

CMDh BEST PRACTICE GUIDE ON THE PROCESSING OF RENEWALS IN THE MUTUAL RECOGNITION AND DECENTRALISED PROCEDURES

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1. INTRODUCTION

This Best Practice Guide is intended to facilitate 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.

This Best Practice Guide (BPG) does not apply to simplified registrations for medicinal products referred to in Articles 14 (homeopathic medicines) and 16a (traditional herbal medicines) of Directive 2001/83/EC. Traditional herbal medicines that have been mutually recognised will be covered by this BPG however; the clinical overview addendum may be abbreviated (see below).

For renewal applications submitted from 1st January 2015, CMDh will be piloting a new streamlined procedure:

- Certain elements of the clinical overview addendum can be omitted for products authorised under Articles 10(1) and 10a of Directive 2001/83/EC and for traditional herbal medicines registered in more than one MS under Article 16a and mutually recognised, unless there is an obligation to submit PSURs for the product as laid down in a condition to the Marketing Authorisation or it is indicated in the list of European Union Reference Dates (EURD) that PSURs are required for products authorised or registered under these articles and containing the substance or combination of substances concerned,

2. LEGAL FRAMEWORK

In accordance with Article 24 of Directive 2001/83/EC, a marketing authorisation (MA) is valid for 5 years and may be renewed on the basis of a re-evaluation of the benefit/risk balance by the competent authority of the authorising Member State. Once renewed, the MA shall be valid for an unlimited period unless the competent authority decides, on justified grounds relating to pharmacovigilance, including exposure of an insufficient number of patients to the medicinal product, to proceed with one additional five-year renewal. The marketing authorisation holder (MAH) shall provide the competent authority with a consolidated version of the file in respect of quality, safety and efficacy including an evaluation of data contained in suspected adverse reaction reports, Periodic Safety Update Report (PSUR) data (if applicable) and any relevant new information affecting the benefit/risk of the product together with a list of all variations introduced since the MA was granted. The application for renewal should be provided at least 9 months before expiry of the MA.

In cases where the MAH does not submit a renewal application, the MA will lapse.

With the approval of the reference Member State (RMS) and concerned Member States (CMS), certain changes to the MA particulars may be made at renewal, and these changes shall not trigger a

variation procedure. Further details of permitted changes are given in Section 3.9 - Assessment Process. However, none of the SmPC changes introduced at renewal should substitute for the MAH obligation to update the MA throughout the life of the product by variation procedure as data emerge. The MAH has an obligation to ensure that the product information is kept up to date with current scientific knowledge including the conclusions of assessments and recommendations made publicly available by means of the European medicines web-portal.

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 product, the International Birth Date and/or the European Birth Date. The common renewal date is set by the RMS at the completion of the initial mutual recognition procedure based on the date that the national MA was originally granted (The MAH may comment on the proposal within 30 days of Day 90).

The principle applies that the MAH 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 MAH agrees an alternative date with the RMS. 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 the CMS.

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 RMS 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 (see also Section 3.3).

For products authorised through the decentralised procedure the common renewal date should be proposed by the RMS and agreed on completion of the procedure (the MAH may comment on the proposal within 30 days of end of procedure).

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 CMS 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 MAH 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 MA for a period of 5 years. The MA in the concerned Member States will therefore have the same renewal date.

- b. The mutually recognised product in the RMS may be renewed immediately afterwards, ahead of the usual 5 year renewal date on the basis of the agreed SmPC and any minor changes arising from mutual recognition discussions. **This change of renewal date would be a voluntary request by the MAH to the RMS.**
- c. 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 MAH could apply for a renewal earlier than the 5 years, in order to synchronise the renewal date with the date in the RMS.

3.3 Mutual Recognition Procedures where unlimited validity has already been agreed in the RMS (Including Repeat Use Procedures)

In some cases the first MR procedure or initial granting of the MA may have been concluded more than 5 years before the MR procedure or Repeat Use Procedure (RUP) and the authorisation may have been granted unlimited validity in the RMS and, in the case of RUP, the ‘old’ CMS. In order to comply with Article 24(1) of Directive 2001/83/EC, which states that an MA shall be valid for 5 years, any new authorisations granted as a result of mutual recognition will be subject to a renewal procedure. For legislative reasons the default is that a renewal will be required; however some MS may accept the previously granted unlimited validity in the RMS and not require a renewal and should confirm this to the RMS before the end of the procedure. The RMS will confirm whether an additional renewal is required or not in the end of procedure letter.

