

CMDv/BPG/007

BEST PRACTICE GUIDE

for

Handling Renewals in the Mutual Recognition and Decentralised Procedure

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1. INTRODUCTION

In accordance with Article 28 of Directive 2001/82/EC as amended by Directive 2004/28/EC (hereafter called "the Directive") a marketing authorisation is initially valid for five years, after which it may be renewed on the basis of a re-evaluation of the benefit-risk 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.

2. AIM AND SCOPE

This Best Practice Guide (BPG) has been prepared for use in renewal procedures for products authorised via the Mutual Recognition (MRP) and Decentralised Procedure (DCP) by Reference Member States (RMS), Concerned Member States (CMS) as well as the applicant in order to facilitate the smooth running of the procedure.

The BPG has been established in accordance with the "Guideline on the processing of Renewals in the Mutual Recognition and Decentralised Procedure" published in the Notice to Applicants (NtA).

3. REFERENCES and RELATED DOCUMENTS

- Directive 2001/82/EC as amended by Directive 2004/28 EC.
- NtA, Volume 6C: Guideline on the processing of Renewals in the Mutual Recognition and Decentralised Procedure.
- NtA, Volume 6A, Chapter 7.
- NtA, Volume 9: Pharmacovigilance - Veterinary medicinal products – Guidance and procedures for marketing authorisation holders.

Full list of CMDv documents related to this BPG can be found in Annex 3 of the document.

4. DESCRIPTION OF PROCEDURE

4.1 Date of Renewals

The Competent Authority, in the role of the RMS, should agree with the MAH on a common renewal date at completion of the initial MRP or the DCP.

For Repeat Use Procedures, the renewal date should follow that of the first procedure. Even if the veterinary medicinal product has been renewed before the Repeat Use

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procedure was initiated, a further renewal should be conducted in the new CMS and this will be coordinated by the RMS.

Flexibility should be maintained as recommended in the "Guideline on the processing of Renewals in the Mutual Recognition Procedure".

For those products for which a common renewal date has not been agreed at the end of the initial MRP/DCP, the MAH and the RMS should agree on a common renewal date later on, but this date cannot extend beyond 5 years after authorisation in the RMS. An earlier renewal is always possible.

4.2 Dates for Submission

The application should be submitted at least 6 months ahead of the agreed common renewal date simultaneously to all concerned Member States (MS). The aim is to grant the renewal before the expiry of the marketing authorisation.

If the renewal takes longer than 6 months to resolve and the risk-benefit ratio remains favourable, the product may remain on the market whilst the renewal application is being processed.

Only in exceptional and justified cases, may a variation run during the renewal procedure. Therefore, the MAH should consider carefully the date of submission of variations. In situations where the renewal has to be submitted to be in accordance with the agreed common renewal date and an ongoing variation is completed during renewal, the MAH should update relevant renewal documents (e.g. SPC, labelling, package leaflet). All changes arising from the approved variation should be highlighted in the replaced renewal documents and the MAH should provide a declaration that no other changes have been introduced.

4.3 Documents to submit

For the renewal of a Marketing Authorisation (MA), the MAH is required to submit a consolidated list of all documents submitted in respect of quality, safety and efficacy, including all variations introduced since the MA was granted. However, the RMS/CMS may request submission of the listed documents at any time.

The application should be made in accordance with the legal basis applied for. Guidance on format, appropriate number of copies of the dossier, language requirements, fees etc can be found in Chapter 7, Volume 6A of the NtA. Fee requirements for national authorisations are also available in the CMDv website.

A full set of SPC, labelling and package leaflet should be submitted using the agreed templates. Text proposals only in English are acceptable with the submission of the dossier. It is strongly recommended that mock-ups using 3 times the English language should be submitted at the beginning of the procedure and during the procedure, if necessary.

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A detailed description of documents to be submitted is given in the NtA, Vol. 6C, "Guideline on the processing of Renewals in the Mutual Recognition and Decentralised Procedure".

