



London, 20 October 2005  
EMEA/CHMP/2990/00 rev. 3

**COMMITTEE FOR HUMAN MEDICINAL PRODUCTS  
(CHMP)**

**GUIDELINE ON THE PROCESSING OF RENEWALS IN THE  
CENTRALISED PROCEDURE**

<b>TRANSMISSION TO CPMP</b>	November 2000
<b>RELEASE FOR CONSULTATION</b>	December 2000
<b>DEADLINE FOR COMMENTS</b>	17 March 2001
<b>ADOPTION BY CPMP</b>	May 2001
<b>DATE OF ENTRY INTO FORCE</b>	June 2001
<b>UPDATE ADOPTED BY CHMP &amp; TRANSMISSION TO EC</b>	25 July 2005
<b>RELEASE FOR CONSULTATION</b>	12 August 2005
<b>DEADLINE FOR COMMENTS</b>	7 September 2005
<b>ADOPTION BY CHMP</b>	13 September 2005
<b>PUBLICATION EMEA Web &amp; TRANSMISSION TO NTA</b>	20 October 2005
<b>DATE OF ENTRY INTO FORCE</b>	20 November 2005

## 1. Introduction

This paper 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 following consultation of the CHMP and the European Commission.

## 2. Legal Framework

In accordance with Article 14 (1-3) of Regulation (EC) No. 726/2004, a marketing authorisation is valid for five years, except when a “conditional marketing authorisation”<sup>1</sup> has been granted. The marketing authorisation may be renewed upon application by the marketing authorisation holder at least six months before expiry. The renewal dossier and assessment should be based on a general re-evaluation of the benefit/risk balance of the product.

Article 12(1) of Regulation (EC) No 726/2004, indicates that authorisation shall be refused where the labelling and patient information leaflet do not comply with the requirements of Title V of Directive 2001/83/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 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 the product by variation procedure as data emerge.

Once renewed, the marketing authorisation shall be valid for an unlimited period<sup>2</sup>, unless the competent authority decides, on justified grounds relating to pharmacovigilance, to proceed with one additional five-year renewal.

In addition, in accordance with Article 16(2) of Regulation (EC) No 726/2004, the EMEA 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

Marketing authorisation holders must apply at least six months in advance of the expiry date, i.e. the 5-year anniversary of the Commission Decision granting the marketing authorisation, for the application to be valid under Article 14 of Regulation (EC) No. 726/2004.

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<sup>1</sup> According to Article 14(7) of Regulation (EC) 726/2004. Conditional marketing authorisations shall be valid for one year. Guidance on the renewal of such conditional MAs will be included at a later stage or will be subject of a separate guidance document.

<sup>2</sup> Marketing Authorisations which have already been renewed under the system in force before the application of the new Regulation, should be renewed once more under the new system before the authorisation may gain unlimited validity.

Flexibility will be maintained as to the basis of the renewal date and will take account of the International Birth Date, and the maintenance of synchronisation of PSURs. The marketing authorisation holder should agree in advance the submission date of the renewal application with the EMEA and the Rapporteur/Co-Rapporteur.

In order to facilitate the preparation of the renewal application, a pre-renewal submission meeting with the EMEA (and Rapporteur) is advisable. Such meeting should ideally take place 10-12 months before expiry of the marketing authorisation.

### **3.2 Timetable**

The MAH shall submit the renewal application at the latest by the recommended submission dates published on the EMEA website.

In order to allow sufficient time for the scientific evaluation of the data submitted and the adoption of a Commission Decision, and acknowledging that the overall process should be finalised in 6 months, the timetable (of max. 120 days) for the scientific evaluation by the CHMP is as follows (see also Annex 1):

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

- Start of the procedure (see published dates on EMEA website): Day 1
- Rapporteur's Assessment Report sent to Co-Rapporteur: day 45
- Joint Rapporteur/Co-Rapporteur Assessment Report: day 60.  
(Circulate to CHMP and MAH, highlighting major issues if any)
- Comments CHMP members: day 80
- First discussion at CHMP: day 90.
  - If no outstanding issues: adoption of opinion
  - If outstanding issues\*: adoption of list of outstanding issues + decision on possible oral explanation by MAH
- MAH provides answers to list of outstanding issues to (Co-)Rapporteur, CHMP and EMEA: day 100.
- Revised Assessment Report from Rapporteur/Co-Rapporteur: day 110  
(Circulate to CHMP and MAH)
- Adoption of CHMP Opinion/oral explanation by MAH: day 120.

