EUROPEAN COMMISSION
ENTERPRISE AND INDUSTRY DIRECTORATE-GENERAL

Consumer goods
Pharmaceuticals

Brussels, 01.02.2006
ENTR/F2/KK D(2006)

Revision 2006

NOTICE TO APPLICANTS
VETERINARY MEDICINAL PRODUCTS

GUIDELINE ON THE PROCESSING OF RENEWALS IN THE MUTUAL RECOGNITION AND DECENTRALISED PROCEDURE

FEBRUARY 2006

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

Rue de la Loi 200, B-1049 Bruxelles/Wetstraat 200, B-1049 Brussel - Belgium - Office: BREY 10/073.
Telephone: direct line (+32-2)299.15.11, switchboard 299.11.11. Fax: (+32-2)299.80.46.
Karin.Krauss@cec.eu.int

GUIDELINE ON THE PROCESSING OF RENEWALS IN THE MUTUAL RECOGNITION AND DECENTRALISED PROCEDURE

1. INTRODUCTION

This guideline considers issues associated with the processing of renewals for products authorised through the mutual recognition procedure (MRP) or decentralised procedure (DCP), with an aim of giving procedural advice to Member States and marketing authorisation holders and to ensure a consistent and beneficial approach to renewals. It has been developed following consultation with the Notice to Applicants Working Group and CMD(v)[1].

The guideline has been updated to reflect new pharmaceutical legislation in accordance with Directive 2001/82/EC, as amended by Directive 2004/28/EC. Member States shall have brought into force all laws, regulations and administrative provisions necessary to comply with this Directive no later than 30 October 2005.

2. LEGAL FRAMEWORK

In accordance with Article 28 of Directive 2001/82/EC 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 Competent Authorities (RMS/CMS) may decide to proceed with one additional five-year renewal, after which the authorisation will become valid for unlimited period of time.

Directive 2001/82/EC requires the submission of a consolidated list of all documents submitted in respect of quality, safety and efficacy, including all variations introduced since the MA was granted, at least six months before expiry of the marketing authorisation. The renewal dossier should contain all information relevant to the safe and effective use of the veterinary medicinal product.

With the approval of the reference Member State and concerned Member States, 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 27(3) of Directive 2001/82/EC the Competent Authorities (RMS/CMS) may at any time ask the marketing authorisation holder to forward data demonstrating that the benefit-risk balance remains favourable.

3. PRINCIPLES OF SUBMISSION AND EVALUATION

3.1. DATE FOR RENEWAL

The agreement of a common renewal date by Member States and marketing authorisation holders is the key to the successful operation of the renewal procedure for products authorised through the MRP or DCP, and to the continued monitoring of the pharmacovigilance of the product through the synchronised submission of Periodic Safety Update Reports (PSUR).

Flexibility will be maintained as to the basis of the renewal date and will take account of the applicant's preference in agreeing a common renewal date for all presentations of the actual prod-

[1] CMD(v) – Veterinary Coordination Group for Mutual Recognition and Decentralised Procedures

uct, the International Birth Date and/or the European Birth Date, and the maintenance of synchronisation of PSURs.

The marketing authorisation holder should agree the common renewal date with the reference Member State at the completion of the initial mutual recognition procedure or decentralised procedure.

The principle applies that the marketing authorisation holder may apply for a renewal earlier than 5 years, but the period before application may not extend beyond 5 years. Submission therefore will be based on the earliest renewal date in any one Member State, unless the marketing authorisation holder agrees an alternative date with the reference Member State.

For repeat mutual recognition procedures, so called “Repeat Use” procedures, the renewal timetable should follow that of the first procedure.

In addition, in order to put in place measures facilitating work-sharing of PSUR assessment among competent authorities, a harmonisation of the renewal dates and/or PSUR cycles of veterinary medicinal products containing the same active substances may be proposed by the Marketing Authorisations Holders or the competent authorities.

3.2 DATE FOR SUBMISSION

The applicant submits the renewal application simultaneously to all concerned Member States. The renewal submission is required no later than 6 months before the expiry date.

3.3 TIMETABLE

Member States have agreed the need for a timetable approach to renewals. The use of a preliminary assessment report as well as a finalised assessment report, and a clock off period, will allow Member States to input to the renewal process as required and give marketing authorisation holders the opportunity to resolve issues within the renewal process.

A 90 day procedure is followed using the Type II variation model, with the possibility of clock-off for no more than 30 days. In exceptional circumstances only, and with agreement of the reference Member state, the clock-off period may be extended. A timetable is given in Annex 1.

The existing reference Member State takes the lead in the procedure, proposes the timetable and prepares the assessment report etc.

