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Guideline on the processing of renewals in the centralised procedure

~~Draft~~

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Guideline on the processing of renewals in the centralised procedure

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Processing of renewals in the centralised procedure

1. Introduction

This guideline considers issues associated with the processing of renewals in the centralised procedure, with an aim of giving procedural guidance to marketing authorisation holders (MAHs). It has been developed by the CHMP following consultation of the interested parties and the European Commission Services.

This guideline is not legally binding, and in case of doubt, reference should be made to the appropriate EU Directives and Regulations.

This document should be read in connection with the Notice to Applicants' documents.

Renewal of conditional marketing authorisations (i.e. only valid for one year) is not covered in this guideline. Guidance regarding renewal of such marketing authorisation is provided in a separate document[1]. Marketing authorisations approved under exceptional circumstances are covered by this guideline.

2. Legal Framework

In accordance with Article 14(1-3) of Regulation (EC) No. 726/2004, a marketing authorisation (MA) is valid for five years~~, , from the date of notification of the Commission Decision to the MAH,~~ except when a "conditional marketing authorisation"[2] has been granted. The 5-years period will be counted from the date of notification of the Commission Decision to the MAH. The marketing authorisation may be renewed upon application by the marketing authorisation holder at least nine months before its expiry. ~~The renewal assessment must be based on a general re-evaluation of the benefit/risk balance of the product.~~

In order for a marketing authorisation to remain valid, a renewal is required five years after the granting of the marketing authorisation (irrespective of whether the marketing authorisation is suspended). The renewal assessment must be based on a general re-evaluation of the benefit-risk balance of the product.

Once renewed, the marketing authorisation 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 concerned, to proceed with one additional five-year renewal.

In the case where a MAH does not submit the renewal application, the MA will expire by law.

Article 12(1) of Regulation (EC) No 726/2004, indicates that an authorisation shall notably be refused where the labelling and package leaflet do not comply with the requirements of Title V of Directive2001/83/EC.
Certain changes to the marketing authorisation particulars may be made at renewal, and these changes shall not trigger a variation procedure. Further details of such permitted changes are given in Section 3.3 and 3.4. However, none of the changes introduced at renewal should substitute for the marketing authorisation holder's obligation to update the marketing authorisation throughout the life of

[1] Guideline on the scientific application and the practical arrangements necessary to implement Commission Regulation (EC) No 507/2006 on the conditional marketing authorisation for medicinal products for human use falling within the scope of regulation (EC) No 726/2004 (EMEA/509951/2006).
[2] According to Article 14(7) of Regulation (EC) 726/2004, conditional marketing authorisations shall be valid for one year on a renewable basis.

the product by a variation ~~procedure~~ application as data emerge, in accordance with the relevant legal dispositions applicable to variations. ~~procedures.~~

~~Once renewed, the marketing authorisation 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 concerned, to proceed with one additional five-year renewal.~~

In any case, in accordance with Article 16(3) of Regulation (EC) No 726/2004, the marketing authorisation holder has an obligation to ensure that the product information is kept up to date with the current scientific knowledge including the conclusions of the assessment and the recommendations made public by means of the European medicines web-portal.[3]

It is to be noted that i~~I~~n accordance with Article 16(~~4~~3a) of Regulation (EC) No 726/2004, the EMA may request data at any time from the MAH to assess whether the benefit-risk balance remains favourable.

3. Principles of submission and evaluation

3.1. Date for renewal

In accordance with Article 14 (2) of Regulation (EC) No 726/2004, for the renewal application to be valid ~~under Article 14 of Regulation (EC) No 726/2004~~, marketing authorisation holders must apply at least nine months before the expiry date, i.e. the 5-year anniversary of the notification of the Commission Decision granting the marketing authorisation, irrespective of whether the marketing authorisation is suspended.

