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NOTICE TO APPLICANTS
VETERINARY MEDICINAL PRODUCTS

GUIDELINE ON
THE PROCESSING OF RENEWALS IN
THE CENTRALISED PROCEDURE

DECEMBER 2005

This guideline will be included in The Rules governing Medicinal Products in the European Community Volume 6C Regulatory guidelines

GUIDELINE ON THE PROCESSING OF RENEWALS IN THE CENTRALISED PROCEDURE

EXECUTIVE SUMMARY

This guideline has been updated in preparation for the coming into force of Title III of Regulation (EC) No. 726/2004.

1. INTRODUCTION

This guideline considers issues associated with the processing of renewals in the centralised procedure, with an aim of giving procedural guidance to marketing authorisation holders (MAHs). It has been developed following consultation with the CVMP.

2. LEGAL FRAMEWORK

In accordance with and Article 39 of Regulation (hereafter called “the Regulation”) a marketing authorisation is valid for five years, after which it may be renewed on the basis of a re-evaluation of the risk-benefit balance. Once renewed, the marketing authorisation shall normally be valid for an unlimited period of time. However, on justified grounds relating to pharmacovigilance, the Commission may decide to proceed with one additional five-year renewal, after which the authorisation will become valid for unlimited period of time.

Article 37(1) of Regulation (EC) No 726/2004 indicates that authorisation shall be refused where the application does not fulfil the specific requirements as provided in accordance with Article 31 of the Regulation. It shall also be refused if the labelling and package leaflet do not comply with the requirements of Title V of the Directive 2001/82/EC.

Certain changes to the marketing authorisation particulars may be made at renewal, and these changes shall not trigger a variation procedure. However, none of the changes introduced at renewal should substitute for the marketing authorisation holder's obligation to update the marketing authorisation throughout the life of the product by variation procedure as data emerge.

In addition, in accordance with Article 41(4) of Regulation (EC) No 726/2004 the EMEA may request data at any time from the MAH to assess whether the benefit/risk balance remains favourable.

3. PRINCIPLES OF SUBMISSION AND EVALUATION

3.1. DATE FOR RENEWAL

Marketing authorisation holders must apply at least **6** months in advance of the expiry date, i.e. the 5 year anniversary of the Commission Decision granting the marketing authorisation, for the application to be valid. The marketing authorisation holder should agree in advance the submission date of the renewal application with the EMEA. The MAH may consider to co-ordinate the submission of the renewal with the regular cycle of the PSUR. In order to facilitate the procedure, Marketing Authorisation Holders are encouraged to attend a pre-submission meeting with the EMEA approximately **8** months before the anniversary of the Marketing Authorisation.

The renewal shall be granted before the anniversary of the marketing authorisation to ensure synchronisation is maintained. When issued, the renewal decision will take the expiry date of the preceding marketing authorisation. Where a second renewal is considered necessary on the basis of pharmacovigilance information, the renewed authorisation will expire at the end-of the 5-year period from the date of the previous expiry.

3.3 TIMETABLE

The MAH shall submit the renewal application at the latest by the recommended submission dates published on the EMEA website.

In order to allow sufficient time for the scientific evaluation of the data submitted and the adoption of a Commission Decision, and acknowledging that the overall process should be finalised in 6 months, the timetable (of max. 120 days) for the scientific evaluation by the CVMP is as follows (see also Annex 1): The EMEA will acknowledge receipt of a valid renewal application and shall start the procedure in accordance with the recommended starting dates published on the EMEA website. The MAH will be informed of the adopted timetable at the start of the procedure.

- Start of the procedure (see published dates on EMEA website): Day 1
- Rapporteur's Assessment Report sent to Co-Rapporteur: day 45
- Joint Rapporteur/Co-Rapporteur Assessment Report: day 60.
(Circulate to CVMP and MAH, highlighting major issues if any)
- Comments CVMP members: day 80
- First discussion at CVMP: day 90.
 - If no outstanding issues: adoption of opinion
 - If outstanding issues*: adoption of list of outstanding issues + decision on possible oral explanation by MAH
- MAH provides answers to list of outstanding issues to (Co-)Rapporteur, CVMP and EMEA: day 100.
- Revised Assessment Report from Rapporteur/Co-Rapporteur: day 110
(Circulate to CVMP and MAH)
- Adoption of CVMP Opinion/oral explanation by MAH: day 120.

