the LoQ by the applicant, care should be taken to update all relevant sections of the SO accordingly. Any remaining outstanding issues should be clearly identified.

The considerations above for a LoQ apply similarly to the preparation of the LoOIs at day 180 of the procedure, if any such issues remain at this stage. It is important to give a clear message to the applicant if the product, or a part of the proposed indication, seem unacceptable at this stage of the procedure.

If the benefit risk evaluation is concluded positively but there are still important outstanding issues, these can be carried forward as “Conditions of the marketing authorisation” (very crucial and legally enforceable) or “Recommendations in the assessment report” (advice to the applicant for improvement of the product or data, not enforceable).

5.5. Applications under the decentralised procedures

The principles for preparing an assessment report and LoQ outlined above apply for the decentralised procedure.

5.6. Applications under the mutual recognition procedure

The principles for preparing an assessment report outlined above apply equally for the mutual recognition procedure.

The assessment report should be based on the Reference Member State’s (RMS) pre - assessment reports.

Where data do not comply with current guidelines because the marketing authorisation has been granted before the entry into force of some guidelines, and if no valid justification has been provided, the assessor should indicate why the authority has considered the data acceptable or, where new requirements have been introduced subsequent to the initial authorisation, how the dossier has been updated.

The RMS assessment report should be based on the updated dossier so that assessors from the Concerned Member State(s) (CMS(s)) 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 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.

The RMS assessment report should have a reference as to whether or not the detailed and critical summaries provided by the applicant 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.

6. Extensions and variations

The principles described above apply for assessment reports for extension applications. For type II variation applications no separate SO document is being prepared but the CVMP assessment report is prepared from the rapporteur’s assessment report omitting descriptive details of the studies and discussion of the assessment for a more concise CVMP assessment report.

7. MRL assessment reports

The principles described above apply for assessment for MRL applications. However, different to the initial marketing authorisation procedures, the detailed rapporteur's assessment report is updated following the response to the LoQ and LoOIs leading to a detailed CVMP assessment report. The concise document adopted by the CVMP that will be published following adoption of the MRL recommendation by the European Commission is the European Public MRL Assessment Report (EPMAR).

8. Referrals

For referrals the detailed rapporteur's assessment report or where applicable the co-rapporteur's assessment report is updated throughout the procedure and is the basis for the CVMP assessment report. No separate SO document is prepared.

References

- Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency. Available at: http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2004:136:0001:0033:en:PDF
- Directive 2001/82/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to veterinary medicinal products. Available at: http://ec.europa.eu/health/files/eudralex/vol-5/dir_2001_82_cons2009/dir_2001_82_cons2009_en.pdf
- Annex I to Directive 2001/82/EC (Commission Directive 2009/9/EC of 10 February 2009 amending Directive 2001/82/EC of the European Parliament and of the Council on the Community code relating to medicinal products for veterinary use). Available at: http://ec.europa.eu/health/files/eudralex/vol-5/dir_2009_9/dir_2009_9_en.pdf
- Commission Regulation (EC) No 1234/2008 of 24 November 2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products/ Available at: http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32008R1234&rid=1
- Regulation (EC) No 470/2009 of the European Parliament and of the Council of 6 May 2009 laying down Community procedures for the establishment of residue limits of pharmacologically active substances in foodstuffs of animal origin, repealing Council Regulation (EEC) No 2377/90 and amending Directive 2001/82/EC of the European Parliament and of the Council and Regulation (EC) No 726/2004 of the European Parliament and of the Council. Available at: http://eur-lex.europa.eu/legal-content/EN/TXT/HTML/?uri=CELEX:32009R0470&rid=3
- Notice to Applicants (Volume 6 of the Rules governing medicinal products in the EU). Available at: http://ec.europa.eu/health/documents/eudralex/vol-6/index_en.htm
- CVMP and CVMP/VICH guidelines. Available at: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000173.jsp&mid=WC0b01ac058002d89a
- European Pharmacopoeia (Ph. Eur.) monographs. Available at: https://www.edqm.eu/en/european-pharmacopoeia-8th-edition-1563.html

CVMP guidelines on MUMS data requirements:

- Quality data requirements for veterinary medicinal products intended for minor uses or minor species. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/10/WC500004277.pdf
- Safety and Residue Data Requirements for Veterinary Medicinal Products intended for Minor Uses or Minor Species. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/10/WC500004581.pdf
- Efficacy and target animal safety data requirements for veterinary medicinal products intended for minor uses or minor species. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/10/WC500004678.pdf
- Data requirements for immunological veterinary medicinal products intended for minor use or minor species. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2010/04/WC500089628.pdf