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Evaluation of Medicines for Human Use

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OVERVIEW OF EXTERNAL COMMENTS RECEIVED, AND EMEA/CHMP FEEDBACK/ACTION ON EACH COMMENT

COMMITTEE FOR HUMAN MEDICINAL PRODUCTS (CHMP)

GUIDELINE ON THE PROCESSING OF RENEWALS IN THE CENTRALISED PROCEDURE

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Table 1: Organisations that commented on the draft Guideline as released for consultation

	Organisation
1	AMGEN Ltd
2	Association of the European Self-Medication Industry (AESGP)
3	European Federation of Pharmaceutical Industries and Associations (EFPIA)
4	Paul-Ehrlich-Institut (PEI)
5	Pharmacovigilance Working Party

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Ref.	Comments/Issue	Discussion/action
1a	We question why the date of entry into force is 30 October 2005, when the relevant provisions of Regulation 726/2004 (Article 14) apply from 20 November 2005. We propose that the date of entry into force should be amended accordingly.	Valid comment. Change to be implemented (see above).
1b	It should be noted that companies need some time to change their internal procedures to adopt the new timelines. It would have been preferable that this guideline be issued earlier in order to provide companies with enough time to make the changes prior to the coming into force of the new regulation.	Acknowledged. EMEA has held pre-submission discussions/ meetings with MAH for upcoming renewal submissions and informed them of the draft requirements before the guideline was released.

PROCESSING OF RENEWALS IN THE CENTRALISED PROCEDURE

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"[1] 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 ~~Section~~ 3.4 ~~Assessment Process~~. 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[2], unless the competent authority decides, on justified grounds relating to pharmacovigilance, to proceed with one additional five-year renewal.

[1] 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.

[2] 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.

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.

Ref.	Comments/Issue	Discussion/action
2a	Paragraph 3, 2nd sentence: Suggest expand cross-reference to sources of information: ***"Further details of permitted changes are given in Section 3.3-Documents to submit and Section 3.4-Assessment process"***	Valid comment. Change to be implemented
2b	The second footnote asks that already renewed authorisations be renewed one last time under the new legal framework. We believe that this provision should not be applied retrospectively to already renewed marketing authorisations (unless there are justified pharmacovigilance grounds) as the risk benefit assessment should be done continuously by the applicant (and the agency) independently from a renewal."	This footnote is based on the legal position of the European Commission.

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. 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.

Ref.	Comments/Issue	Discussion/action
3	Should the MAH submit the renewal application to the EMEA and to the Rapporteur and / or to all CMS at the same time (Distribution-list)?	The renewal application should be submitted to EMEA and (Co-)Rapporteur at the same time. Copies for all other CHMP members are sent upon validation. Such practical details are included in the EMEA Post-Authorisation Guidance (PAG) document. A cross-reference to the PAG could however be included in section 3.3.
4	Will in future the timetable be published by the CHMP Table of Decision or how will the Rapporteur get the information about "Start of the procedure"?	Information on renewals start of the procedure is currently given in the annex B of the CHMP Agenda. It could however be considered to provide a quarterly update of the expected workload by means of a listing/report from SIAMED, in order to facilitate work planning by the (Co-)Rapporteur (action for CIG).
5	How long is the time between the submission and the start of the procedure (timeframe for validation at the EMEA)?	Fixed dates for submission of the application and start of procedure are published on the EMEA

		website.
6	The late publication of this document and no reference to a transitional period may have an impact on products for which the marketing authorisation should be renewed between 30th October 2005 and May 2006. Companies need the time to refine their internal procedures taking into consideration the new time lines, therefore it would be practical to introduce a transition period so that the 6-month period for the submission of renewal application is applicable only applicable for marketing authorisations with a renewal date from 1st June 2006 i.e. submission by 1st November 2005. Although a submission 6 months before the expiry date will impact on preparation of PSURs, it is reassuring to see that the authorities will be 'flexible' concerning the documentation to be submitted	Not feasible for legal reasons. EMEA has held pre-submission discussions/ meetings with MAH for upcoming renewal submissions and informed them of the draft requirements before the guideline was released.

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.