The marketing authorisation holder should agree in advance the submission date of the renewal application with the EMA who will liaise with the CHMP and PRAC Rapporteurs, ~~as appropriate~~ taking into account the recommended starting dates published on the EMA website[4] (see also section 3.2). ~~In order to facilitate the preparation of~~ When preparing the renewal application, the MAH is advised to refer to the European Medicines Agency post-authorisation procedural advice for users of the centralised procedure. For any additional question regarding the submission of the Renewal application, the MAH can contact the procedure manager at the EMA ~~at Renewalquery@ema.europa.eu~~ responsible for the product. Exceptionally, i~~I~~f considered necessary by the MAH and further to the confirmation~~consultation~~ with the EMA, a pre-renewal submission meeting can be organised ~~well~~ in advance in a date compatible ~~to~~with the renewal submission.

In the case where a MAH does not submit the renewal application, the MA will expire by law.

3.2. Timetable

The MAH should submit the renewal application by the recommended submission dates published on the EMA website[5] and, in any case, no later than 9 months before the MA ceases to be valid as per Article 14(2) of Regulation 726/2004.

[3] http://www.ema.europa.eu/ema/index.jsp?curl=/pages/home/Home_Page.jsp&jsenabled=true

[4] http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000330.jsp&mid=WC0b01ac05803d8b9c

[5] http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000330.jsp&murl=menus/regulations/regulations.jsp&mid=WC0b01ac05803d8b9c

The timetable for the scientific evaluation by the PRAC and the CHMP should be set in order to allow the Commission Decision to be adopted before the expiry date of the marketing authorisation. (See timetable in Annex 1).

Upon receipt of a technically valid application, ~~a dedicated~~the ~~p~~Procedure ~~M~~manager responsible for ~~will be assigned to the procedure~~the product will perform the validation of the content of the application. Supplementary information may be requested in order to finalise the validation.

The EMA will acknowledge receipt of a valid renewal application and shall start the procedure in accordance with the recommended starting dates published on the EMA website. The MAH will be informed of the adopted timetable at the start of the procedure.

The renewal procedure will involve the CHMP Rapporteur/ CAT Rapporteur as applicable, and the PRAC Rapporteur who have been appointed for that medicinal product and the respective committees.

3.3. Documents to submit

The renewal constitutes a crucial step in the lifecycle of a medicinal product, where a re-evaluation of the benefit-risk balance of the medicinal product takes place. The documentation presented hereafter should be submitted within the renewal application.

The list of documents to submit is given in Annex 2.

Practical details on the renewal application submission are given in the EMA Post-Authorisation ~~Guidance document~~ procedural advice for users of the centralised procedure published on the EMA website (Human Medicines – Application Procedures[6]).

3.3.1. Administrative information

The renewal application form should be completed electronically. The electronic EU renewal form is available from the eSubmission website[7]~~)~~.

The marketing authorisation holder should complete one renewal application form for the Centrally Authorised Medicinal Product (= 1 application per MA~~core~~ EU Number), appending a list of all authorised strengths, pharmaceutical forms and presentations of the product concerned for which renewal is sought. In cases where the MAH does not wish to renew certain presentations (e.g. ~~a~~ certain pharmaceutical form, strength or pack-size), this should be clearly indicated in the cover letter and these should not be included in the appended list.

If a revised Summary of Product Characteristics (SmPC), labelling and/or Package Leaflet (PL) is proposed within the renewal application~~to take account of issues raised by the expert~~, the precise ~~present~~ current 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 change(s) not listed, will not be considered as part of the renewal application.

In general, proposed amendments to the SmPC should be brought to the attention of the EMA before submission ~~, preferably via the query service or during a pre-renewal submission meeting when applicable~~ (see also section 3.1).

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[6] http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000090.jsp&mid=WC0b01ac0580023398&jsenabled=true

[7] http://esubmission.ema.europa.eu/eaf/index.html ~~http://ec.europa.eu/health/documents/eudralex/vol-2/index_en.htm~~

The renewal application form also incorporates a signed declaration ~~to be signed~~ stating 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, where relevant (see Annex 2 Documents to submit: 2.3 Addendum to Quality Overall Summary).

3.3.2. Risk Management Plan (RMP)

For medicinal products which have a Risk Management Plan (RMP), the MAH is requested to submit an update of the RMP within the renewal application in view of re-assessing 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 within the renewal application, given the last RMP updates submitted, this should be highlighted in the cover letter and a relevant justification ~~can~~ should be provided in Module 2.5 Addendum to the clinical overview. Where such statement is provided, the CHMP and the PRAC may nevertheless consider an update of the RMP necessary and ~~can~~ request its submission during the renewal procedure.