* If any remaining outstanding issues are identified, including serious public or animal health concerns which may lead to a negative benefit/risk ratio and a possible non-renewal or to major changes to the marketing authorisation, a list of such issues will be adopted and sent to the MAH to be addressed in writing and/or at an oral explanation.

A limited extension of the timeframe is possible allowing the marketing authorisation holder to respond to the list of outstanding issues and the CVMP to assess the additional data submitted.

3.4 DOCUMENTS TO SUBMIT

For the renewal of a marketing authorisation the marketing authorisation holder is required to submit a consolidated list of all documents submitted in respect of quality, safety and efficacy, including all variations introduced since the marketing authorisation was granted, at least 6 months before the marketing authorisation ceases to be valid. However, the EMEA may request submission of the listed documents at any time.

Because the basis of the renewal is a re-evaluation of the risk-benefit balance of the product, the marketing authorisation holder should also submit an expert statement discussing the risk and benefits afforded by the product in the context of the experience gained since authorisation, including risks to human beings.

The expert statement should address quality, safety and efficacy issues and conclude with a risk-benefit statement. The expert statement should also be signed and accompanied by the CV of the expert.

Regarding quality, the statement should include a declaration of compliance with Article 41(1) of Regulation (EC) No 726/2004 which obliges marketing authorisation holders to "... take account of technical and scientific progress and make any variations that may be required to enable the medicinal products to be manufactured and checked by means of generally accepted scientific methods." The statement should confirm that all changes relating to the quality of the product have been made following applications for variations and that the product conforms to current CVMP quality guidelines. The statement should also include the currently authorised specifications for the active substance and the finished product and the qualitative and quantitative composition in terms of the active substance(s) and the excipient(s). The composition should be provided in tabular format.

A certificate of GMP compliance, not more than three years old, for the manufacturer(s) of the medicinal product, listed in the application should be submitted with the renewal application. (A reference to the Community EudraGMP database will suffice, once this is available). In addition for manufacturing sites of the medicinal product not located in the EEA or in the territory of an MRA partner, a list of the most recent GMP inspections carried out indicating the date, inspection team and outcome.

The renewal application should also be accompanied by declarations by the Qualified Person(s) of the manufacturing authorisation holder(s) listed in the application as responsible for batch release and, if different, where the active substance is used as a starting material stating that the active substance manufacturer(s) referred to in the application operate in compliance with the detailed guidelines on good manufacturing practice for starting materials.

The clinical experience gained with the product in animals and the current risk-benefit for the product on the basis of the compiled PSUR data and the compiled clinical data should be discussed, making reference to any relevant new information in the public domain (e.g. literature references, clinical trials and clinical experience, new treatments available) which may change the outcome of the risk-benefit evaluation made at the time of the original authorisation or last renewal. A clear statement is required from the clinical expert that the product can be safely renewed at the end of a 5-year period, or any action recommended or initiated should be specified and justified. The intention is that the clinical expert takes responsibility in the renewal application for the continued availability of the product on the market. The expert should ensure that the risk-benefit evaluation has been updated adequately, taking account of all relevant new information, either by endorsement of the statement within the PSUR or by appropriate supplementation within the expert statement. Confirmation that the product remains efficacious (e.g. no lack of efficacy reports) should be provided.

The expert should confirm that the authorities have been kept informed of any additional data (e.g. results from clinical studies) significant for the assessment of the risk-benefit ratio of the product concerned.

Furthermore the user safety of the product should be discussed, including a discussion of user and consumer safety, which reviews the available relevant information that has come to light in the reporting period e.g. sufficient warnings on the product literature, sufficient withdrawal period etc.

In order for the risk-benefit balance to be re-evaluated, the expert should also address the risks of any undesirable effects on the environment¹.

A full set of product literature Annexes should be submitted and the number of copies of the documentation is as follows:

EMEA (Day 0): Three copies of the application and Part IA; one copy of the EN product literature (hard copy and electronic) and other additional data.

(Co)-Rapporteur (Day 0): Two copies of the documentation including EN product literature (hard copy) for each Rapporteur.

¹ Further guidance on this aspect will be available shortly.

CVMP members (within 10 days after validation): Dossier requirements are provided in the list of CVMP Members' requirements on the EMEA web page and in Chapter 7 of the Notice to Applicants.

The European renewal application form should be completed and the documents listed in the renewal application form should be attached (see also Appendix 3). The renewal application form is available in the Notice to Applicants (Volume 6C) at <http://pharmacos.eudra.org/F2/eudralex/vol-6/home.htm> - 6c.