Ref.	Comments/Issue	Discussion/action
7a	First paragraph: Reference is made to the recommended submission dates published on the EMEA website. These dates are located under CHMP meetings. This is not necessarily the obvious place where to look for this information. A locator (on the website home page) would be helpful. Suggest additional text be included to recommend that applicants consider holding a pre-renewal submission meeting with EMEA (rapporteurs) to facilitate the process/review. This would be helpful generally for all MA renewals but this should be recommended when the MAH plans to propose changes to the SPC.	Valid comment. CIG to consider making the submission dates table more prominent and easier to find on the EMEA website. A direct link to the submission dates table is provided in the PAG. Agreed. A sentence advising a pre-renewal submission meeting is included in section 3.1. A meeting in case of SPC changes, is already addressed in section 3.3.
8	Paragraph 3: Suggest inclusion of length of time for EMEA validation or to clarify by how many days before the target CHMP meeting the renewal application should be filed.	Fixed dates for submission of the application and start of procedure are published on the EMEA website
9a	Paragraph 3: The draft guideline proposes an increase in the overall duration of the renewal procedure from 90 to 120 days. It allows for an extra 5 days for the preparation of the Rapporteur's Assessment Report (AR), an extra 5 days for the preparation of the joint AR, and to incorporate an extra step of 20 days to enable CHMP members to comment prior to the CHMP discussion on day 90. However, following adoption of the list of questions at day 90, the MAH has only 10 days to respond to the list of outstanding questions and to send them to the Rapporteur, Co-Rapporteur, CHMP and EMEA. This short response time frame can pose difficulties for Companies. In order to partly address this major concern, it is suggested that on Day 60, the EMEA may liaise with marketing authorisation holders to update them on the preparation of the Opinion / draft list of Outstanding issues. **In addition, the response time should be extended** and a possible clock stop of 42 days (30-working days) on top of the 10 days should be allowed.	As stated in the guideline, the company already receives a copy of the AR at day 60, which should provide an indication of any possible questions to be sent to the MAH, and which should allow preparatory work from the MAH in advance of receiving the LoQ at Day 90 (if any). An increased response time for the applicant is not feasible as the Regulation does not foresee a clock-stop in the assessment procedure, and also in view of the expiry of the MA.
9b	The timetable for the renewal procedure is prolonged from 90 to 120 days with this revision. We wonder the reason of this extension of the duration of the procedure as Regulation 726/2004 does not seem to provide a basis for this change.	The proposed 90(120) timetable is based on the fact that there is now only one renewal, and that sufficient time should be available for the R/B re-assessment. This is also compatible with a submission requirement of 6-months before expiry of the MA.

10	Penultimate paragraph: We assume that the review date referred to in text when *"remaining outstanding issues are identified, including serious risk to public health concerns."* – is day 120, however this should be clarified.	No, this refers to Day 90. This will be clarified and cross-referenced.
11	Last paragraph: Suggest further clarification is needed regarding what period of time for submission by MAH /review by CHMP is required; also when this is to occur i.e. Day 120? Is the review date referred to in the text when "remaining outstanding issues are identified" day 90 or day 120?	See 10.
12	***New paragraph:*** A 6th paragraph should be added to **confirm that if the assessment period extends beyond the renewal date, the Marketing Authorisation will remain valid until such time as an Opinion is issued and adopted by the Commission.**	This paragraph of the current guideline was removed following EC comments. From experience, however, the product can remain on the market whilst the renewal decision is awaited. The renewal decision will be valid as of expiry of the MA = bridging the "gap" (if any).

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.

Ref.	Comments/Issue	Discussion/action
13	Paragraph 3: Suggest text relating to EMEA pre-submission meeting should be promoted ahead of existing 2nd paragraph in order that this precedes the detailed content of how product information proposals should be presented. Cross-reference to earlier citation of EMEA meeting should also be made (suggested comment for section 3.2).	Valid comment, will be implemented.
14	Paragraph 4: It would be helpful to suggest a preferable time for pre-renewal submission meeting.	See section 3.1 – new sentence introduced recommending a PSM 10 to 12 months before expiry of the MA.

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. ~~. The Addendum Report should supplement the most recently completed PSUR and should cover a period of less than 6 months when a 6 month reporting cycle applies and should cover a period of less than 1 year in the case yearly or longer period PSURs apply.~~

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~~es~~ not provide an in depth-analysis of the additional cases ~~included in the PSUR addendum report~~, 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.