The format and content of the RMP must follow the requirements set out in the Commission Implementing Regulation (EU) 520/2012 on the performance of pharmacovigilance activities and Module V of the Good pharmacovigilance practices.

For medicinal products which do not have a Risk Management Plan (RMP), the MAH should state in the cover letter that no RMP has been submitted for the concerned product as not available.

3.3.3. Addendum to quality overall summary / non-clinical overview/clinical overview

Addendum to quality overall summary

There is no ~~updating~~ update of Part II/Module 3 quality data at renewal. The marketing authorisation holder has an obligation to keep this module updated on an on-going basis throughout the life of the product using variation ~~procedures~~applications.

The Addendum shall be signed and accompanied by the CV of the expert (Module 1.4.1).

The Addendum should include a declaration of compliance with Article 16(1) of Regulation (EC) No 726/2004, which obliges marketing authorisation holders to "take account of technical and scientific progress and introduce any changes that may be required to enable the medicinal products to be manufactured and checked by means of generally accepted scientific methods".

The Addendum 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. 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 in tabular format. Alternatively there is no need to provide the tables if active hyperlinks are available in the addendum to the quality overall summary.

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 variation classification guideline.

A certificate of GMP compliance, not more than three years old, for the manufacturer(s) of the medicinal product listed in the application should be submitted with the renewal application (A reference to the Community EudraGMP database, 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 of the most recent GMP inspections carried out indicating the date, the inspection team(s) and the outcome of the inspection(s) should be provided.

The renewal application should also be accompanied by declaration(s) by the Qualified Person(s) of the manufacturing authorisation holder(s) listed in the application as responsible for batch release. Such declaration should also be provided for Manufacturing Authorisation Holders (i.e. located within the EEA) 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 the case where no new non-clinical data have been ~~gathered~~ generated since the granting of the initial MAA or the last renewal or there is no new relevant information in the public domain, this may be stated in the Addendum to the Clinical Overview.

When new data are submitted in the non-clinical Addendum, it should consist of a critical discussion supporting the benefit-risk balance re-evaluation for the product taking into account any new non-clinical data accumulated since the granting of the initial MAA or the last renewal, or any relevant new information in the public domain.

The non-clinical Addendum shall 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.

Addendum to clinical overview

The marketing authorisation holder should submit 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 a consolidated version of safety/efficacy data accumulated since the initial MA or the last renewal, taking into account Periodic Safety Update Reports (PSURs) submitted, suspected adverse reactions reports, additional pharmacovigilance activities and the effectiveness of risk minimisation measures contained in the RMP, if applicable. New signal assessment and new potential or identified risks raised during the renewal period that have not been subject to previous assessment (e.g. in PSURs) should be clearly highlighted in the data provided. 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 outcome of the benefit-risk evaluation conducted at the time of the original authorisation or last renewal. The discussion should also clearly reflect the data included in the previous PSURs and the new data that have been collected since the DLP of the last PSUR up to the DLP of the renewal that should not exceed 90 days prior to the renewal submission.

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 marketing authorisation.

The Addendum to the Clinical Overview should contain the information indicated in Annex 2.

This Addendum should be signed and accompanied by the CV of the clinical expert (Module 1.4.3). The clinical expert should have the necessary technical or professional qualifications and may, but should not necessarily, be the same as the qualified person responsible for pharmacovigilance.

In any event, a clear conclusive statement is required from the clinical expert (See Annex 2) that the product can be safely renewed at the end of a 5-year period for an unlimited period. Any action recommended or initiated should be specified and justified. The clinical expert should ensure that the updated benefit-risk balance 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 the authorities have been kept informed of any additional data (e.g. results from clinical studies) significant for the assessment of the benefit-risk balance of the product concerned. In addition, the statement should confirm that the product information has been kept up to date with current scientific knowledge including the conclusions of the assessment and the recommendations made public by means of the European medicines web-portal.

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 an analysis of the impact of the findings overall on the benefit-risk balance of the medicinal product.