For RUPs finalised within five years of the granting of the initial MA, where unlimited validity has not been granted, the date of renewal should follow that of the first procedure i.e. the common renewal date will apply.

Where a further renewal is required and unlimited validity has already been agreed in some MS, an administrative renewal with reduced documentation is possible when agreed upon by the Member States concerned (see section 3.12)

It is preferable that the application for renewal with reduced documentation is submitted within a year of finalisation of the MRP or RUP so that the approval of the renewal can be based on the outcome of the MRP or RUP, particularly with respect to the product information.

3.4 Following informed consent and duplicate applications

For MAs granted following an informed consent or duplicate application, the CMDh may agree to an administrative renewal application with reduced documentation in accordance with Section 3.12 provided that all the following are fulfilled:

- The MA for the medicinal product to which the informed consent/duplicate application makes reference to (the ‘mother licence’) has already been granted unlimited validity in the RMS
- The MAH for the informed consent/duplicate is the same as the MAH of the ‘mother licence’, or belongs to the same group of companies
- The CMSs for the informed consent/duplicate authorisation have also been authorised for ‘mother licence’ that has been granted unlimited validity
- Confirmation is provided that the informed consent/duplicate authorisation and the ‘mother licence’ have been updated in parallel.

3.5 Extension Applications

When a medicinal product has been granted an initial MA, any extension shall be considered as belonging to the same global marketing authorisation, in particular for the purpose of the rules on data protection and market exclusivity.

As an extension application may result in a new MA which has to be renewed after 5 years or may be included in an already existing MA for which no further renewal is necessary, MS concerned by the extension application should clearly state before the end of the procedure if they do not require a renewal. Since most Member States issue a separate MA for a medicinal product authorised via an extension application, this means that a renewal will be required by default. In case not all Member States concerned by the procedure have clearly indicated that there is no need for a renewal, a five-year renewal will be required, independent of how the MA has been issued nationally for the extension application.

This renewal will not cover other parts of the Global Marketing Authorisation for which an unlimited renewal has been already issued, but will be restricted to the content of the former application for the extension application (e.g. new strength, new pharmaceutical form). The renewal will have to follow the MR renewal procedure.

3.6 Following Article 30 and 31(1) Referral Procedures

Following an Article 30 or 31(1) referral procedure the allocated RMS should, taking into consideration the agreed harmonised birth date, agree a common renewal date with the MAH. This date should wherever possible be defined as the earliest renewal date in a Member State that allows for submission within 6 months after implementation of the decision from the Commission.

If in all the MS no further renewal is considered necessary, due to previous granting of unlimited validity, the common renewal date may be taken as the date of the Commission Decision.

If unlimited validity of the MA has not been agreed in all the MS, an administrative renewal with reduced documentation is possible when agreed upon by the Member States concerned (see section 3.12)

It should be noted that the application for renewal with reduced documentation should be submitted immediately after finalisation of the Article 30 or 31(1) referral procedure so that the approval of the renewal should be based on the outcome of the referral.

3.7 Date for submission

The applicant submits the renewal application simultaneously to all concerned Member States. The renewal should be submitted no later than **9 months before the MA expiry date**.

3.8 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 RMS, the clock-off period may be extended. A timetable is given at Annex 1. If a deviation from the regular timetable is made during the procedure,

this should be communicated by e-mail to alert the CMS.
The RMS takes the lead in the procedure and circulates the timetable (see Annex 1)

3.9 Documents to submit

A consolidated version of the file is requested consisting of the documents listed in Annex 2.

3.9.1 Administrative Information

The European renewal application form should be completed. The form is available in the Notice to Applicants (Volume 2C) at http://ec.europa.eu/health/documents/eudralex/vol-2/index_en.htm

The MA holder normally should submit one renewal application form for each MA. If a revised SmPC, 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 a 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 SmPC should be discussed and agreed with the RMS 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 MAH is responsible for ensuring that the dossier is kept up to date throughout the life of the product by way of the variation process.