Ref.	Comments/Issue	Discussion/action
15	In order to be consistent with the recommendations as agreed by the PhWP in the revised Volume 9, we propose to add also the need to provide the information containing in the PSUR Summary bridging Report as a stand-alone document or in the clinical Overview. After the paragraph (*) we propose the following statement: ***This data should be completed by:*** - ***A PSUR Summary Bridging report, bridging all PSURs (even those already submitted) covering the period of 4 years and 4 months,*** ***or*** - ***The information of the PSUR Summary report included in the Clinical Overview***	CHMP confirmed their agreement with the current wording and the proposed cross-references to Volume 9 and ICH E2C.
16	Paragraph 8: It would be helpful to confirm or clarify the following: - Paragraph 8 provides that a bridging summary is only required when the MAH submits 2 or more PSURs, therefore it is our understanding that when one PSUR + PSUR addendum report are submitted, no bridging summary is needed. When the period to be covered falls within the usual PSUR reporting cycle in force under current legislation (i.e. initially 4 x 6 months, followed by 3 x 1 year PSURs under current legislation), no bridging summary will be needed.	Yes, this is in line with EMEA/CHMP understanding. See also comment 15 and revised text proposal.
17	Paragraph 5: PSUR data for inclusion with the renewal – clarification would be appreciated in this paragraph. Currently interpretation is not absolutely clear as to when each of the options ((1) PSUR; (2) PSUR + PSUR Addendum report or (3) PSUR Addendum report) would be filed, in particular (3)).	Proposal to clarify text (see text above). Each situation will have to be considered on a case-by-case basis depending on the MAH's PSUR cycle and renewal date. EMEA experience so far does not indicate any difficulties in applying the different options given.
18	Paragraph 5: ICH E2C issued by EMEA on 20 Feb 2003 provides that "when the additional period is less than 3 months for a 6-month or annual PSUR, or 6 months for a longer duration PSUR, line listings and/or summary tabulations covering the additional period with comment on whether the data reveal a new and important risk" are sufficient. "An addendum report is required when the additional period is greater than 3 months for a 6-month or annual PSUR, or 6 months for a longer duration PSUR". This option, (submission of line listings + comment only) is not addressed in the new guideline	See revised text proposal + see also 17.

19	Paragraphs 1 & 9 : The draft guideline makes reference to Volume 9 of the Rules Governing Medicinal Products, which we understand is also undergoing revision and will be released for consultation shortly. The following comments concerning PSURs are therefore based on the assumption that industry additional detail will be provided in Volume 9 upon which interested parties will have an opportunity to comment.	Yes, EFPIA will have an opportunity to comment on the updated Volume 9.

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 intention is that the clinical expert takes responsibility in the renewal application for the continued availability of the product on the market.~~ The expert should ensure that the updated 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 ~~ration~~ ratio of the product concerned.

Ref.	Comments/Issue	Discussion/action
20	Paragraph 2: Regarding requirement for a non-clinical expert statement within the clinical expert statement, where appropriate, it may be optimal to have a stand-alone non-clinical expert statement. This may be particularly appropriate in scenarios where there have been a significant number of non-clinical & clinical studies completed post authorisation which become available and where the MAH may not be considering a variation submission. If such a non-clinical expert statement is appropriate, it should be provided as a separate statement in Module 2.4 and signed by an appropriate non-clinical expert. The clinical expert statement would then only refer to the non-clinical expert statement.	Agreed. In case non-clinical data are to be discussed, a separate statement is preferable.
21	A Non clinical Expert Statement should be separated, if necessary	See 20
22	The risk management plan will be part of the dossier of the MA. In this context, we consider important that an update of actions ongoing or finalised within the risk management plan should be submitted with the renewal application.	The draft guideline on Risk Management (section 4.13) requires any new information on the RMP to be provided as part of the PSURs (unless other requirements have been laid down as a condition of the MA).
23	Paragraph 4: It is not possible to ask the clinical expert to take responsibility in the renewal application for the **continued availability** of the product on the market. This is legally the responsibility of the marketing authorisation holder (Directive 2001/83/EC as amended by Directive 2004/27/EC, Article 81, second paragraph). Consequently the second sentence of paragraph 4 reading "The intention is that the clinical experts takes responsibility in the renewal application for the continued availability of product on the market" **should be deleted**	Valid comment, sentence to be deleted.
24	Paragraph 5: Typo: replace "ration" by ratio	Done

~~Updating of Quality –~~ 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. ~~and, if different~~ 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.