\* If any remaining outstanding issues are identified, including serious public health concerns which may lead to a negative benefit/risk ratio 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.

A limited extension of the timeframe is possible allowing the marketing authorisation holder to respond to the list of outstanding issues and the CHMP to assess the additional data submitted.

### 3.3 Documents to submit

A list of documents to submit is given in Annex 2. Details on the number of copies of the dossier to be submitted are given in Chapter 7 of the Notice To Applicants (Volume 2A) at <http://pharmacos.eudra.org/eudralex/vol-2/home.htm#2a>

Practical details on the renewal application submission are given in the EMEA Post-Authorisation Guidance document on the EMEA website (Human Medicines – Application Procedures).

#### *a. Administrative information*

The European renewal application form should be completed. The form is available in the Notice To applicants (Volume 2C) at <http://pharmacos.eudra.org/eudralex/vol-2/home.htm#2c>

The marketing authorisation holder should complete one renewal application form for the Centrally Authorised Medicinal Product (= 1 application per core EU Number), appending a list of all authorised strengths, pharmaceutical forms and presentations of the product concerned for which renewal is sought.

If a revised SPC, labelling and/or PL is proposed to take account of issues raised by the expert, the precise present and proposed wording should be specified on the form. Alternatively, such listing may be provided as a separate document attached to the application form under a tabular format (indicating the current and proposed texts). Any changes not listed, will not be considered as part of the renewal application.

In general, proposed amendments to the SPC should be brought to the attention of the EMEA before submission, preferably through a pre-renewal submission meeting (see also section 3.1).

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, where relevant.

#### *b. PSUR:*

Reference should be made to the new Volume 9 of the Rules Governing Medicinal Products in the European Union on Pharmacovigilance (Notice to Marketing Authorisation Holders). In accordance with such Notice to Marketing Authorisation Holders the following principles should be taken into account:

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

The marketing authorisation holder should submit the renewal application at least 6 months before the expiry of the marketing authorisation in the EU. This may be submitted earlier in order to facilitate co-ordination with the regular cycle of the PSUR.

A PSUR has to be submitted within the renewal and should cover the period from the Data Lock Point of the last submitted PSUR until the data lock point which is within 60 days of renewal submission date.

When the period to be covered falls outside the usual PSUR reporting cycle, the use of line-listings and/or summary tabulations or a PSUR Addendum Report is recommended to cover the data outside the defined period for PSUR submission.

Therefore, the data to be included in the renewal application can be presented as

- a PSUR, or
- a PSUR + line-listing/summary tabulation, or
- a PSUR + PSUR Addendum Report, or
- a line-listing/summary tabulation or PSUR Addendum Report,

depending on the period to be covered, and the MAH's PSUR reporting cycle.

As the line-listing/summary tabulation or PSUR addendum Report do not provide an in depth-analysis of the additional cases, the MAH is requested to include such analysis within the clinical overview. The MAH should also include the cases reported in the line-listing/summary tabulation or addendum report again in the next PSUR.

Where the MAH submits two or more PSURs (e.g. multiples of 6 months PSURs, multiples of 1 year PSURs) for a period over which normally a single report is required, an additional Summary Bridging Report, providing a brief summary 'bridging' the multiple PSURs, is required.

The requirements and format of the PSURs, line-listing/summary tabulation, PSUR Addendum Reports and Summary Bridging Report are set out in Volume 9 and ICH E2C.

### *c. Expert Statements*

Clinical Expert Statement. The marketing authorisation holder submits an expert statement to accompany the renewal application which addresses the current benefit/risk for the product on the basis of a consolidated version of safety/efficacy data accumulated since the initial MAA or the last renewal, the PSUR data, and makes reference to any relevant new information in the public domain e.g. literature references, clinical trials and clinical experience, new treatments available, which may change the outcome of the benefit/risk evaluation at the time of the original authorisation or last renewal.

The clinical expert statement should include a non-clinical expert statement as part of the renewal application, if applicable, 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 expert statement must be signed and accompanied by a CV of the expert (Module 1.4.3). The clinical expert should be medically qualified and may, but should not necessarily, be the same qualified person responsible for pharmacovigilance.