3.9.2 Risk Management Plan (RMP)

For medicines that have a RMP the MAH will be required to submit an update of the RMP with the renewal application in view of reassessing the overall benefit/risk balance of the medicinal product concerned. In case the MAH considers that there is no need to change the latest RMP, on the basis of analysis of additional data, given the last RMP updates submitted, a relevant justification can be provided. Nevertheless, during the assessment it may be considered that an update of the RMP is necessary and this can be requested by the RMS.

The format and content of the RMP should follow the requirements set out in *Commission Implementing Regulation on the performance of pharmacovigilance activities provided for in regulation (EC) No 726/2004 and Directive 2001/83/EC of the European Parliament and of the Council* and for which guidance is provided in Module V of the Guidelines on Good pharmacovigilance practices.

Where the product does not have an RMP the MAH should indicate this in Module 1.8.2

3.9.3 Addendum to the Clinical Overview /Quality Overall Summary/Non-clinical Overview

Addendum to the Clinical Overview:

The applicant submits an addendum to the clinical overview. This addendum should consist of a critical discussion addressing the current benefit/risk balance 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, taking account of PSUR data (if applicable), suspected adverse reaction reports, additional pharmacovigilance activities and the effectiveness of risk minimisation measures contained in the RMP. In addition, it should make 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 benefit/risk evaluation made at the time of the original authorisation or last renewal.

The information shall include both positive and negative results of clinical trials and other studies in all indications and populations, whether or not included in the marketing authorisation, as well as data on the use of the medicinal product where such use is outside the terms of the MA.

The addendum to the clinical overview should contain the information indicated in Annex 3. Some information can be omitted from the addendum to the clinical overview for products authorised under Articles 10(1) and 10a and registered under Article 16a, unless there is an obligation to submit PSURs for the product as laid down in a condition to the MA or it is indicated in the list of European Union Reference Dates (EURD) that PSURs are required for products authorised or registered under these articles and containing the substance or combination of substances concerned. It should be noted that where PSURs are not required to be submitted, the MAH is still obliged to monitor the safety of the product, detect signals and evaluated these and if necessary submit updates through the appropriate regulatory procedure.

The addendum should be signed and accompanied by the CV of the expert. The clinical expert should have the necessary technical or professional qualifications and may, but not necessarily, be the same qualified person responsible for pharmacovigilance.

In any event, a clear conclusive 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 expert should ensure that the updated benefit/ risk evaluation has been addressed adequately, taking account of the consolidated version of the file and all relevant new information.

The clinical expert should also confirm that no new (pre-clinical or clinical) data are available which change the benefit/risk or results in a new benefit/risk evaluation. Where there are new pre-clinical data, the MAH may submit an addendum to the non-clinical overview as appropriate.

In addition, the expert should confirm that the product information has been kept up to date with current scientific knowledge including the conclusions of assessments and recommendations made publicly available on the European medicines web-portal.

If some information has been omitted from the clinical overview, due to the product being authorised under article 10(1), 10a or 16a, a clinical expert statement will still be required confirming that the product can be safely renewed for an unlimited period.

The addendum to the clinical overview shall also include the history of pharmacovigilance system inspections conducted during the period covered by the renewal as well as analysis of the impact of the findings on the overall benefit/risk balance of the medicinal product.

Addendum to the Quality Overall Summary:

There is no updating of Module 3 quality data at renewal. The MA holder has an obligation to keep this updated on an on-going basis throughout the life of the product using variation procedures.

The Addendum should be signed and accompanied by the CV of the expert.

The Addendum should include a declaration of compliance with Article 23 of Directive 2001/83/EC, which obliges MA holders to "...take account of technical and scientific progress and introduce any changes..." The addendum should 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 where relevant. 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) should also be included.

The MAH 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. A certificate of compliance with Good Manufacturing Practice (GMP), which is not older than 3 years, 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, if available, will suffice.) In addition, for manufacturing sites of the medicinal product not located in the EEA or in the territory of an MRA partner, a list should be provided 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 declarations 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

Addendum to Non-Clinical Overview

An Addendum to the Non-clinical Overview is not systematically required as part of the renewal application. In cases where no new non-clinical data have been gathered since the initial MAA or last renewal, this may be stated in the addendum to the Clinical Overview.