Ref.	Comments/Issue	Discussion/action
25	"Updating of Quality" should be deleted (same headline as section "Clinical Expert Statement)	Valid comment, wording to be deleted.
26	Paragraph 4,1st sentence: Suggest clarification is needed regarding "needs only to inform competent authorities should a problem arise together with…"	Comment unclear.
27	Paragraph 4, last sentence: Suggest inserting the term "Competent Authority" as follows: "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 ***Competent Authority*** GMP inspections carried out indicating the date, inspection team and outcome."	Invalid comment as it applies to any GMP inspection not only by EEA competent authorities.
28	Paragraph 5: The new requirement for QP statement(s) on the GMP compliance of active substance manufacturer(s) requires clarification. If the manufacturing sites that use the active substance as starting material are located outside the EEA, they may not have a QP, and would therefore not be able to provide a QP statement: in such cases, only a statement from the QP of the manufacturing authorisation holder responsible for batch release in the EEA would be available. This paragraph, and the requirement in Annex 2, should be amended accordingly.	Agreed. The intention of this statement was not to refer to manufacturing sites outside the EMEA. As this appears not to be clear, the sentence will be reworded. To be clarified in the text as follows: […] listed in the application as responsible for batch release. In addition, such declaration should also be provided for Manufacturing Authorisation Holder (i.e. located within the EEA) where the active substance……

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[3].

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.

Ref.	Comments/Issue	Discussion/action

[3] 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.

29a	In this section it is not clear differentiated, on what time at the procedure (before or after) what kind of information should be provided. Furthermore it is unclear in which cases the MAH should file a variation -	Unclear comment. The guideline clearly indicates which documents are to be submitted at the start of the procedure (Annex II) and refers to the responses to the LoQ in section 3.2. Decisions on whether proposed changes would rather require a variation etc … are taken on a case-by-case basis as part of pre-submission discussions/meetings with the EMEA.
29b	It would add clarity to the process if it could be stated that it is possible to apply for a variation during the renewal process. From informal discussions with EMEA we understand that this is possible but would like to see this reflected in the guideline.	The guideline does not say that it is not possible. Further information on the handling of variations in parallel with renewal applications is given in the PAG on the EMEA website.
30	The risk management plan will be part of the dossier of the MA. In this context, we consider important that an update of actions ongoing or finalised within the risk management plan should be submitted with the renewal application.	See 22
31	General: There is some inconsistency between "*No updating of Part II/module 3 Quality data at renewal*" (Updating of Quality, first paragraph), the reference to stability in the 4th paragraph which refers to the principles of the type I variation dossier and the statement in the paragraph which reads that "*major changes to the product, such as … extension of shelf life, may not be modified through the renewal procedure."* The second statement could suggest that some minor changes could be performed at renewal. Some clarification would be helpful.	Unclear comment, as minor changes to the product information can indeed be included as part of the renewal, but never any quality-related changes for which a variation is required.
32	Paragraph 1: In order to avoid any misunderstanding regarding the meaning of "*consolidated version of the file*" in this guideline, we suggest referring to paragraph 3.3 and Annex 2 e.g. in stating "*on the basis of a consolidated version of the file per paragraph 3.3 and Annex 2*"	Not agreed, as this sentence is intended to reflect the text of the Regulation. .
33	Paragraph 2, Footnote 3: We are not sure what "*taking into account experience gained* "means. We believe that detailed guidance on the criteria or factors considered by CHMP when requiring one additional five-year renewal needs **not** be released immediately. However it is necessary that objective "breakpoints" for requesting an additional renewal are determined and made known to MAH (they may be refined when experience had been gained) to help ensure consistent standards of assessment for all products are applied. This is especially important because many other provisions contained in the new pharmaceutical legislation are aimed at verifying that the benefit/risk balance for the product is acceptable, e.g. PSUR submission at regular intervals, obligation to update the Marketing Authorisation throughout the life of the product as data emerge, 'authorisation granted under exceptional circumstances' with annual reassessment of the benefit/risk profile, etc. Thus we suggest that "taking into account experience gained" should be deleted from the footnote	Not agreed.