In any event, a clear statement is required from the clinical expert that the product can be safely renewed at the end of a 5-year period for an unlimited period, or any action recommended or initiated should be specified and justified. The expert should ensure that the updated benefit/risk evaluation has been addressed adequately, taking account the consolidated version of the file and all relevant new information, by appropriate discussion within the expert statement.

The expert should 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 ratio of the product concerned.

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

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

The statement should confirm that all changes relating to the quality of the product have been made following applications for variations and that the product conforms to current CHMP quality guidelines. The statement should also include the currently authorised specifications for the active substance and the finished product and the qualitative and quantitative composition in terms of the active substance(s) and the excipient(s). The expert statement must be signed and accompanied by a CV of the expert (Module 1.4.1).

The marketing authorisation holder will continue to monitor the stability of the product in accordance with agreed stability protocols but needs only to inform competent authorities should a problem arise together with a recommended course of action. This reflects the principles of the Type I variation dossier requirement guideline. A 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 will suffice, once this is available). In addition for manufacturing sites of the medicinal product not located in the EEA or in the territory of an MRA partner, a list of the most recent GMP inspections carried out indicating the date, inspection team and outcome.

The renewal application should also be accompanied by declarations by the Qualified Person(s) of the manufacturing authorisation holder(s) listed in the application as responsible for batch release. In addition, such declaration should also be provided for Manufacturing Authorisation Holders (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.

#### Non-Clinical Expert Statement.

A non-clinical expert statement is not systematically required, only in case new non-clinical data have been gathered since the initial MAA or last renewal. In such case, a non-clinical expert statement should be submitted as part of the renewal application, 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 expert statement must be signed and accompanied by a 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.

### **3.4 Assessment process**

The assessment will consist of a benefit/risk balance re-evaluation, on the basis of a consolidated version of the file, making use of the PSUR data and any relevant new information affecting the benefit/risk 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).

The CHMP may recommend to grant unlimited validity to the Marketing Authorisation, or to require one additional five-year renewal<sup>3</sup>.

Where there are adequate and objective reasons not to renew the marketing authorisation in its existing terms and changes are necessary to the SPC, labelling and PL arising from the 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 initiate a separate variation procedure.

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

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

**None of the changes introduced at renewal should substitute for the marketing authorisation holder's obligation to update the marketing authorisation throughout the life of the product by variation procedure as data emerge.**

In very exceptional cases, if as part of the renewal assessment, new studies are required, but these are not of such importance to delay issue of the renewal, then these may be considered as on-going post-authorisation commitments (Follow-Up measures) after the issue of the renewal. The marketing authorisation holder will be required to provide written assurance that it will undertake the on-going commitments ((Follow-Up measures) within an agreed time frame. If the results of new studies lead to changes in the product information, these will be processed through a separate Type II variation procedure (see also section 3.5.1.2).

As part of the renewal process, the EMEA, in collaboration with the Member States, will check that the SPC, labelling and package leaflet conform to the requirements of Directive 2001/83/EC, as amended, and relevant Commission and CHMP guidelines.

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<sup>3</sup> Guidance on the criteria or factors considered by CHMP when requiring one additional five-year renewal will be provided in due time taking into account experience gained.

### **3.5 The Committee's opinion**

The CHMP will adopt an opinion on the renewal in the light of the final recommendation of the Rapporteur and Co-Rapporteur. The draft opinion is prepared by the EMEA and then adopted by the CHMP.

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 Rapporteur, in co-ordination with the Co-Rapporteur and the EMEA Product Team Leader, taking account of the full scientific debate within 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 another five-year validity, the following documents will be annexed and/or appended to the opinion.

- A draft Summary of Product Characteristics as referred to in Article 11 of Directive 2001/83/EC, as amended;
- Manufacturing and/or importing conditions and conditions of the marketing authorisation;
- A classification for the supply of the medicinal product;
- A draft Labelling and Package leaflet presented in accordance with Title V of Directive 2001/83/EC;
- The CHMP renewal assessment report;
- Where relevant, divergent positions of Committee Members with signatures and with their grounds for not supporting the opinion

Any follow-up measures agreed upon by the CHMP will be included in the renewal assessment report and referenced in a “letter of undertaking” signed by the Marketing Authorisation Holder which will be annexed to the assessment report (see also 3.5.1.2).