3.4. Assessment process

The assessment will consist of a benefit-risk balance re-evaluation, on the basis of a consolidated version of the file in respect of quality, safety and efficacy, including evaluation of data contained in suspected adverse reactions reports, the PSUR data and any relevant new information affecting the benefit-risk balance for the product. A full re-evaluation of the whole dossier normally should not take place. 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 (see also section 3.5.2) 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) and potential impact of the findings on the benefit-risk balance of the medicinal product will be reviewed during the assessment of the renewal application.

At time of renewal, compliance by the MAH with the conditions imposed on the medicinal product will be evaluated. As a result, these conditions could be modified and/or new conditions could be imposed.

In addition, it will be checked during the assessment whether the Marketing authorisation holder complies with his obligation to maintain the product information up to date with the current scientific knowledge including the conclusions of assessments and the recommendations which are made public on the European medicines web-portal.

The renewal procedure will involve the CHMP, the CAT for Advanced Therapy Medicinal Products as applicable, and the PRAC.

On the basis of the overall re-evaluation of the risk-benefit balance, the CHMP may recommend to grant unlimited validity to the Marketing Authorisation, or to require one additional five-year renewal. The grounds on which the CHMP may decide to require an additional renewal will be duly justified and

relate to pharmacovigilance, including for example exposure of an insufficient number of patients to the medicinal product. Criteria considered by CHMP are set out in the CHMP "Reflection Paper Criteria for requiring one additional five-year renewal for Centrally Authorised Medicinal Products".

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

Other issues arising from assessment and changes due to the revision of the SmPC guideline, other relevant guidelines impacting on the product information, or EMA/QRD Product Information Templates should be considered within the renewal process. Proposed changes to the SmPC, labelling and PL must be indicated on the renewal application form.

None of the changes introduced at renewal can substitute for the marketing authorisation holder's obligation to update the marketing authorisation throughout the life of the product by variation ~~procedure~~ application as data emerge, provided that the implemented changes fall within the scope of application of the Regulation (EC) No 1234/2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products.

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

Accordingly, no new studies should be submitted within the renewal unless these impact the benefit-risk balance 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 (See section 3.5.1.)

As part of the renewal process, the EMA, in collaboration with the ~~Member States~~ CHMP and the PRAC, will check that the SmPC, labelling and package leaflet conform to the requirements of Directive 2001/83/EC and Regulation (EC) No 726/2004 as well as ~~of~~ to the relevant Commission and CHMP/EMA guidelines.

3.5. The Committee's opinion

The CHMP will adopt an opinion on the renewal in the light of the final recommendation of the CHMP Rapporteur, the CAT as applicable, and the PRAC Rapporteur~~s~~.

The CHMP opinion, which may be favourable (recommending renewal of the Marketing Authorisation with unlimited validity, or requiring one additional five-year renewal) or unfavourable (non-renewal), is, wherever possible, reached by scientific consensus. If such consensus cannot be reached, the Opinion shall be adopted by a majority of the members. When divergent positions have been expressed, they will be referenced in the CHMP Opinion. Members expressing such divergent positions shall state clearly the grounds on which they are based. The divergent positions will be appended to the Opinion.

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

The position of the Norwegian and Icelandic CHMP members, who do not take part in the CHMP vote as such, is nevertheless recorded in the opinion.

The CHMP Rapporteur or the CAT Rapporteur as applicable, in coordination with the PRAC Rapporteur and the EMA procedure manager (PM) and if applicable the EMA product lead (EPL), taking account of CHMP comments, the CAT outcome as applicable, the PRAC outcome and the full scientific debate within the Committees ~~PRAC and the CHMP~~ and the conclusions reached, prepares the final renewal assessment report, which, once adopted by the CHMP, becomes the CHMP renewal assessment report and is appended to the CHMP opinion.

3.5.1. Favourable opinion

In the event of an opinion in favour of renewal of the authorisation, either with unlimited validity or for five-year validity, the following documents will be annexed or appended to the opinion.