The marketing authorisation holder should complete one renewal application form for the Centrally Authorised Medicinal Product, i.e. including all authorised presentations of the product concerned (= 1 application per core EU Number).

The approved manufacturers should be included in the application form. All sites involved in the manufacture of both the active substance and the finished product should be listed indicating the respective activities of each site.

The box "Qualitative and Quantitative composition" of the application form does not need to be completed for centralised products; however, the relevant information should be provided.

If a revised SPC is proposed to take account of issues raised by the marketing authorisation holder, the precise current and proposed wording should be specified on the form. In general, proposed amendments to the SPC should be brought to the attention of the EMEA before submission, preferably through a pre-renewal submission meeting and all proposed changes should be highlighted in the product literature.

The renewal application form also incorporates a declaration to be signed that the quality of the product, in respect of the methods of preparation and control, has been regularly updated by variation procedure to take account of technical and scientific progress, and that the product conforms with current quality guidelines, where relevant.

Summary bridging report on safety

A summary bridging report should be included in the renewal application to bridge the information submitted in the previous PSURs.

The Marketing Authorisation Holder should submit the renewal application at least 6 months before the expiry of the marketing authorisation in the EU. This may be submitted earlier in order to facilitate coordination with the regular cycle of the PSUR.

For the renewal five years after the marketing authorisation, the Summary Bridging Report should cover the period from the authorisation date up to 60 days before the agreed submission date of the renewal application.

When the period to be covered falls outside the usual PSUR reporting cycle, the use of a PSUR Addendum Report is recommended to cover the data outside the defined period for PSUR submission. The Addendum Report should supplement the most recently completed PSUR and needs to include the additional safety reports received since the end date of the previous PSUR reporting cycle up to 60 days before the agreed submission date². In general it should be presented in the format of a PSUR as detailed in the guideline on pharmacovigilance for veterinary medicinal products – guidance on procedures for marketing authorisation holders (EMEA/CVMP/183/96-Rev.1).

The Summary Bridging Report should include for the period from the authorization date until 60 days before the agreed submission date:

- 1) Overview of regulatory or MAH actions taken for safety reasons
- 2) Overview of the reported incidences of adverse reactions (in animal and in human)
- 3) Overview of the reported information related to investigations of insufficient withdrawal period, lack of expected efficacy, adverse reactions related to off-label use or any potential environmental problems.

² The normal PSUR cycle is however not affected by this PSUR addendum report nor the summary bridging report for the renewal application. The next PSUR should therefore also include all data already submitted via the addendum report.

4) Overall safety evaluation

3.5 ASSESSMENT PROCESS

The assessment will focus on a safety evaluation, making use of the PSUR data and any relevant new information affecting the risk-benefit for the product, thus allowing for a re-evaluation of the risk-benefit of the product. A full re-evaluation of the whole dossier normally should not take place. Serious public or animal health or environmental concerns should be addressed as part of the renewal process and the product will not be renewed if serious public or animal health or environmental issues remain at the end of the procedure (see also section 3.6.2).

Where there are adequate and objective reasons not to renew the marketing authorisation in its existing terms and changes are necessary to the SPC and product literature arising from the data evaluation, the marketing authorisation holder may submit additional information and/or change the product information as part of the renewal process to address the concerns raised. Such changes may not, necessarily, initiate a separate variation procedure.

Other issues arising from assessment and changes due to the revision of the SPC guideline, or EMEA/QRD Product Information Templates should be considered within the renewal process. Product literature submitted should follow the latest QRD templates. Proposed changes to the SPC and product literature should be indicated on the renewal application form. All changes should also be clearly indicated in every language by using track changes.

Major changes to the product, such as the introduction of new indications or an extension of shelf life, may not be modified through the renewal procedure and have to be assessed through a variation procedure.

None of the SPC changes introduced at renewal should substitute for the marketing authorisation holder's obligation to update the marketing authorisation throughout the life of the product by variation procedure as data emerge.

In very exceptional cases if, as part of the renewal assessment, new studies are required but these are not of such importance as to delay the issuing of the renewal Opinion, then these may be considered as on-going post-authorisation commitments (Follow-Up Measures) after the renewal Opinion has been issued. The marketing authorisation holder will be required to provide written assurance that they will undertake the on-going commitments (Follow-Up measures) within an agreed time frame. If the results of new studies lead to changes in the SPC, these will be processed through a separate Type II variation procedure (see also section 3.6.2).