Where a non-clinical overview Addendum is included it should consist of a critical discussion supporting the benefit/risk re-evaluation for the product taking into account any new non-clinical data accumulated since the initial MAA or the last renewal, or any relevant new information in the public domain. The non-clinical Addendum should be signed and accompanied by the CV of the non-clinical expert (Module 1.4.2).

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

3. 10 Assessment process

The assessment approach of the Member States will consist of a benefit/risk balance re-evaluation, on the basis of a consolidated version of the file and any relevant new information affecting the benefit/ risk for the product. Serious public health concerns should be addressed as part of the renewal process and the product will not be renewed if serious public health issues remain at the end of the procedure or if an existing suspension on the marketing authorisation cannot be lifted.

Inspection status, in particular as regards to the pharmacovigilance system as well as GMP compliance status of the manufacturer(s) will be reviewed during the assessment of the renewal application and potential impact of the findings on the benefit/risk balance of the medicinal product will be evaluated.

At time of renewal, the compliance of the MAH to fulfil any conditions imposed on the medicinal product will be reviewed. As a result, these conditions could be modified and/or new conditions could be imposed.

The MAH should update the SmPC, package leaflet and label as necessary throughout the life of the product.

In addition, it will be checked during the assessment whether the MAH has complied with obligations to keep the product information up to date in the light of current scientific knowledge taking into account conclusions of assessments and recommendations which are made public on the

EMA web-portal.

If the RMS finds that the MAH did not fulfil these obligations and major changes are required, the SmPC and PL should be updated through the appropriate variation procedure after conclusion of the renewal. The RMS may accept introduction of minor changes at renewal to avoid additional submissions. Parallel variation submissions under Category C.I impacting on product information should be managed and concluded before the start of the renewal procedure, wherever possible.

The Pharmacovigilance Risk Assessment Committee (PRAC) may be involved in the assessment of the renewal and advice may be sought in the following situations:

- If the product contains a substance listed as subject to additional monitoring
- If the application includes a new or updated RMP that requires PRAC agreement
- If the RMS has proposed a further 5-year renewal based on pharmacovigilance grounds

Advice may be sought from the PRAC on an informal basis where the assessment indicates that there may be a new safety signal. Where PRAC advice is needed it should be sought at the earliest opportunity and preferably around the time of circulation of the preliminary assessment report.

If the assessment has raised new significant safety issues, particularly if these affect a therapeutic class of medicinal products an Article 30 referral should be initiated.

Where there are adequate and objective reasons not to renew the MA in its existing terms and changes are necessary to the SmPC, labelling and PL arising from the evaluation or other information, the MAH may submit an amended SmPC 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 SmPC guideline or other guidelines that lead to a change in the SmPC, labelling and PL may be considered within the renewal process as deemed appropriate by the RMS. Proposed changes to the SmPC 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 and changes to the quality dossier such as an extension of shelf life, may not be changed through the renewal procedure and have to be assessed through the appropriate variation procedure.

None of the SmPC changes introduced at renewal should substitute for the MAH obligation to update the MA throughout the life of the product by the appropriate variation procedures as data emerge.

Accordingly, no new studies should be submitted within the renewal unless these impact on the benefit/risk of the medicinal product. However, any new data should be discussed in the Addendum to the relevant overview.

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 Post Authorisation Measures (PAMs).

The MA 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 SmPC, these will be processed through a separate variation procedure.

3.11 Outcome of Assessment

3.11.1 Unlimited Validity

If there is agreement at the end of the procedure that the benefit/risk of the product remains favourable and there are no pharmacovigilance issues that would require a further renewal, the MA may be granted unlimited validity.

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

3.11.2 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, increased PSUR frequency or benefit/risk review if needed. Indeed the MAH can be asked to perform a benefit/risk evaluation at any time. In cases where a further renewal is considered based on pharmacovigilance grounds PRAC advice may be sought.