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. However, the reference Member State or concerned Member States may request submission of the listed documents at any time.

The consolidated list of documents to be submitted by the marketing authorisation holder is given in Annex 2.

Application Form

The European application form for renewal of a marketing authorisation should be completed and the documents listed in the renewal application form should be attached. The European renewal application form is included in the Notice to Applicants (Volume 6C), electronically available at http://pharmacos.eudra.org/F2/eudralex/vol-6/home.htm .

The marketing authorisation holder should normally submit one renewal application form for each marketing authorisation.

The number of copies of the documentation to be submitted is defined in Chapter 7, Volume 6A of Notice to Applicants.

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

The renewal application form should also incorporate a declaration indicating that the quality of the product, in respect of the methods of preparation and control, has been regularly updated by variation procedures to take account of technical and scientific progress in compliance with Article 27(1) of Directive 2001/82/EC. The product should conform to current *Ph.Eur.* monographs and quality guidelines, where relevant.

The marketing authorisation holder is responsible for ensuring that the dossier is kept up to date throughout the life of the product by way of the variation process.

The renewal application should also be accompanied by declarations of the Qualified Person(s) of the marketing 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.

A certificate of Good Manufacturing Practice (GMP) compliance, not more than three years old, for the manufacturer(s) of the veterinary medicinal product listed in the application, should be submitted with the renewal application. In addition, for manufacturing sites of the veterinary medicinal product not located in the EEA or in the territory of a Mutual Recognition Agreement (MRA) partner, a list of the most recent GMP inspections carried out indicating the date, inspection team and outcome should be submitted.

TSE status

The renewal application should also include a declaration of the current TSE status with updated EDQM certificates of suitability, if appropriate (compliance with the actual version of the TSE guideline).

Summary of product characteristics (SPC), labelling and package leaflet

If a revised SPC is proposed by the marketing authorisation holder, the precise current and proposed wording should be specified in the application form. All proposed changes should be highlighted in SPC, labelling and package leaflet. In general, proposed amendments to SPC, labelling and package leaflet should be discussed and agreed with the RMS in advance of submission.
A full set of SPC, labelling and package leaflet should be submitted using the agreed templates.

Periodic Safety Update Report (PSUR)/Summary bridging report on safety

Reference should be made to Volume 9 of the Rules Governing Medicinal Products in the European Union on Pharmacovigilance (Notice to marketing authorisation holders). In accordance with the Notice to Applicants the following principles should be taken into account:

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 co-ordination 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 authorisation date up to 60 days before the agreed submission of the renewal application.

As part of a mutual recognition/decentralised renewal application the PSUR data will generally take the form of the PSUR(s) prepared since grant together with an Addendum/Summary Bridging Report as necessary.

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 date[2].
As the PSUR Addendum Report does not provide an in depth-analysis of the additional cases, the marketing authorisation holder is requested to include such analysis within the clinical overview. The marketing authorisation holder should also include the cases reported in the Addendum Report again in the next PSUR.

A summary bridging report should be included in the renewal application to bridge the information submitted in the previous PSURs and should include for the period from the authorisation date until 60 days before the agreed submission date:

1) Overview of regulatory or marketing authorisation holder 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.
4) Overall safety evaluation

The requirements and format of the PSURs, PSUR Addendum Reports and Summary Bridging Report are set out in Volume 9.

Expert Statements

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

[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.

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 a CV of the expert.

Expert statement regarding quality

There is no updating of Part II quality data at renewal. The marketing authorisation holder has an obligation to keep this updated on an on-going basis throughout the life of the product using the variation procedure.

The quality expert statement should include a declaration of compliance with Article 27(1) of Directive 2001/82/EC which obliges marketing authorisation holders to "... take account of technical and scientific progress and introduce any changes..." 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 *Ph.Eur.* monographs and CVMP quality guidelines. The statement should also include the currently authorised specifications for the active substance and the finished product as well as the qualitative and quantitative composition in terms of the active substance(s) and the excipient(s).

The marketing authorisation holder will continue to monitor the stability of the product in accordance with agreed stability protocols but needs only to inform competent authorities should a problem arise together with a recommended course of action.

Expert statement regarding safety and efficacy

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

The expert should confirm that the Competent Authorities have been kept informed of any additional data (e.g. results from clinical studies) important 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 environment.[3]

3.5 ASSESSMENT PROCESS

The assessment approach of the Member States will focus on a safety evaluation, making use of the PSUR data and on 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. Potential serious risk to human or animal health or to the environment should be addressed as part of the renewal process and the product will not be renewed if potential serious risk to human or animal health or to the environment remains at the end of the procedure.