- A draft Summary of Product Characteristics as referred to in Article 11 of Directive 2001/83/EC (Annex I)
- Information on the manufacturer(s) of the biological active substance(s) and manufacturer(s) responsible for batch release (Annex II)
- Conditions or restrictions regarding supply and use (Annex II)
- Other conditions and requirements of the Marketing Authorisation (Annex II)
- A draft Labelling and Package leaflet presented in accordance with Title V of Directive 2001/83/EC (Annex III)
- Where relevant, conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States (Annex related to Article 127a).
- Where relevant, grounds for requesting an additional renewal (Annex IV)
- The CHMP renewal assessment report
- Where relevant, signed divergent positions of Committee Members ~~with signatures and~~ with their grounds for not supporting the opinion

Opinion on products authorised under exceptional circumstances

For such medicinal products authorised under exceptional circumstances, in accordance with Article 14(8) of Regulation (EC) No. 726/2004 and Part II.6 of the Annex to Directive 2001/83/EC, as amended, the CHMP will have to consider whether any specific obligations have been fulfilled.

Post-authorisation measures

Specific obligations

When a renewal Opinion is adopted stating that there remain grounds for the marketing authorisation to be renewed under exceptional circumstances, the marketing authorisation holder is obliged to submit the requested data to the CHMP and/or CAT as applicable and/or the PRAC Rapporteurs and Members as applicable depending on the nature of the specific obligation and the EMA, in the agreed

timeframe after the renewal as set out in Annex II of the Commission Decision. The specific obligations are to be reviewed at the intervals indicated and at the latest annually within the annual review which includes a re-assessment of the benefit-risk balance of the medicinal productbenefit/risk profile.

Other Post-authorisation measures

For all favourable opinions of the CHMP (whether the MA is or not under the exceptional circumstances) of Article 14(8) of the Regulation), the need for new and/or changed post-authorisation measure(s) might arise from the renewal procedure. They will be classified either as conditions imposed on the marketing authorisation and reflected in the Annex II of the Commission Decision, or as additional pharmacovigilance activities in the RMP or as recommendations included in the CHMP assessment report. The data should be reviewed in accordance with the agreed deadline where applicable. Marketing authorisation holders will be informed of the outcome of CHMP discussions by the EMA.

3.5.2. Unfavourable opinion

The CHMP will adopt a negative opinion recommending not renewing the marketing authorisation if there are serious public health issues raised.

Reasons for marketing authorisation not being renewed could include notably grounds provided for in Article 116 of the Directive 2001/83/EC, i.e. where the product proves to be harmful, or where its lacks therapeutic efficacy according to the SmPC is lacking, or that the benefit/ risk balance is not positivefavourable, 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 to the marketing authorisation have not been fulfilled, or when the appropriate controls on the manufacturing process or on the finished product have not been carried out.

Additionally, for a marketing authorisation which is suspended at the time of its renewal application, if the marketing authorisation holder is not able to provide data to demonstrate that the benefit-risk balance is positive and identify measures for the safe and effective use of the medicinal product to allow lifting the suspension, the marketing authorisation shall expire.

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

The following documents will be annexed or appended to the opinion:

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

A 'Summary of Opinion' will be published by the EMA. This will include information on unfavourable CHMP opinions and the reasons for such opinion.

In case of non-renewal, where applicable an Article 20 or 107i procedure might be initiated.

3.6. Follow-up to the CHMP opinion

3.6.1. Translation and transmission of the CHMP opinion

If amendments to the proposed product information are required following the adoption of the CHMP opinion, the marketing authorisation holder will have to provide the EMA and all CHMP members with the relevant amended translations of the SmPC, labelling and package leaflet within 5 days after the CHMP opinion.

After adoption of the Opinion, a review of the quality of the translations will be carried out by the EMA in co-operation with the Member States. The Icelandic and Norwegian translations will be checked by the Icelandic and the Norwegian authorities in co-operation with the EMA.

If within 15 days after receipt of the opinion, the marketing authorisation holder does not inform in writing the EMA of any intention to request a re-examination of the opinion, the EMA will then forward the opinion (and the required annexes and appendi~~x~~ces), to the Commission, the Member States, Norway and Iceland and the marketing authorisation holder. ~~together with the CHMP assessment report.~~ The Norwegian and Icelandic Authorities will issue corresponding national authorisations subsequent to the Commission Decision.