3.11.3 Non-renewal

Member States will not renew the MA if there are serious public health issues remaining at the time of renewal. The criteria for non renewal are specified in Article 116 of Directive 2001/83/EC, as amended. 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 benefit/risk balance is not positive under the normal conditions of use, or where its qualitative and quantitative composition is not as declared. Therapeutic efficacy is considered to be 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 where any conditions of the marketing authorisation have not been fulfilled, 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 MA 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, CMDh 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 the new Day 60 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 the RMS.

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

3.12 Administrative Renewal Procedure

As stated above in sections 3.3 and 3.4 and 3.6, CMDh may in certain situations agree on an administrative renewal. The documentation requirements in these administrative renewals may be reduced for the consolidated file if agreed by all MS concerned. In such cases, the MAH should request the RMS to raise an item for discussion and agreement at CMDh that the documentation requirements can be reduced for the product in question. The minimum documentation requirements for the administrative renewal are given in Annex 3.

The application for an administrative renewal should be submitted only to the RMS and those MS that require the renewal. It should be noted that for an informed consent/duplicate all CMSs will be involved. The MAH should clearly state in the cover letter that the submission for the administrative renewal procedure has been agreed by the CMDh (including the date of the CMDh meeting where

the administrative renewal was agreed).

After receipt of the application, the RMS will create a case in CTS that includes all CMS, but will note in the annotation field for the “Application received” box in the “Pre-Procedure” tab that the renewal is administrative and which CMS are concerned. The RMS circulates a start e-mail to all CMS, indicating which CMS are concerned by the present administrative renewal. The RMS will also manually modify the timetable in CTS (in accordance with the expedited timetable for administrative renewals, see Annex 2).

CMS may comment on the application at the latest on day 20. Between day 20 and day 30, the RMS will be able to liaise with the MAH to reach an agreement on any necessary amendments to the application or need for future updates to the product information. The RMS will close the procedure at day 30 with circulation of the End of Procedure letter for renewals to the concerned CMS (clearly stating if any updates to the product information are required through a subsequent variation procedure). No assessment report will be circulated, since no new evaluation of the benefit/risk balance is made.

ANNEX 1

RENEWAL TIMETABLE

Day 0	Start of procedure. The CMS are informed via CTS, there will be no additional mail
Day 40	RMS to circulate preliminary assessment report to CMS The preliminary report may also be circulated to PRAC members if appropriate (see section 3.9)
Day 55	Receive comments from CMS (and PRAC members if appropriate)
Day 59	RMS to send request for supplementary information to MA holder and CMS via e-mail (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 80	CMS to advise acceptance/non-acceptance of decision
Day 90*	Issue renewal or refer to Co-ordination Group, CMDh for 60 day referral procedure End of the procedure. If the MAH had proposed changes to the SmPC, labelling and package leaflet and/or additional changes had been agreed during the procedure; the RMS checks the highlighted track-change versions, provided by the MAH in electronic format. The RMS circulates the clean and track-change versions with a statement that it has endorsed the changes made to the MAH and CMSs. It is recommended to upload the clean documents to CTS for transfer to the MRI Product Index. The MAH will provide the CMSs with the relevant amended translations of the SmPC, labelling and package leaflet within 5 days of the end of procedure.
Within 30 days start referral, Day 0	
New Day 0 – 60	Follow procedure in CMDh SOP Disagreement in Procedures – Referral to CMDh
New Day 60*	Issue renewal or refer to CHMP

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

Starting the procedure

There should be an automatic validation process for starting the procedure. The RMS will start the procedure on the basis of an assurance from the MAH that renewal applications have been submitted to all CMS and that the relevant national fee has been paid where appropriate, i.e. there is no requirement for acknowledgement of receipt from CMS. Positive validation should only be indicated in CTS, not via e-mail.

(The applicant should e-mail a single document to the RMS and CMS listing all the despatch dates of the renewal application when despatch is complete, and state that the relevant national fees have been paid.)