34	Paragraph 4, 1st sentence: We do not see the necessity to add the term "due to the revision of … other relevant guidelines" as the renewal could be seen as a second assessment of the medicinal products based on new criterions after five years. While MAHs must take account of technical and scientific progress and make any variations that may be required to be manufactured and checked by means of generally accepted scientific methods (Article 16(1) of Regulation (EC) No 726/2004 already referred to in 3.3 c) the "Procedure for European Union Guidelines and Related Documents within the Pharmaceutical Legislative Framework" Ref. EMEA/P/24143/2004 which came into operation on 1 September 2005 clearly provides (section 4.10, 4th paragraph) that "guidelines are normally prepared for application prospectively". This procedure further clarifies that "*there may be exceptional situation in relation to risks to public and/or animal health where a guideline would need to be applied to medicinal products already authorised and on the market"*. It adds that "in such circumstances, this would be announced" and that *"a clear statement to this effect will be included in the final published guideline"*. The guideline on renewals could refer to this procedure.	The statement will be clarified by adding "impacting on product information."
35	6th paragraph (bold highlighted text): Clarification is sought relating to the appropriate process for sharing post authorisation study reports (non-clinical and clinical), which become available and where the MAH may not be considering a variation submission. Distinct from the non-clinical statement, which is a required, the renewal submission may not be the most appropriate vehicle for submission/ review of these reports.	Valid comment but it should be covered by a separate guidance, not within this guideline.

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).

Ref.	Comments/Issue	Discussion/action
36	General: Suggest inclusion of Summary of Opinion will be published on EMEA website – this would be consistent with subsequent section with unfavourable opinion.	Not agreed. An announcement on the renewal is included in the CHMP monthly report. In addition, the EPAR will be updated. A SmOP is considered required for unfavourable opinions because of the impact on patients.

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.

Ref.	Comments/Issue	Discussion/action
37	The risk management plan will be part of the dossier of the MA. In this context, we consider important that an update of actions ongoing or finalised within the risk management plan should be submitted with the renewal application.	See 22.

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.

Ref.	Comments/Issue	Discussion/action
38a	2nd paragraph, 2nd sentence: We would like to obtain details on how "therapeutic efficacy" would be assessed. This is relevant since it is anticipated that post-marketing safety will constitute the major part of new clinical based data.	This could be identified from post-marketing information (e.g. increased hyperglycaemia events, reduced immunogenicity …)

38b	Paragraph 2, last sentence: It is not clear whether the "Summary of Opinion" will be published in the scenario that the MAH intends to request re-examination. This should be clarified.	SmOP are always published immediately, not awaiting any re-examination notification. In case an unfavourable opinion becomes a favourable opinion following re-examination, a further SmOP will be published (this is covered in section 3.6.3).

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~~During the evaluation procedure~~, 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 ~~and Icelandic~~ translations will be checked by the Icelandic authorities and the Norwegian ~~and Icelandic~~ 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 ~~appeal~~ 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.

Ref.	Comments/Issue	Discussion/action
39	Paragraph 2, 3rd (last) sentence: Propose to delete "*if necessary*" in the 3rd (last) sentence of this paragraph as we believe that additional new experts usually help the re-assessing issues with a fresh eye. The word "*appeal*" should be replaced by "re-examination" to be consistent with the terminology used in section 3.6	It is up to the Rapporteur to decide whether any additional experts are needed for the assessment. In addition, the MAH may request the consultation of a SAG (see draft Re-examination guideline and CHMP Rules of Procedure). Done

3.6.4 European Public Assessment Report (EPAR)

The EMEA will prepare an update of the EPAR, reflecting the renewal assessment and CHMP opinion. ~~The draft updated EPAR will be circulated to members of the CHMP at a subsequent meeting. Once the CHMP has agreed on the updated text and a~~After the Commission Decision on the renewal ~~has been made~~, the updated EPAR shall be published. ~~made available from the date of the Commission's Decision to renew the marketing authorisation.~~