As part of the renewal process, the EMEA will check that the SPC, labelling and package insert conform to the requirements of the Directive.

3.6. THE COMMITTEE'S OPINION

The CVMP will adopt an Opinion on the renewal in the light of the final recommendation of the Rapporteur and Co-Rapporteur. The draft Opinion is prepared by the EMEA and then adopted by the CVMP.

The CVMP Opinion, which may be favourable or unfavourable, is, wherever possible, reached by scientific consensus. If such consensus cannot be reached, the Opinion shall be adopted by a majority of the members. When divergent positions have been expressed, they will be referenced in the CVMP Opinion. Members expressing such divergent positions shall state clearly the grounds on which they are based. The divergent positions will be appended to the Opinion.

Where the Opinion is adopted by a majority vote, the number of votes shall be clearly mentioned in the Opinion. In the absence of a majority position the CVMP Opinion is deemed to be negative.

The position of the Norwegian and Icelandic CVMP members (who do not take part in the CVMP vote as such) is nevertheless recorded in the Opinion.

The Rapporteur, in co-ordination with the Co-Rapporteur and the project manager, taking account of the full scientific debate within the CVMP and the conclusions reached, prepares the final renewal assess-

ment report, which, once adopted by the CVMP, becomes the CVMP renewal assessment report and is appended to the CVMP Opinion.

3.6.1 FAVOURABLE OPINION

In the event of an Opinion in favour of renewal of the authorisation, the following documents will be annexed and/or appended to the Opinion.

- A draft Summary of Product Characteristics as referred to in Article 14 of Directive 2001/82/EC;
- Manufacturing and/or importing conditions and conditions of the marketing authorisation;
- A classification for the supply of the veterinary medicinal product;
- A draft Label and Package insert presented in accordance with Title V of Directive 2001/82/EC;
- The CVMP renewal assessment report;
- Where relevant, divergent positions of Committee Members with signatures and with their grounds for not supporting the Opinion

Any follow-up measures agreed upon by the CVMP will be included in the renewal assessment report and referenced in a letter of undertaking signed by the Marketing Authorisation Holder which will be annexed to the assessment report (see also 3.6.1.2).

3.6.1.1 OPINION ON PRODUCTS AUTHORISED UNDER EXCEPTIONAL CIRCUMSTANCES

The fifth annual re-assessment of medicinal products authorised under exceptional circumstances will take place at the renewal of the product concerned.

For such medicinal products authorised under exceptional circumstances, in accordance with Article 39 (6) of Regulation (EC) No 726/2004, the CVMP will have to consider whether there remain grounds for the marketing authorisation to be kept under exceptional circumstances. If no such grounds remain, a recommendation will be made to renew the marketing authorisation under normal circumstances.

3.6.1.2 POST-AUTHORISATION COMMITMENTS

Specific obligations

When a renewal Opinion is granted, stating that there remain grounds for the marketing authorisation to be renewed under exceptional circumstances, the marketing authorisation holder is obliged to submit the requested data to the Rapporteur, Co- Rapporteur, CVMP Members and the EMEA, in the agreed time-frame after the renewal. These “specific obligations” to provide such data, are set out in Annex II of the Opinion and are detailed in the Letter of Undertaking of the marketing authorisation holder as adopted at the time of the Opinion. The specific obligations are to be reviewed at the intervals indicated and at the longest annually. The annual review includes a re-assessment of the risk-benefit profile.

The marketing authorisation holder should send a copy of the documentation relating to specific obligations to the Chairman of the CVMP, all CVMP members and EMEA. Such documentation should be reviewed in accordance with the agreed timetable.

Follow-up measures

For all Opinions of the CVMP (whether or not under the exceptional circumstances of Article 39(7) of the Regulation), it might be necessary to establish follow-up measures. Unless otherwise requested by CVMP members, the data on the fulfilment of follow-up measures should be sent by the marketing authorisation holder to the Rapporteur and the EMEA. The data should be reviewed in accordance with the agreed timetable. Marketing authorisation holders will be informed of the outcome of CVMP discussions by the EMEA.

Resulting variation applications

Marketing authorisation holders are encouraged to submit any variation application resulting from the fulfilment of follow-up measures and / or specific obligations at the same time as the fulfilment of the follow-up measures/specific obligations to minimise the processing and review time.