### **3.5.1.1 Opinion on products authorised under exceptional circumstances**

The fifth annual re-assessment of medicinal products authorised under exceptional circumstances will take place at the time of the renewal of the product concerned.

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 there remain grounds for the marketing authorisation to be kept under exceptional circumstances or not. If no such grounds remain, a recommendation will be made to renew the marketing authorisation under normal circumstances.

### **3.5.1.2 Post-Authorisation commitments**

#### *Specific obligations*

When a renewal Opinion is granted, 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 Rapporteur, Co- Rapporteur, CHMP Members and the EMEA, in the agreed timeframe after the renewal. These “specific obligations” to provide such data, are set out in Annex II of the Commission Decision and are detailed in the Letter of Undertaking of the marketing authorisation holder as adopted at the time of the Opinion. The specific obligations are to be reviewed at the intervals indicated and at the longest annually. The annual review includes a re-assessment of the benefit/risk profile.

Such documentation should be reviewed in accordance with the agreed timetable.

#### *Follow-up measures*

For all opinions of the CHMP (whether or not under the exceptional circumstances of Article 14(8) of the Regulation), it might be necessary to establish follow-up measures. The data should be reviewed in accordance with the agreed timetable. Marketing authorisation holders will be informed of the outcome of CHMP discussions by the EMEA.

### **3.5.2. Unfavourable opinion**

The CHMP will adopt a negative opinion recommending not to renew the marketing authorisation if there are serious public health issues raised. The criteria specified in Article 116 of Directive 2001/83/EC, as amended, regarding the suspension, withdrawal or revocation of authorisation to market medicinal products form the basis for the refusal to renew the marketing authorisation.

These criteria include where the product proves to be harmful in the normal conditions of use, or where its therapeutic efficacy according to the SPC is lacking, or that 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 lacking when it is established that therapeutic results cannot be obtained with the medicinal product. Additionally, non-renewal may be considered where the particulars supporting the application for renewal are incorrect or have not been updated, or when the controls on the manufacturing process or on the finished product have not been carried out.

Additionally, non-renewal or suspension 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 and/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 EMEA. This will include information on unfavourable CHMP opinions and the reasons for such opinion.

### **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 provide the EMEA and all CHMP members with the relevant amended translations of the SPC, 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 EMEA 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 EMEA.

If within 15 days of receipt of the opinion, the marketing authorisation holder does not inform the EMEA of any intention to request a re-examination of the opinion, the EMEA will then forward the opinion (and the required annexes), 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 EMEA/CHMP of their intention of to request a re-examination of the opinion, the EMEA will inform the Commission about such negative opinion and re-examination request. The final CHMP opinion will be forwarded to the Commission upon finalisation of the re-examination procedure (see 3.6.3).

#### **3.6.2 Mock-ups and specimens**

Where the package leaflet and outer and inner labelling have been amended as a result of the renewal procedure, no mock-ups are required to be provided within the renewal procedure. However, one “worst-case” (multi-lingual pack for e.g. Belgium, Nordic or Baltic countries) specimen of the currently marketed outer and inner labelling and printed package leaflet for each pharmaceutical form should be provided as part of the renewal application.

Revised specimens for all Member States implementing the changes agreed as part of the renewal must be provided to the EMEA before launch. Revised specimens for Iceland and Norway must be provided to the respective authorities directly.

### **3.6.3. Re-examination**

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

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

Within 60 days from 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. Once the CHMP issues a final opinion, it is forwarded (with the required annexes), to the 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 EMEA will publish a ‘Summary of Opinion’ of the CHMP `s final Opinion.

### **3.6.4 European Public Assessment Report (EPAR)**

The EMEA 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.

### **3.6.5 Negative decision**

Following a Commission Decision on the refusal to renew the marketing authorisation, which, in accordance with Article 12.2 of the Regulation, constitutes a prohibition to maintain on the market the medicinal product concerned throughout the Community, the EMEA shall make information on such a final decision publicly available, in accordance with Article 12.3 of the Regulation.

