

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

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1. INTRODUCTION

This paper considers issues associated with the processing of renewals in the mutual recognition and decentralised procedures, with an aim of giving procedural advice to assist member states and applicants, in order to ensure a consistent and beneficial approach to renewal.

2. LEGAL FRAMEWORK

In accordance with Article 24 of Directive 2001/83/EC, as amended, a marketing authorisation may be renewed after 5 years on the basis of a re-evaluation of the risk:benefit balance by the competent authority of the authorising member state. Once renewed, the marketing authorisation shall be valid for an unlimited period unless the competent authority decides, on justified grounds relating to pharmacovigilance, to proceed with one additional five-year renewal. The marketing authorisation holder shall provide the competent authority with a consolidated version of the file in respect of quality, safety and efficacy including all variations introduced since the marketing authorisation was granted at least 6 months before expiry of the marketing authorisation.

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. Further details of permitted changes are given in Section 3.6 Assessment Process. However, none of the SPC changes introduced at renewal should substitute for the marketing authorisation holder obligation to update the marketing authorisation throughout the life of the product by variation procedure as data emerge.

3. PRINCIPLES OF SUBMISSION AND EVALUATION

3.1. Date for renewal

For the mutual recognition procedure a common renewal date should be agreed by the member states and the applicant. 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 product, 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** (in practice this should be within 30 days of Day 90).

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 example, an optional procedure to synchronise renewal dates between member states or for all presentations of the same product is detailed in Section 3.2. In practice this may mean the period between authorisation and renewal will be less than 5 years in concerned member states.

An option is to fix the renewal date on Day 90 of the mutual recognition procedure for medicinal products approved through the mutual recognition process, and apply for early renewal of the reference Member State product using the optional procedure. For those products already licensed nationally via a harmonising procedure, agreement should be sought on a common renewal date. For repeat mutual recognition procedures, so called 'repeat use' procedures, the renewal timetable should follow that of the first procedure.

For products authorised through the decentralised procedure the common renewal date should be agreed on completion of the procedure (in practice within 30 days of end of 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 medicinal products containing the same active substances may be proposed by the Marketing Authorisations Holders or the competent authorities.

3.2 Optional procedure for earlier renewal

For medicinal products, which have benefited from mutual recognition, there are advantages in having a common renewal date in all concerned Member States for the one 5-year renewal. Therefore, the following procedure has been set out. **It must be stressed that this is an optional procedure, to be followed on a voluntary basis by the marketing authorisation holder and Member States**

- a. At the end of the 90 day European phase in the mutual recognition procedure, the basis for a mutually recognised product will have been agreed and concerned Member States will grant a marketing authorisation for a period of 5 years. The marketing authorisation in the concerned Member States will therefore have the same renewal date.
- b. The mutually recognised product in the reference Member State may be renewed immediately afterwards, ahead of the usual 5 year renewal date on the basis of the agreed SPC and any minor changes arising from mutual recognition discussions. **This change of renewal date would be a voluntary request by the marketing authorisation holder to the reference Member State.**
- c. A PSUR will not normally be required at this time.
- d. In the event of a repeat use of the mutual recognition procedure, that is when the mutual recognition procedure is used more than once for subsequent applications to other Member States in relation to the same medicinal product, the marketing authorisation holder could apply for a renewal earlier than the 5 years, in order to get the renewal dates synchronised with the date in the reference Member State.

3.3 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.

3.4 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 companies 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 to allow for the applicant to provide the responses required. In exceptional circumstances only, and with agreement of the reference Member State, the clock-off period may be extended. A timetable is given at Annex 1.

The reference Member State takes the lead in the procedure and circulates the timetable (see Annex 1)

3.5 Documents to submit

A consolidated version of the file is requested consisting of the documents listed in Annex 2. Renewal applications should be submitted using the EU-CTD format. It is recommended that MA holders take the opportunity to reformat the quality part of the dossier (Module 3) into CTD-format and, although it will not be obligatory until 2009, provide this in electronic format (please refer to NTA CTD Questions and Answers no 2).