3.6.2. UNFAVOURABLE OPINION

The CVMP will adopt a negative Opinion recommending not renewing the marketing authorisation if there are serious public or animal health or environmental issues raised. The criteria specified in Article 83 of the Directive 2001/82/EC regarding the suspension or revocation of authorisation to market medicinal products form the basis for the refusal to renew the marketing authorisation.

These criteria include where the product proves to be harmful in the normal conditions of use, or where its therapeutic efficacy is lacking or where its qualitative and quantitative composition is not as declared. Therapeutic efficacy is lacking when it is established that therapeutic results cannot be obtained with the medicinal product. Additionally, non-renewal may be considered where the particulars supporting the application for renewal are incorrect or have not been updated, or when the controls on the manufacturing process or on the finished product have not been carried out, or when commitments have not been fulfilled.

Additionally, non-renewal will be considered if the marketing authorisation holder fails to respond to the issues raised during assessment within the timescale given and where no adequate justification or explanation is given.

The following documents will be annexed and/or appended to the Opinion:

- the appended CVMP assessment report stating the reasons for its negative conclusions.
- where appropriate, divergent positions of Committee Members with their grounds.

3.7 FOLLOW-UP TO THE CVMP OPINION

3.7.1 TRANSLATION AND TRANSMISSION OF THE CVMP OPINION

If amendments to the proposed product information are required following the adoption of the CVMP Opinion, the marketing authorisation holder will provide the EMEA and all CVMP members with the relevant amended translations of the SPC, labelling and package insert within 5 days after the CVMP Opinion (electronic copies only). All changes to the previous versions should be clearly indicated in each language version.

If changes to the product literature have been made, a review of the quality of these translations will be carried out by the EMEA in co-operation with the Member States. The Norwegian and Icelandic translations will be checked by the Norwegian and Icelandic authorities in co-operation with the Marketing Authorisation Holder.

If within 15 days of receipt of the Opinion and CVMP renewal assessment report, the marketing authorisation holder does not inform the EMEA of any intention to appeal, the EMEA will forward the Opinion (and the required annexes), to the Commission, the Member States, Norway and Iceland together with the CVMP renewal assessment report.

The Decision-Making Process of the Commission starts once the Opinion with annexes in all official EU languages has been received. The Norwegian and Icelandic Authorities will issue corresponding national authorisations subsequent to the Commission Decision.

Where the CVMP adopted a negative Opinion and the marketing authorisation holder notified the EMEA/CVMP of their intention of appeal, the EMEA will inform the Commission of the negative Opinion and appeal. The final CVMP Opinion will be forwarded to the Commission upon finalisation of the appeal procedure (see 3.7.3).

3.7.2 MOCK-UPS AND SPECIMENS

Where the package insert and outer and inner labelling have been significantly amended as a result of the renewal procedure, updated mock-ups should be provided to the EMEA.

For Norway and Iceland, new mock-ups for all product presentations covered by the renewal application should be provided to the Norwegian and Icelandic authorities (with a copy of the cover letter to the EMEA) in all cases. One set of the product literature approved by the Norwegian and Icelandic authorities should be sent by the MAH to the EMEA for information.

3.7.3. RE-EXAMINATION

The marketing authorisation holder may notify the EMEA/CVMP of their intention to appeal within 15 days of receipt of the Opinion (after which if he does not appeal, he shall be deemed to have agreed with the Opinion and it becomes a final Opinion).

The grounds for appeal must be forwarded to the EMEA within 60 days of receipt of the Opinion. If the marketing authorisation holder wishes to appear before the CVMP for an oral explanation, the request should also be sent at this stage. The CVMP shall appoint a different Rapporteur and, where necessary, a different Co-Rapporteur, for whom MAHs can express their preference, to co-ordinate the appeal procedure, accompanied, if necessary, by additional experts. Within 60 days from the receipt of the grounds for appeal, the CVMP will consider whether its Opinion is to be revised. If considered necessary, an oral explanation can be held within this 60-day timeframe.

Once the CVMP issues a final Opinion, it is forwarded (with the required annexes), to the Commission, the Member States, Norway and Iceland and the marketing authorisation holder stating the reasons for its conclusion.

3.7.4 EUROPEAN PUBLIC ASSESSMENT REPORT (EPAR)

The EMEA will prepare an update of the EPAR, reflecting the renewal assessment and CVMP Opinion. Once the Commission Decision on the renewal has been made, the updated EPAR shall be made available as soon as possible after notification of the Commission's Decision to renew the marketing authorisation.