Where the CHMP adopted a negative opinion and the marketing authorisation holder notified the EMA/CHMP of its intention ~~of~~ to request a re-examination of the opinion, the EMA will inform the European Commission about such negative opinion and the re-examination request. The final CHMP opinion will be forwarded to the European Commission, to the Member States, Norway, Iceland and to the marketing authorisation holder upon finalisation of the re-examination procedure (see 3.6.3).

3.6.2. Re-examination

The marketing authorisation holder may notify the EMA/CHMP in writing of its intention to request a re-examination of the Opinion within 15 days after receipt of the opinion; ~~(after which~~ if such a request is not made within these 15 days, the opinion becomes final~~)~~.

The detailed grounds for the request must be forwarded to the EMA within 60 days after receipt of the opinion. If the marketing authorisation holder wishes to appear ~~before~~ at the CHMP for an oral explanation, such request should also be sent at this stage. ~~The CHMP will appoint a~~A new CHMP Rapporteur, new CAT Rapporteur as applicable, and a new PRAC Rapporteur, different from those for the initial opinion will be appointed~~,~~ to co-ordinate the re-examination procedure, accompanied, if necessary, by additional experts.

Within 60 days after the receipt of the detailed grounds for re-examination, the CHMP will re-examine its opinion. If considered necessary, an oral explanation can be held within this 60-day ~~timeframe~~procedure. Once the CHMP issues a final opinion, it is forwarded (with the required annexes and appendixes), to the European Commission, the Member States, Norway and Iceland and the marketing authorisation holder. ~~stating the reasons for its conclusion.~~

At the end of the re-examination procedure, the EMA will publish a 'Summary of Opinion' of the CHMP final Opinion.

3.6.3. European Public Assessment Report (EPAR)

The EMA will prepare an update of the EPAR, reflecting the renewal assessment and CHMP opinion. After the Commission Decision on the renewal, the updated EPAR shall be published.

3.6.4. Negative decision

Following a Decision of the European Commission ~~Decision~~ on the refusal to renew the marketing authorisation, which, in accordance with Article 12(2) of the Regulation, constitutes a prohibition to place ~~on the market~~ the medicinal product concerned on the market throughout the Union, the EMA shall make ~~information on~~ such final decision and the reasons for it publicly available, in accordance with Article 12(3) of the Regulation.

Annex 1

Renewal timetable (CHMP)

Day 1	Start of the procedure (see published dates on EMA website).
Day 60	CHMP Rapporteur and PRAC Rapporteur Joint Assessment Report.
	Circulate to CHMP and PRAC members.*
Day 66	Comments from CHMP and PRAC members on the Joint Assessment Report.
Day 73-76	Discussion at PRAC Meeting (if applicable):
Day 76	PRAC Outcome (endorsement of the Joint Assessment Report)*
Day 90	Discussion at CHMP (if applicable):
	- If no outstanding issues: adoption of opinion.
	- If outstanding issues**: adoption of List of Outstanding Issues.
Day 91	MAH provides answers to list of outstanding issues to CHMP/PRAC Rapporteurs, CHMP/PRAC members and EMA.
Day 96	CHMP Rapporteur and PRAC Rapporteur Joint Assessment Report.
	Circulate to CHMP and PRAC members.*
Day 98	Comments from CHMP and PRAC members on the Joint Assessment Report.
Day 103-106	Discussion at PRAC (if applicable).
Day 120	Discussion at CHMP (if applicable). Adoption of CHMP opinion.

For ATMP, the CAT Rapporteur will assess the renewal application together with the PRAC Rapporteur and will prepare a draft opinion for the CHMP as the basis for the CHMP's final opinion. Further information with regards to the CAT involvement is provided in the "Procedural advice on the evaluation of advanced therapy medicinal product" published on the EMA website.

**Document shared with the MAH*

***** *If any remaining outstanding issues are identified including serious public health concerns which may lead to a negative benefit-risk ~~ratio~~ balance and a possible non-renewal or to major changes to the marketing authorisation, a list of such issues will be adopted and sent to the MAH to be addressed in writing and/or at an oral explanation. At the time of adoption of the List of Outstanding Issues,a clock stop will be set, in order for the marketing authorisation holder to respond to the List of Outstanding Issues. Normally, the clock stop will be of 30 days in order to ensure sufficient time for the CHMP opinion and subsequent Commission decision to be adopted prior to the expiry of the marketing authorisation*.