The European renewal application form should be completed. The form is available in the Notice to Applicants (Volume 2C) at <http://pharmacos.eudra.org/eudralex/vol-2/home.htm#2c>. The marketing authorisation holder normally should submit one renewal application form for each marketing authorisation. If a revised SPC, labelling and/or package leaflet (PL) is proposed to take account of issues raised by the expert, the precise present and proposed wording should be specified on the form. Alternatively such listing may be provided as a separate document attached to the application form under a tabular format (indicating the current and proposed texts). Any changes not listed will not be considered as part of the renewal application.

In general, proposed amendments to the SPC should be discussed and agreed with the reference Member State in advance of submission. 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 CHMP quality guidelines.

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.

Periodic Safety Update Reports (PSURs): 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.

The PSUR should be submitted within 60 days of the last data lock point (DLP). Marketing authorisation holders should lock their data no more than 60 days before submitting the application for renewal.

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 to cover the period since grant of the MA or last renewal.

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. As the PSUR addendum Report does not provide an in depth-analysis of the additional cases, the MAH is requested to include such analysis within the clinical overview. The MAH should also include the cases reported in the addendum report again in the next PSUR. Where the additional period is less than 3 months for a 6 month or annual PSUR, or 6 months for a longer duration PSUR, line-listings and/or summary tabulations may be submitted to cover the additional period together with a comment on whether the data reveal a new or important risk.

Where the MAH submits two or more PSURs (e.g. multiples of 6 months PSURs, multiples of 1 year PSURs) to cover the relevant period a Summary Bridging Report, providing a brief summary 'bridging' the multiple PSURs, is required.

Therefore at renewal the MAH should submit the PSUR or the PSUR and/or an addendum report or line listings and/or summary tabulations covering the period since the data lock point of the last PSUR. The safety data of the PSUR and or addendum report together with any PSURs previously submitted should cover a period of 4 years and 4 months since grant of the marketing authorisation or last renewal. In addition, a PSUR Summary Bridging Report covering all the PSURs (even those already submitted) should be submitted with the renewal application. It is accepted that previously submitted PSURs are not re-submitted provided that a listing of the original submission dates is appended to the Summary Bridging Report and these are available on request by the national competent authority.

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

Clinical Expert Statement: The applicant submits an expert statement to accompany the renewal application which addresses the current risk/benefit for the product on the basis of the consolidated version of safety/efficacy data accumulated since the granting of the initial MA or the last renewal, the PSUR data and makes 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 risk/benefit consideration made with the original authorisation or last renewal.

It is recognised that the PSUR required to be included in the renewal submission should already contain a summary addressing a risk/benefit evaluation conforming to ICH guideline E2C. This summary could be considered as an addendum to the clinical expert statement.

The expert statement must be signed and accompanied by a CV of the expert. The clinical expert should be medically qualified and may, but not necessarily, be the same qualified person responsible for pharmacovigilance.

In any event, a clear statement is required from the clinical expert that the product can be safely renewed at the end of the 5 year period for an unlimited period or any action recommended or initiated, for example, recommendation for further review in 5 years time 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 updated risk/benefit evaluation has been addressed adequately, taking account of the consolidated version of the file and all relevant new information, either by endorsement of the statement within the PSUR or by appropriate supplementation within the expert statement.

The clinical expert should also confirm that no new (pre-clinical or clinical) data are available which changes or results in a new benefit-risk evaluation. Where there are new pre-clinical data the MAH may submit a non-clinical expert report as appropriate.

Where a single PSUR has been submitted covering several pharmaceutical forms and strengths for a given active substance, provided the renewal date across a product range has been synchronised, it will be acceptable to submit a combined clinical expert statement covering several marketing authorisations. The marketing authorisations should have a common renewal date and the renewal submissions including the combined expert statement will be made at the same time.

Quality Expert Statement: There is no updating of Part II/Module 3 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 23 of Directive 2001/83/EC, as amended, 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 CHMP quality guidelines where relevant. 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 expert statement must be signed and accompanied by a CV of the expert.