Ref.	Comments/Issue	Discussion/action
40	Consistent with approach of initial MA approval, we believe that **MAH should have the opportunity to review the draft EPAR at renewal** in order to check that all items of any commercially confidential nature have been deleted. Proposed rewording (insert one sentence):*"3.6.4 European Public Assessment Report (EPAR) The EMEA will prepare an update of the EPAR, reflecting the renewal assessment and CHMP opinion. The draft updated EPAR will be circulated to members of the CHMP at a subsequent meeting. Once the CHMP has agreed on the updated text and after the Commission Decision on the renewal has been made,* ***the draft updated EPAR will be circulated to the MAH for any amendment before the document is finalised by the EMEA and prior to the release of the E.U. Commission decision on the renewal****. The updated EPAR shall be made available from the date of the Commission's Decision to renew the marketing authorisation."*	EPAR updating at renewal is currently a rather minimal, administrative process which does not require any pre-discussion with the MAH. The EPAR paragraph (3.6.4) however needs revision as CHMP is not adopting the revised EPAR (again because of the minimal, administrative nature of the update).

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.

Ref.	Comments/Issue	Discussion/action
41	Day 80 is missing here; it is included in the text referring to this timetable.	Valid comment. Table to be amended accordingly.

ANNEX 2

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)[4] referred to in the application form operate in compliance with the detailed guidelines on good manufacturing practice for starting materials[5].

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 ~~all 21 languages (EU, IS, NO)~~ English should be provided electronically (highlighted~~, as one document per language~~).
~~*Note*: For submission to CHMP members only the relevant language version(s) are to be provided in addition to the English product information~~

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)

[4] 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.

[5] ~~Starting materials manufactured from~~ ~~B~~blood or blood components are excluded from this requirement.

Ref.	Comments/Issue	Discussion/action
42	Paragraph 1: The guideline states that renewal applications "*have to contain a consolidated version of the file, containing at least the documents listed below.*" It is our understanding that the documents listed in Annex 2 comprise the "consolidated version of the file". However, if additional documentation may be required, it would be helpful to clarify very briefly under which exceptional circumstances this would be the case.	This is also EMEA's understanding. The list provides 'minimum' requirements. In the exceptional case where additional documents would be required or are proposed to be submitted by the MAH, this could be discussed at the Pre-submission meeting.
43	1.2, 1st bullet: A requirement to provide a list of all post-authorisation submissions has been added to Annex 2. Such a list, however, is already included within the renewal application form. We see no need to repeat this information, and suggest that this bullet be deleted.	The list was included following a comment from the Commission. It will be removed from the application form in order to avoid duplication.
44	1.2, last bullet: The new requirement for QP statement(s) on the GMP compliance of active substance manufacturer(s) requires clarification. If the manufacturing sites that use the active substance as starting material are located outside the EEA, they may not have a QP, and would therefore not be able to provide a QP statement: in such cases, only a statement from the QP of the of the manufacturing authorisation holder responsible for batch release in the EEA would be available. This bullet, and the requirement in section 3.3, should be amended accordingly.	Text to be amended – see also 28.
45	1.3.1, Paragraph 2, 2nd sentence: *"A full set of Annexes in all 21 languages..."* - Not clear when to submit – clarify if at Day 120, at Adoption of CHMP Opinion?	Following discussions on the revised PIPIT timelines, EMEA proposes to require translations only after adoption of the opinion. Text to be amended accordingly.
46	**1.3.2?** There is no 1.3.2 (skips from 1.3.1 to 1.3.3)	Intentional omission, no mock-ups are required as part of the renewal application.

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 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 ration 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.

Ref.	Comments/Issue	Discussion/action
47	(As per comments in text for 3.3.c) Regarding requirement for a non-clinical expert statement within the clinical expert statement, where appropriate, it may be optimal to have a stand-alone non-clinical expert statement. This may be particularly appropriate in scenarios where there have been a significant number of non-clinical & clinical studies completed post authorisation which become available and where the MAH may not be considering a variation submission. If such a non-clinical expert statement is appropriate, it should be provided as a separate statement in Module 2.4 and signed by an appropriate non-clinical expert. The clinical expert statement would then only refer to the non-clinical expert statement.	See 20
48	Clinical overview: In case there are no pre-clinical changes. Otherwise a separate Pre-Clinical Expert Statement should be provided.	See 20