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

4.4 Time table and procedure

A description of the evaluation process is given in the NtA, Vol. 6C, "Guideline on the processing of Renewals in the Mutual Recognition and Decentralised Procedure". The assessment approach of the MS will focus on a safety evaluation, making use of the PSUR data and on new information affecting the benefit-risk balance for the product, thus allowing for a re-evaluation of the benefit-risk balance of the product. A full re-evaluation of the whole dossier normally should not take place.

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

The renewal procedure, including the submission of a preliminary (PRAR) and finalised renewal assessment report (FRAR) as well as the possibility of a clock-off period, will allow MS to participate in the renewal process, as required, and will give companies the opportunity to resolve issues within the renewal process.

In case of disagreement between MS a referral to CMD(v) according Article 33 of the Directive will be set off.

The RMS takes the responsibility in the procedure by proposing the timetable and preparing the assessment reports.

All communications between RMS and CMS will be by e-mail or CTS in accordance with the relevant guidance documents (see Annex 3). All competent authorities should maintain IT mutual recognition databases (CTS and MR Product Index) and ensure that their information is updated regularly throughout the procedure.

Submission and validation

One week before the intended submission date, the MAH should contact the RMS to obtain the renewal procedure number in accordance with the relevant guidance documents (see Annex 3). The MAH should then send the application simultaneously to the RMS and all CMS, with the procedure number stated in the application form. The RMS creates the renewal procedure in the CTS Client.

When dispatch is completed, the MAH should notify the RMS of the dispatch dates, together with a statement confirming that the relevant national fees have been paid, where relevant. This information has to be sent in a single document. Once the RMS is informed that the application has been submitted to all CMS, the RMS will start the

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automatic validation period (14 days) by sending an e-mail to all CMS and to the applicant in accordance with the relevant guidance documents (see Annex 3).

The CMDv has agreed to follow automatic validation procedure for MRP applications as defined in CMDv/BPG/008. All MS involved in the procedure should validate the application within 14 calendar days. CMS have the duty to update the status of CTS continuously to reflect the current validation status.

Start of the procedure (by Day 0)

At the end of the automatic validation period if no notification of an invalid application has been received, the RMS starts the renewal procedure by notifying the MAH (by e-mail) and the CMS (by CTS Client and email) of the procedure start date (day 0) and timetable.

RMS assessment by Day 40

The RMS has to ensure that the PRAR is released to the CMS and MAH by the agreed date. The MAH should understand that at this stage of the procedure, the PRAR is for information and transparency purposes only.

In the PRAR, the RMS will recommend approval or refusal of the renewal. The RMS clearly indicates whether it endorses the SPC/labelling/package leaflet changes proposed by the MAH. Moreover, the RMS should propose SPC/labelling/package leaflet changes, if appropriate. In the PRAR, the RMS must clearly indicate all issues arising from the assessment (if any) to be addressed by the Applicant

CMS comments by Day 55

The CMS should clearly express their opinion (approval or non- approval) about the PRAR and the SPC/labelling/package leaflet proposed by the RMS. Comments should be sent to the RMS by the agreed date. If a CMS does not send any comment, the RMS will consider this as agreement with the RMS proposal.

In the event that no issues have been identified by the RMS in the PRAR and no issues have been raised by any of the CMS at Day 55, the RMS should prepare and circulate the FRAR and complete the procedure in accordance with provisions of Day 90 by Day 60 already.

Request for supplementary information by Day 59 and clock-off period

If the RMS or any of the CMS do not approve the data submitted with the renewal application, the RMS will send a request for supplementary information (RSI) (to include both RMS and CMS outstanding issues) to the MAH. A copy of the request should be sent to all CMS.. A 30-day clock-off period is started, which may be extended only in exceptional circumstances and with the RMS' agreement.

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Clock re-start by Day 60

After receiving the supplementary information from the MAH the RMS evaluates the response and may discuss any issues with the CMS who raised objections. The RMS prepares the Final Renewal Assessment Report (FRAR) within 60 days after receiving the response to the RSI. The clock re-starts on day 60 when the FRAR, including the evaluated RSI and the revised SPC/labelling/package leaflet documents is circulated to all CMS for comments, and to the MAH for information.