3.7.5 NEGATIVE DECISION

Following a Commission Decision to refuse to renew the marketing authorisation, which, in accordance with Article 37(2) of the Regulation constitutes a prohibition to maintain on the market the medicinal product concerned throughout the Community, the EMEA shall, upon request, inform any person concerned of the final Decision, in accordance with Article 37(3) of the Regulation (EC) No 726/2004.

APPENDIX I

RENEWAL TIMETABLE (CVMP)

Day 1	Start of procedure (as per the EMEA published starting dates)
Day 45	Receipt of Rapporteur's Assessment Report sent to Co-Rapporteur
Day 60	Receipt of Joint Rapporteur / Co-Rapporteur Assessment report – circulated to EMEA, CVMP members and MAH. EMEA may liaise with MAH in preparation of the opinion/List of Outstanding Issues.
Day 80	Comments of CVMP members on the Joint Assessment report.
Day 90	First discussion at CVMP. - Possible adoption of opinion. - In case of outstanding issues: adoption of List of Outstanding Issues + decision on possible oral explanation by MAH
Day 100	MAH provides answers to list of outstanding issues to Rapporteur, Co-Rapporteur, CVMP and EMEA
Day 110	Receipt of Rapporteur / Co-Rapporteur Assessment Report on MAH's answers - circulated to EMEA, CVMP members and MAH
Day 120	Adoption of CVMP opinion. Possible oral explanation by MAH

The MAH shall submit the renewal application at the latest by the recommended submission dates published on the EMEA website. Once the renewal application is validated by the EMEA, the timetable is adopted and the clock starts according to the published starting date. The MAH will be informed of the adopted timetable at the start of the procedure.

APPENDIX 2

DOCUMENTS TO SUBMIT

The marketing authorisation holder submits a renewal application to the EMEA and all CVMP members comprising the European renewal application form with the following annexes:

- 1.1 List of all authorised product presentations in tabular format (following the template for Annex A to CVMP Opinions). Such information can also be found e.g. in module 2 of the EPAR (“All authorised presentations”);
- 1.2 Part IA of the dossier including details of:
 - the qualified person in the EEA for Pharmacovigilance
 - the contact person in the EEA with overall responsibility for product defects and recalls
 - the name and contact details of a contact person at the address of the Marketing Authorisation Holder (if different from the address of the contact person during the procedure)
- 1.3 List of EU Member States / Norway / Iceland / Liechtenstein where the product is on the market and indicating for each country which presentations are marketed and the launch date.
- 1.4. Chronological list of Follow-up measures and Specific Obligations submitted since grant of marketing authorisation or last renewal indicating scope, status, date of submission and date when issue has been resolved
- 1.5. Revised list of all remaining Follow-up measures and Specific Obligations and signed letter of commitment (where applicable)
2. Proposed texts for SPC, outer and inner labelling and package insert (EN only).
- 3.1 A Risk-Benefit statement to include:

Quality expert statement:

Currently authorised specifications for the active substance and the finished product (with date of latest approval + procedure number).

Qualitative and quantitative composition in terms of the active substance(s) and the excipient(s) (with date of latest approval + procedure number).

A certificate of GMP compliance, not more than three years old, for the manufacturer(s) of the medicinal product listed in the application issued by an EEA Competent Authority or MRA partner authority. A reference to the Community EudraGMP database will suffice, once this is available.

For manufacturing sites of the medicinal product not located in the EEA or in the territory of an MRA partner, a list of the most recent GMP inspections carried out indicating the date, inspection team and outcome.

In accordance with Article 50(f) of Directive 2001/82/EC manufacturing authorisation holders are required to use as starting materials only active substances which have been manufactured in accordance with the detailed guidelines on good manufacturing practice for starting materials as adopted by the Community. The following declarations are required: A declaration by the Qualified Person (QP) of each of the manufacturing authorisation holders listed in the application form where the active substance is used as a starting material. A declaration by the Qualified Person (QP) of the manufacturing authorisation holder(s) listed in the application as responsible for batch release. These declarations should state that all the active

substance manufacturer(s) referred to in the application form operate in compliance with the detailed guidelines on good manufacturing practice for starting materials.

Clinical expert statement

Safety expert statement

Including User and Target Animal Safety and an Evaluation of any risk of undesirable effects on the Environment

4. Summary Bridging Report and, where appropriate, PSUR addendum report
5. Declaration of the current TSE status, e.g. EDQM certificates of suitability (if appropriate).