ANNEX 2

ADMINISTRATIVE RENEWAL PROCEDURE TIMETABLE

Day 0	Start of procedure. The CMS are informed via e-mail of the start of the procedure and advised which CMS are concerned by the administrative renewal.
Day 20	CMS to advise acceptance/non-acceptance of the application
Day 30	RMS to issue EoP letter

ANNEX 3

DOCUMENTS TO SUBMIT

Renewal applications have to contain a consolidated version of the file, containing at least the documents listed below. Further documentation should be available from the MAH on request if considered necessary to complete the benefit/risk assessment.

In certain cases (see sections 3.3, 3.4, 3.6 and 3.12 above) the consolidated file may be reduced to a cover letter from the MAH accompanied by an application form (without annexes) and a declaration that full documentation will be available for submission on request of a CMS. The cover letter should include confirmation that now new data are available that changes, or would result in a re-evaluation of, the benefit/risk balance and that the product information is up to date with current scientific knowledge (or otherwise a commitment to update the product information by the appropriate variation within 3-months of the finalisation of the renewal). In cases where the administrative renewal concerns a MA following an informed consent/duplicate, the MAH should also confirm in the cover letter that the dossier of the 'mother licence' and the dossier of the informed consent/duplicate are still identical.

The consolidated file should be presented as follows in accordance with the appropriate headings and numbering of the EU-CTD format:

- Module 1:**
- 1.0** Cover letter
 - 1.1** Comprehensive table of contents
 - 1.2** Renewal Application form with the following annexes:
 - List of all authorised product presentations for which renewal is sought, in tabular format
 - Details of contact persons:
 - Qualified person in the EEA for pharmacovigilance
 - Contact person in the EEA with the overall responsibility for product defects and recalls
 - Contact person for scientific service in the EEA 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 MA or last renewal: a list of all approved or pending Type IA & Type IA_{IN}, Type IB and Type II variations, Extensions, Art 61(3) Notifications, and PSURs giving the procedure number (where applicable), date of submission, date of approval (if approved) and brief description of the change
 - Chronological list of conditions/post-authorisation commitments submitted since the granting of the MA or the last renewal indicating scope, status, date of submission and date when issue resolved (where applicable)
 - A revised list of all remaining conditions (where applicable)
 - 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, if available, will suffice.

- 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 Union. 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.** Summary of Product Characteristics, Labelling and Package Leaflet
A relevant example of the proposed texts for SmPC, outer and inner labelling and Package Leaflet in English has to be provided with any proposed changes (highlighted).
- 1.4** Information about the Experts
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)
 - 1.4.2** Information about the Expert – Non-Clinical (incl. signature + CV) – if applicable
 - 1.4.3** Information about the Expert – Clinical (incl. Signature + CV)

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.

1.8.1 Summary of Pharmacovigilance System Master File – PSMF (if applicable)³

Proof that the MAH has at his disposal a qualified person responsible for pharmacovigilance and a statement signed by the MAH to the effect that the applicant has the necessary means to fulfil the tasks and responsibilities listed in Title IX of Directive 2001/83/EC.

Member State in which the QPPV resides and operates his/her tasks

Contact details of the QPPV

PSMF location (country)

1.8.2 Risk Management Plan

The updated RMP and where relevant, the new RMP.

Where there are no new data justifying changes to the latest approved RMP, the MAH should provide such a declaration and confirm that the current approved RMP remains unchanged and applicable.

If there is not an RMP for the product and this is not required this should be stated in this section

Module 2: 2.3 Addendum to the Quality Overall Summary

The Quality Expert 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 that may be required to enable the medicinal product to be manufactured and checked by means of generally accepted scientific methods.

The Addendum to the Quality Overall Summary 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)

³ According to transitional provisions set out in Article 3 of Regulation (EU) No 1235/2010, where the renewal is taking place before 2nd July 2015, the MAH has the obligation to maintain and make available on request a PSMF from the renewal onwards.

2.4 Addendum to the Non-clinical Overview

An Addendum to the Non-clinical Overview is not systematically required as part of the renewal application.

If no new non-clinical data have been gathered, this will be reflected in the addendum to the clinical overview

If an addendum to the non-clinical overview is provided this should include a critical discussion supporting the benefit/risk re-evaluation of the product taking into account any new non-clinical data accumulated since the initial MAA, or the last renewal, or any relevant new information in the public domain.