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. This reflects the principles of the Type I variation dossier requirement guideline. A copy of an updated statement of compliance with Good Manufacturing Practice from the competent authority, which is not older than 3 years, 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. In addition, such declaration should also be provided for Manufacturing Authorisation Holders, 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.

3.6 Assessment process

The assessment approach of the member states will focus on new information affecting the risk/benefit of the product, and the PSUR data. Potential serious risk to public health concerns should be addressed as part of the renewal process and the product will not be renewed if potential serious public health issues remain at the end of the procedure.

Changes to the product information: The MAH should update the SPC, patient leaflet and label as necessary throughout the life of the product.

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 PL arising from the PSUR evaluation or other information, the marketing authorisation holder may submit an amended SPC as part of the renewal process to address the concerns raised. This will not initiate a separate variation procedure.

Other issues arising from assessment and changes due to the revision of the SPC guideline or other guidelines that lead to a change in the SPC, labelling and PL may be considered within the renewal process as deemed appropriate by the reference Member State. Proposed changes to the SPC will be indicated on the renewal application form. These agreed changes should not trigger a separate variation procedure.

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 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 to delay issue 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, these will be processed through a separate Type II variation procedure.

Updated and harmonised leaflets and labels must be agreed at renewal if national versions still exist.

3.7 Authorisation documents

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

3.8 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 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. Indeed the MAH can be asked to perform a benefit-risk evaluation at any time.

3.9 Non-renewal

Members States will not renew the marketing authorisation if there are serious public health issues remaining at the time of renewal. The criteria specified in Article 116 of Directive 2001/83/EC, as amended, regarding the suspension, withdrawal or revocation of authorisation to market 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 the risk-benefit balance is not positive under the normal conditions of use, or where its qualitative and quantitative composition is not as declared. Therapeutic efficacy is lacking when it is established that therapeutic results can not 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 for Mutual Recognition and Decentralised – human, CMD(h) where member states have divergent opinions.

In cases where there is a divergent view amongst Member States at the end of the 90 day renewal procedure, by analogy with Articles 28-29 of Directive 2001/83/EC, as amended, there will follow a 60 day referral process to CMDh. If by new Day 60 the CMDh has not achieved a common position, a scientific evaluation of the matter would be undertaken by the CHMP. In the case of no agreement in the renewal procedure the formal referral to arbitration should be made by either the RMS or CMS who cannot approve the renewal. (In cases where the reference Member State is against renewal supported by some CMS only, 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 concerned Member States, then non-renewal action will be taken without a referral to CHMP.

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

RENEWAL TIMETABLE

Day 0	Start of procedure
Day 40	RMS to circulate preliminary assessment report to CMS
Day 55	Receive comments from CMS
Day 59	RMS to send request for supplementary information to marketing authorisation holder (if necessary)
	Clock-off up to 30 days (opportunity to prolong in exceptional circumstances only with agreement of RMS)
Day 60	RMS to circulate finalised assessment report with draft decision
Day 85	CMS to advise acceptance/non-acceptance of decision
Day 90*	Issue renewal or refer to Co-ordination Group, CMD(h) for 60 day referral procedure
Within 30 days start referral, Day 0	
New Day 0 – 60	Follow procedure in CMDh SOP Disagreement in Procedures – Referral to CMDh http://www.hma.eu/uploads/media/CMD_ref_SOP.pdf
New Day 60*	Issue renewal or refer to CHMP

* Allow 30 days for NCA to receive and approve updated PL, SPC and translations, and issue approval.

Starting the procedure

There should be an automatic validation process for starting the procedure. The reference Member States will start the procedure on the basis of an assurance from the marketing authorisation holder that renewal applications have been submitted to all concerned Member States and that the relevant national fee has been paid where appropriate, i.e. there is no requirement for acknowledgement of receipt from concerned Member States.

(The applicant should fax or e-mail a single document to the reference Member States and concerned Member States all the despatch dates of the renewal application when despatch is complete, and state that the relevant national fees have been paid.)