Where there are adequate and objective reasons not to renew the marketing authorisation in its existing terms and changes are necessary to the SPC, labelling and package leaflet arising from the data evaluation, the marketing authorisation holder may submit additional information and/or change SPC, labelling and package leaflet 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 Product Information Templates should be considered within the renewal process. SPC, labelling and package leaflet submitted should follow the latest annotated QRD templates for mutual recognition or decentralised procedures. Proposed changes to the SPC, labelling and package leaflet should be indicated on the renewal application form.

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 or labelling and package leaflet 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, then these may be considered as on-going commitments after the issue of the renewal. The marketing authorisation holder will be required to provide written assurance that it will undertake the on-going commitments within an agreed time frame. If the results of new studies lead to changes in the SPC or in labelling and package leaflet, these will be processed through a separate variation procedure.
Updated and harmonised labelling and package leaflet must be agreed at renewal if national versions still exist.

3.6 AUTHORISATION DOCUMENTS

Renewal documents issued will include the SPC as amended and harmonised labelling and package leaflet.

[3] Further guidance on this aspect will be available shortly.

3.7. FURTHER RENEWAL

In some circumstances an additional 5-year renewal may be required. This should be determined on Pharmacovigilance grounds. In circumstances where, for example, a new indication or target species is granted following the renewal other pharmacovigilance provisions are available outside the renewal process, for example, additional PSUR frequency or benefit-risk review if needed.

3.8 NON-RENEWAL

Members States will not renew the marketing authorisation if there is potential serious risk to human or animal health or to the environment remaining at the time of renewal. The criteria specified in Article 83 of Directive 2001/82/EC regarding the suspension, withdrawal or revocation of authorisation to market veterinary medicinal products may 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, Member States will consider non-renewal or suspension 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.

By analogy to the procedure for mutual recognition/decentralised applications use will be made of the Co-ordination Group where Member States have divergent opinions.

In cases where there is a divergent view amongst Member States at the end of the renewal process and the Co-ordination Group has not achieved a common position, a scientific evaluation of the matter would be undertaken by the CVMP, following a referral based on Article 34 or 35 of Directive 2001/82/EC. The formal referral to arbitration should be made by those concerned Member States, which oppose the opinion of the reference Member State. In cases where the reference Member State alone is against renewal, the reference Member State will refer the issue to arbitration.

If the draft decision of the reference Member State is unfavourable, and there is agreement by all Member States, then non-renewal action will be taken without a referral to CVMP. In such cases consideration by the Co-ordination Group is recommended. Similarly, if a marketing authorisation holder fails to respond to issues raised during assessment, non-renewal of the marketing authorisation will result.

ANNEX 1

RENEWAL EVALUATION TIMETABLE

–7 days prior to submission to CMS	MAH to send application and documentation to RMS, RMS to assign of procedure number
submission to CMS	Dispatch of documentation; start of automatic validation (14 days)
Day 0	Start of procedure by RMS
Day 40	RMS to circulate Preliminary Renewal Assessment Report (PRAR) to CMS and MAH.
Day 55	CMS to send comments to RMS
Day 59	RMS to send request for supplementary information (RSI) to MAH (if necessary)
	Clock-off up to 30 days (opportunity to prolong in exceptional circumstances only with agreement of RMS)
Day 60	RMS to circulate Final Renewal Assessment Report (FRAR) with draft decision to CMS and MAH
Day 85	CMS to indicate acceptance/non-acceptance of decision
Day 90	Renewal (RMS to circulate revised final SPC to CMS and MAH) or non-renewal or referral to Co-ordination group

Note: A Day 60 completion should be possible.

ANNEX 2

DOCUMENTS TO SUBMIT

Together with a cover letter and a comprehensive table of content the marketing authorisation holder submits a renewal application to the reference Member State and concerned Member States comprising the European renewal application form with the following annexes:

1.1 A list of all authorised product presentations for which renewal is sought in tabular format

1.2 Details on contact persons:

- Qualified person in the EEA for Pharmacovigilance and the QP for Pharmacovigilance in the MS, if different.
- 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)

1.6. Proof of payment of fee, where relevant.

2. The currently mutually recognised SPC and proposed texts for SPC, labelling and package leaflet to take account of issues raised by the expert. All changes must be clearly highlighted (EN and relevant national translations).

3. Periodic Safety Update Report (PSUR) and Summary Bridging Report on safety, if applicable

4. Clinical expert statement / Safety expert Statement

5.1. Quality expert statement

5.2. A statement, or when available, 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.

5.3. 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 by other authorities indicating the date, inspection team and outcome.

5.4. 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;

i. 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.

ii. Where different, 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 n compliance with the detailed guidelines on good manufacturing practice for starting materials.

6. Declaration of the current TSE status