CMS comments by Day 80

CMS should advise the RMS and MAH whether they accept the FRAR or not, by the agreed date. The RMS may discuss any issues with the CMS who still have objections.

4.5 Outcome of the renewal procedure

Day 90

On day 90 the RMS circulates a notification indicating the final conclusion of the RMS and the outcome of the procedure together with the harmonised revised final SPC/labelling/package leaflet to MAH and CMS.

If all CMS agree to renew the MA for the product, MS concerned will proceed nationally the renewal of the MA.

The RMS will remind the MAH that the national translations of the complete revised English SPC, as agreed in the renewal procedure, and correspondingly updated and agreed labelling and package leaflet which is additionally in accordance with national provisions should be provided. These should be received by CMS within 10 working days after completion of the renewal procedure.

Once renewed, the authorisation will be valid for an unlimited period. Where an additional renewal of the product concerned based on pharmacovigilance grounds is considered necessary by the RMS/CMS, the renewed authorisation will expire at the end-of the 5-year period from the previous common renewal date.

Non-Renewal on Day 90

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 the Directive 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 EMEA/CMDv/115373/2006

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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 MAH 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 the Directive. The formal referral to arbitration should be made by those CMS, which are against the opinion of the RMS. (In cases where the RMS alone is against renewal, the RMS will refer the issue to arbitration).

If the draft decision of the RMS 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 MAH fails to respond to issues raised during assessment, non-renewal of the marketing authorisation will result.

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ANNEX 1

RENEWAL TIMETABLE

-7 days prior to submission CMS	to MAH to send notification to RMS, to RMS to assign of procedure number
submission CMS	to 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) (30 days for the applicant to provide the responses, and 60 days for the RMS to prepare the FRAR)
Day 60	RMS to circulate Final Renewal Assessment Report (FRAR) with draft decision to CMS and MAH
Day 80	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.

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ANNEX 2

LIST OF DOCUMENTS TO SUBMIT

Together with a cover letter and a comprehensive table of content the MAH submits a renewal application to RMS and CMS 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 all post authorisation submissions (variations, extensions etc), Follow-up measures and Specific Obligations submitted since grant of marketing authorisation or last renewal indicating scope, status, date of submission, date when issue has been resolved and procedure number when applicable.
- 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.

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- 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 in compliance with the detailed guidelines on good manufacturing practice for starting materials.
6. Declaration of the current TSE status

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ANNEX 3

LIST OF RELATED DOCUMENTS

Directive 2001/82/EC

CMDv/GUI/003	Guidance for Management of e-mail use during procedures and standardisations of subheadings
CMDv/GUI/015	CMDv Guidance for CTS Minimum data input
CMDv/ROP/001	CMDv Rules of Procedure
CMDv/BPG/003	BPG for Repeat use procedures
CMDv/SOP/001	CMDv SOP: Disagreement in procedures – referral to CMDv
CMDv/TEM/006	CMDv Annotated QRD template for MRP and DCP (English and translations)
CMDv/BPG/008	BPG for Automatic Validation of Applications in the Mutual Recognition / Decentralised Procedures
CMDv/SOP/003	CMDv SOP for the allocation of the Mutual Recognition/Decentralised Procedure Application Number
	Guideline on the specifications for veterinary e-submissions

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ANNEX 4

LIST OF ABBREVIATIONS

DCP	Decentralised Procedure
MA	Marketing Authorisation
MS	Member State(s)
MAH	Marketing Authorisation Holder
MRP	Mutual Recognition Procedure
BPG	Best Practice Guide
RMS	Reference Member State(s)
CMS	Concerned Member State(s)
CMDv	Co-ordination Group for Mutual Recognition and Decentralised Procedures - veterinary
CTS	Communication Tracking System
SPC	Summary of Product Characteristics
NtA	Notice to Applicants
PRAR	Preliminary Assessment Report
FRAR	Assessment Report
RSI	Request for Supplementary Information
PSUR	Periodic Safety Update Report
CVMP	Committee for Veterinary Medicinal Products