DOCUMENTS TO SUBMIT

Renewal applications have to contain a consolidated version of the file, containing at least the documents listed below. They should be presented as follows, preferably in a tab-separated dossier and in accordance with the appropriate headings and numbering of the EU-CTD format:

- Module 1:**
- 1.0** Cover letter
 - 1.1** Comprehensive table of content
 - 1.2** Renewal Application form with the following annexes:
 - List of all authorised product presentations for which renewal is sought in tabular form
 - Details of contact persons:
 - Qualified person for pharmacovigilance
 - Contact person with the overall responsibility for product defects and recalls
 - Contact person for scientific service in charge of information about the medicinal product
 - List of EU Member states/Norway/Iceland where the product is on the market and indicating for each country which presentations are marketed and the launch date
 - Chronological list of all post-authorisation submissions since grant of the Marketing Authorisation or last renewal: a list of all approved or pending Type IA/IB and Type II variations, Extensions, Art 61(3) Notifications, USR, giving the procedure number (where applicable), date of submission, date of approval (if approved) and brief description of the change.
 - Chronological list of follow-up measures/post-authorisation commitments
 - 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. 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 46(f) of Directive 2001/83/EC manufacturing authorisation holders (i.e. located in the EEA) 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)¹ referred to in the application form operate in compliance with the detailed guidelines on good manufacturing practice for starting materials².

1.3. Product Information:

Summary of Product Characteristics, Labelling and Package Leaflet

A relevant example of the proposed texts for SPC, outer and inner labelling and Package Leaflet in English has to be provided in paper (highlighted).

1.4 Information about the Expert

In cases where MAHs wish to distinguish these declarations from any previous declarations, the renewal procedure number may be included on top.

1.4.1 Information about the Expert – Quality (incl. Signature + CV)

1.4.3 Information about the Expert – Clinical (incl. Signature + CV)

Module 2: 2.3

Quality Overview

(Quality Expert Statement)

The Quality Expert Statement should include a declaration of compliance with Directive 2001/83/EC which obliges the MAH "...to take account of technical and scientific progress and introduce any changes...".

The Quality Expert Statement should also include:

- Confirmation that all changes relating to the quality of the product have been made following applications for variations and that the product conforms to current CHMP Quality guidelines.
- Confirmation of currently authorised specifications for the active substance and the finished product (with date of latest approval and procedure number)
- Qualitative and quantitative composition in terms of the active substance(s) and the excipient(s)(with date of latest approval and procedure number)

¹ According to Article 46a (1) of Directive 2001/83 and Article 50a (1) of Directive 2001/82, manufacture includes complete or partial manufacture, import, dividing up, packaging or presentation prior to its incorporation into a medicinal product, including re-packaging or re-labelling as carried out by a distributor.

² Starting materials manufactured from blood or blood components are excluded from this requirement.

2.5 **Clinical Overview**

(Clinical Expert Statement)

The Clinical Expert Statement should address the current benefit/risk for the product on the basis of the PSUR data and safety/efficacy data accumulated since the granting of the MAA or the last renewal, making reference to relevant new information in the public domain.

The Clinical Expert Statement should:

- Confirm that no new (pre-clinical or clinical) data are available which changes or results in a new benefit-risk evaluation. Where there are new pre-clinical data the MAH may submit a non-clinical expert report as appropriate.
- Confirm 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.
- Confirm that the authorities have been kept informed of any additional data significant for the assessment of the benefit/risk ratio of the product concerned.

Module 5: 5.3.6 Reports of Post-marketing experience

Required Periodic Safety Update Report. The required PSUR and /or PSUR addendum report and/or line listings and/or summary tabulations (i.e. a PSUR and/or PSUR addendum covering the period from the last data lock point of the previous PSUR until a data lock point which is within 60 days of the renewal submission date). The PSUR data together with any PSURs previously submitted should cover a period of 4 years and 4 months since grant of the marketing authorisation or last renewal. A summary bridging report if applicable.