Annex 2

Documents to submit

Renewal applications should be submitted in eCTD format and have to contain the documents listed below.

Module 1:

1.0 Cover letter

1.2 Renewal Application form with the following annexes:

- List of all authorised product presentations for which renewal is sought in tabular format (following the template for Annex A to CHMP Opinion)
- 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 the 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, 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 and Specific Obligations submitted since the granting of marketing authorisation or the last renewal indicating scope, status, date of submission and date when date the condition/ obligation was fulfilled ~~issue has been resolved~~ (where applicable)
- Revised list of all remaining conditions and Specific Obligations (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 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 (i.e. located in the EEA) listed in the application form where the active substance is used as a starting material.
- A declaration by the Qualified Person (QP) of the manufacturing authorisation holder(s) listed in the application as responsible for batch release.

These declarations should state that all the active substance manufacturer(s) referred to in the application form operate in compliance with the detailed guidelines on good manufacturing practice for starting materials.

1.3.1 Summary of Product Characteristics, Labelling and Package Leaflet:

A ~~relevant example of the proposed~~ clean version ~~texts for~~ of the SmPC, Annex II, outer and inner labelling and Package Leaflet in English has to be provided. In addition a word version highlighting ~~the~~ potential changes proposed by the MAH should also be included in the application.

1.3.3 Specimens:

At renewal, EMA will perform a new check of the specimens across all marketed product presentations.

Relevant example specimens should be provided to the EMA as part of the renewal application, for each strength, pharmaceutical form and container type in the smallest marketed pack-size. Ideally multi-lingual specimens should be provided but, if not available, a single-language specimen may be submitted.

As such the EMA will receive and check at least one example specimen of the whole range of marketed product presentations after 5 years, in one submission.

In case the MAH plans to change the overall design and readability of the labelling and/or package leaflet around the time of renewal, submission of specimens of the "old" product design will not be necessary. In case the MAH wishes to receive EM~~E~~A feedback on their proposed new packaging in advance of the specimen submission and review, this approach should however be discussed with the ~~PTL~~EPL/PM in advance of the renewal submission ~~(e.g. at the renewal pre-submission meeting)~~.

1.4 Information about the Expert:

In cases where MAHs wish to distinguish these declarations from any previous declarations, the EMA 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)

~~1.8.1 Summary of Pharmacovigilance System (if applicable):~~

~~• Proof that the applicant has at his disposal a qualified person responsible for pharmacovigilance,~~

- ~~A statement signed by the marketing authorization holder to the effect that the marketing authorization holder has the necessary means to fulfill 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~~
- ~~The contact details of the QPPV~~
- ~~The reference to the location of the pharmacovigilance system master file (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 in the clinical overview declaration and confirm that the current approved RMP remain unchanged and applicable.

Where there is no RMP for the medicinal product, this should be stated in the cover letter.

Module 2:

2.3 Addendum to Quality Overall Summary:

The Addendum should include a declaration of compliance with Article 16(1) of Regulation (EC) No 726/2004, 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.
- 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)

2.4 Addendum to Non-clinical Overview:

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

When new data are submitted in the non-clinical Addendum, a critical discussion must be submitted as part of the renewal application, supporting the benefit-risk balance 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.

In the case where no new non-clinical data have been gathered since the granting of the MA ~~initial MAA~~ or the last renewal, this may be stated in the Addendum to the Clinical Overview.

2.5 Addendum to Clinical Overview**:**

A critical discussion should be provided within the Addendum to the Clinical Overview. It should address the current benefit-risk balance 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, making reference to relevant new information in the public domain. The discussion should clearly reflect the data previously included in the PSURs and the new data that have emerged been collected since the DLP of the last PSUR up to the DLP of the renewal that should not exceed 90 days prior to the renewal submission.