2.5 Addendum to the Clinical Overview

A critical discussion should be provided within the Addendum to the Clinical Overview addressing the current benefit/risk for the product on the basis of the PSUR data and safety/efficacy data accumulated since the granting of the MA (or the last renewal if applicable), making reference to relevant new information in the public domain.

The addendum to the Clinical Overview should contain the following information**:

- History of pharmacovigilance system inspections (date, inspecting authority, site inspected, type of inspection and if the inspection is product specific, the list of products concerned) and an analysis of the impact of the findings overall on the benefit/risk balance of the medicinal product.
- Worldwide marketing approval status: overview of number of countries where the product has been approved and marketed worldwide.
- Actions taken for safety reasons during the period covered since the initial marketing authorisation or since the last renewal (up to 90 days prior to renewal submission): description of significant actions related to safety that had a potential influence on the benefit/risk balance of the approved medicinal product (e.g. suspension, withdrawal, temporary halt or premature ending of clinical trial for safety reasons, issue requiring communication to healthcare professionals...).
- Significant changes to the SmPC (e.g. safety warnings, contraindication, restriction of indication...) during the period covered since the initial marketing authorisation or since the last renewal (up to 90 days prior to renewal submission), or has made changes to the reference safety information that has not yet been agreed for the registered SmPC. Meaningful differences between the reference safety information and the proposals for SmPC should be stated. A proposed SmPC, Package Leaflet and labelling should also be provided
- Estimated exposure: data on cumulative exposure of subjects in clinical trials as well as of patients from marketing exposure. If the marketing authorisation holder becomes aware of a pattern of use of the medicinal product considered relevant for the implementation of safety data, a

brief description should be provided; such patterns may include in particular off-label use.

- Data in summary tabulations: summary tabulations of serious adverse events from clinical trials as well as summary tabulations of adverse reactions from post-marketing data sources reported during the period covered since the initial marketing authorisation or since the last renewal (until 90 days prior to the renewal submission).
- Summaries of significant safety and efficacy findings from clinical trials and non-interventional studies: description of any significant safety findings that had an impact on the conduct of clinical trials or non-interventional studies. It should also address whether milestones from post-authorisation safety studies, post-authorisation efficacy studies, studies from the RMP pharmacovigilance plan and studies conducted as conditions and obligations of the marketing authorisation, have been reached in accordance with agreed timeframes.
- Literature: review of important literature references published during the period covered since the initial marketing authorisation or since the last renewal (up to 90 days prior to the renewal submission) that had a potential impact on the benefit/risk of the medicinal product.
- Risk evaluation: the MAH should summarise any information related to important safety issues, evaluation and characterisation of risks as well as effectiveness of risk minimisation measures for the period covered since the initial marketing authorisation or since the last renewal (up to 90 days prior to the renewal submission).
- Benefit evaluation: the MAH should summarise important efficacy and effectiveness information (including information on lack of efficacy) for the period covered since the initial marketing authorisation or since the last renewal (up to 90 days prior to the renewal submission).
- Benefit/risk balance: a discussion on the benefit/risk balance for the approved indication should be presented, based on the above information.
- Late breaking information: the MAH should summarise the potentially important safety, efficacy and effectiveness findings that arise after the data lock point but during the period of preparation of the addendum to the clinical overview.

* * Marketing authorisation holders are advised to consider the GVP Module VII on PSURs as guidance for the preparation of the above sections of the clinical overview. The above sections can be omitted from the clinical overview for products authorised under Articles 10(1) and 10a and registered under Article 16a and mutually recognised, unless there is an obligation to submit PSURs for the product as laid down in a condition to the Marketing Authorisation or it is indicated in the list of European Union Reference Dates (EURD) that PSURs are required for products authorised or registered under these articles and containing the substance or combination of substances concerned.

In any event a clinical expert statement will be required and the Clinical Expert should:

- Confirm that no new clinical (or pre-clinical data in the absence of a non-clinical overview) are available which changes or results in a new benefit/risk evaluation. Where there are new pre-clinical data the MAH should 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 balance of the product concerned.
- Confirm that the product information is up to date with current scientific knowledge including the conclusions of assessments and recommendations made publicly available on the European medicines web-portal.