## ANNEX 1

### RENEWAL TIMETABLE (CHMP)

Day 1	Start of procedure (as per the EMEA published starting dates)
Day 45	Receipt of Rapporteur's Assessment Report sent to Co-Rapporteur
Day 60	Receipt of Joint Rapporteur / Co-Rapporteur Assessment report – circulated to EMEA, CHMP members and MAH. EMEA may liaise with MAH in preparation of the opinion/List of Outstanding Issues.
Day 80	Comments of CHMP members on the Joint Assessment report.
Day 90	First discussion at CHMP. - Possible adoption of opinion. - In case of outstanding issues: adoption of List of Outstanding Issues + decision on possible oral explanation by MAH
Day 100	MAH provides answers to list of outstanding issues to Rapporteur, Co-Rapporteur, CHMP and EMEA
Day 110	Receipt of Rapporteur / Co-Rapporteur Assessment Report on MAH's answers - circulated to EMEA, CHMP members and MAH
Day 120	Adoption of CHMP opinion. Possible oral explanation by MAH

The MAH shall submit the renewal application at the latest by the recommended submission dates published on the EMEA website. Once the renewal application is validated by the EMEA, the timetable is adopted and the clock starts according to the published starting date. The MAH will be informed of the adopted timetable at the start of the procedure.

## DOCUMENTS TO SUBMIT

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

- Module 1:**
- 1.0** Cover letter
  - 1.1** Comprehensive table of content
  - 1.2** Renewal Application form with the following annexes:
    - List of all authorised product presentations for which renewal is sought in tabular 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 grant of the Marketing Authorisation or last renewal: a list of all approved or pending Type IA/IB and Type II variations, Extensions, Art 61(3) Notifications, USR, giving the procedure number (where applicable), date of submission, date of approval (if approved) and brief description of the change.
    - Chronological list of Follow-Up Measures and Specific Obligations submitted since grant of marketing authorisation or last renewal indicating scope, status, date of submission and date when issue has been resolved (where applicable)
    - Revised list of all remaining Follow-Up Measures and Specific Obligations and signed Letter of Undertaking (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 will suffice, once this is available.
    - For manufacturing sites of the medicinal product not located in the EEA or in the territory of an MRA partner, a list of the most recent GMP inspections carried out indicating the date, inspection team and outcome.
    - In accordance with Article 46(f) of Directive 2001/83/EC manufacturing authorisation holders 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)<sup>4</sup> referred to in the application form operate in compliance with the detailed guidelines on good manufacturing practice for starting materials<sup>5</sup>.

### **1.3.1** Product Information:

Summary of Product Characteristics, Annex II, Labelling and Package Leaflet

A relevant example of the proposed texts for SPC, Annex II, outer and inner labelling and Package Leaflet in English has to be provided in paper (highlighted). A full set of Annexes in English should be provided electronically (highlighted).

### **1.3.3** Specimen

One “worst-case” (multi-lingual pack for e.g. Belgium, Nordic or Baltic countries) specimen of the currently marketed outer and inner labelling and printed package leaflet for each pharmaceutical form should be provided.

### **1.4** Information about the Expert

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

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<sup>4</sup> According to Article 46a (1) of Directive 2001/83/EC, 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.

<sup>5</sup> Blood or blood components are excluded from this requirement.  
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**Module 2: 2.3 Quality Overall Summary  
(Quality Expert Statement)**

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

The Quality Expert Statement should also include:

- Confirmation that all changes relating to the quality of the product have been made following applications for variations and that the product conforms to current CHMP Quality guidelines.
- 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 Non-clinical Overview  
(Non-Clinical Expert Statement)**

If applicable, a non-clinical expert statement must be submitted as part of the renewal application, 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.

**2.5 Clinical Overview  
(Clinical Expert Statement)**

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

The Clinical Expert Statement should:

- Confirm that no new pre-clinical (if applicable) or clinical data are available which change or result in a new risk-benefit 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 ratio of the product concerned.

**Module 5: 5.3.6 Reports of Post-marketing experience**

Required Periodic Safety Update Report – The required PSUR and/or line-listing/summary tabulation or PSUR addendum report (i.e. a PSUR and/or listing/summary tabulation or PSUR addendum covering the period from the data lock point of the previous PSUR until a data lock point which is within 60 days of the renewal submission date). A summary bridging report if applicable.