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 authorisation status: overview of number of countries where the product has been authorised and marketed worldwide.
- Actions taken for safety reasons during the period covered since the initial marketing authorisation or since the last renewal until 90 days prior toto the DLP of the renewal submission: description of all significant actions related to safety that had a potential influence on the benefit-risk balance of the authorised medicinal product (e.g. suspension, withdrawal, temporary halt or premature ending of clinical trial for safety reasons, issue requiring communication to healthcare professionals…). Among these, aActions taken from the DLP of the last PSUR up to the DLP of the renewal should be clearly identified and highlighted.
- Significant changes made to the Reference Information (RI) during the period covered since the initial marketing authorisation or since the last renewal. In this section, it should be clearly identified the changes included in the PSURs and the new changes made from the DLP of the last PSUR up to the DLP of the renewal should be clearly highlighted.
- Estimated exposure and used patterns: data on cumulative exposure of subjects in clinical trials as well as of patients from worldwide post-marketing exposure per EU and non EU regions. If the marketing authorisation holder becomes aware of a pattern of use of the medicinal product considered relevant for the interpretation of the 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 DLP of the last renewal up to the DLP of the renewal.
- Summaries of significant safety and efficacy findings from clinical trials and non-interventional studies during the period covered by the renewal. It should also address whether milestones from post-authorisation safety studies, post-authorisation efficacy studies, studies from the RMPincluded in the pharmacovigilance plan of the RMP and studies conducted as condition and or specific obligations of the marketing authorisation, have been reached in accordance with agreed timeframes. New data since the DLP of the last PSUR up to the DLP of the renewal should be clearly highlighted.

- Overview of signals: High level overview of signals for which evaluation was completed during the period covered by the renewal and any action taken or planned; and high level overview of ongoing signals (i.e. that are undergoing evaluation at the DLP of the renewal application) should be provided. The information should be provided in a table.

- Signal and risk evaluation: the MAH should summarise signals for which evaluation was completed during the reporting period of the renewal. For signals that became important identified or potential risks or are related to a known risk, a characterisation of the risk should be provided. Evaluation of signals completed from the DLP of the last PSUR to the DLP of the renewal should be clearly highlighted. The MAH should discuss whether any changes are considered necessary in the existing safety concerns and whether any additional risk minimisation activities for the product are warranted, considering the data collected during the period covered by the renewal.

Relevant information on patterns of medication errors and potential medication errors (even when not associated with adverse outcomes) during the period covered by the renewal. Such information may be relevant to the interpretation of safety data or the overall benefit-risk balance evaluation.

- Literature: review of important literature references published during the period covered since the initial marketing authorisation or since the DLP of the last renewal ~~until 90 days prior to renewal submission~~ that had a potential impact on the benefit-risk balance of the medicinal product.

- 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 DLP of the last renewal until the DLP of the ~~90 days prior to~~ 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 DLP of the renewal but during the period of preparation of the addendum to the clinical overview.

*** Marketing authorisation holders are advised to consider the Good Vigilance Practice Module VII on PSUR~~s~~ as guidance for the preparation of the above sections of the clinical overview.*

The Clinical Expert Statement should:

- Confirm that no new clinical data are available which change or result in a new benefit-risk balance evaluation.

- 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 ~~ration~~ balance of the product concerned.

- Confirm that the product information is up to date with the current scientific knowledge including the conclusions of the assessments and the recommendations made publicly available on the European medicines web-portal.

Abbreviations

CPMP	Committee for Proprietary Medicinal Products, changed to CHMP
CHMP	Committee for Medicinal Products for Human Use
CV	Curriculum Vitae
DLP	Data Lock Point
eCTD	Electronic Common Technical Document
EC	European Commission
EEA	European Economic Area
EMA	European Medicines Agency
EMA PM	European Medicines Agency Procedure Manager
EMA EPL	European Medicines Agency Product Lead
EPAR	European Public Assessment Report
EU	European Union
GMP	Good Manufacturing Practise
NTA	Notice to Applicants
MA	Marketing Authorisation
MAA	Marketing Authorisation Application
MAH	Marketing Authorisation Holder
MRA	Mutual Recognition Agreements
PL	Package Leaflet
PRAC	Pharmacovigilance Risk Assessment Committee
PSUR	Periodic Safety Update Report
QP	Qualified Person
QPPV	Qualified Persons responsible for Pharmacovigilance
QRD	Quality Review of Documents
RI	Reference Information
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics