Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human

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CMDh Best Practice Guide on the processing of renewals in the Mutual Recognition and Decentralised Procedures

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1. Introduction

This Best Practice Guide (BPG) is intended to facilitate the processing of renewals in the mutual recognition and decentralised procedures, with an aim of giving procedural advice to assist Member States and applicants, to ensure a consistent and beneficial approach to renewal.

This Best Practice Guide does not apply to simplified registrations for medicinal products referred to in Articles 14 (homeopathic medicines) and 16a (traditional herbal medicines) of Directive 2001/83/EC. Traditional herbal medicines that have been authorised via the mutual recognition procedure as well as via the decentralised procedure are however covered by this BPG.

2. Legal framework

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

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

3. Principles of submission

3.1. Date for renewal

For products authorised through the decentralised procedure the common renewal date should be proposed by the RMS and is usually set to five years after the end of procedure.

For the mutual recognition procedure, the common renewal date is set by the RMS at the completion of the initial mutual recognition procedure based on the date that the national MA in the RMS was originally granted, or if the MA in the RMS has already been renewed with unlimited validity, five years after the end of procedure date of the MRP. For repeat mutual recognition procedures, so called 'repeat use' procedures, the common renewal date should be the same as the date set after the first procedure (see also section 3.2).

The principle applies that the MAH may apply for a renewal earlier than 5 years, but the period before application may not extend beyond 5 years. Submission therefore will be based on the earliest renewal date in any one Member State, unless the MAH agrees an alternative date with the RMS. In practice, this may mean the period between authorisation and renewal will be less than 5 years in the CMS.

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

In some cases, the first MR procedure or initial granting of the MA may have been concluded more than 5 years before the MR procedure or Repeat Use Procedure (RUP) and the authorisation may have been granted unlimited validity in the RMS and, in the case of RUP, the 'old' CMS. To comply with Article 24(1) of Directive 2001/83/EC, which states that an MA shall be valid for 5 years, any new authorisations granted as a result of mutual recognition will be subject to a renewal procedure. For legislative reasons, the default is that a renewal will be required; however, some MS may accept the previously granted unlimited validity in the RMS and not require a renewal and should confirm this to the RMS before the end of the procedure. In case not all Member States concerned by the procedure have clearly indicated that there is no need for a renewal, a renewal application will be required. The RMS will confirm whether an additional renewal is required, or not, in the end of procedure letter. The RMS will also, in cases where an additional renewal is necessary, communicate a new common renewal date for the next renewal, set five years after the end of procedure date of the MRP/RUP.

In these cases, the renewal application should be submitted only to the RMS and the CMSs where renewal is necessary (i.e. not to the member states where the MA has already been granted unlimited validity).

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

3.3. Extension Applications

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

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

3.4. Following Article 30 and 31(1) Referral Procedures

Following an Article 30 or 31(1) referral procedure the allocated RMS should, taking into consideration the agreed harmonised birth date, agree a common renewal date with the MAH. This date should, wherever possible, be defined as the earliest renewal date in a Member State that allows for submission within 6 months after implementation of the decision from the Commission. If unlimited validity has already been granted in all MS, no common renewal date has to be set and no renewal application has to be submitted.

If unlimited validity of the MA has not been agreed in all the MS, a renewal application is necessary. The renewal application should be submitted to the RMS and the MS(s) where renewal is necessary.

3.5. Date for submission

The applicant submits the renewal application simultaneously to all Member States concerned by the renewal. The renewal should be submitted no later than 9 months before the defined common renewal date and at least 9 months before the marketing authorisation ceases to be valid in the Member States concerned by the renewal.

3.6. Documents to submit

For all marketing authorisations, regardless of the legal basis, the standard renewal application consists of the renewal cover letter and the renewal electronic application form (without annexes) (see section 3.6.1). As the MAH has the obligation to keep the dossier up to date throughout the lifecycle of the medicinal product no submission of the consolidated dossier is expected (see further information on documentation in Annex 3).

It is possible for the Member States to request additional documentation, for national legislative reasons or, in liaison with the RMS, in relation to concerns regarding the benefit/risk balance. See also section 3.7. Member States requesting additional documentation should do so during the validation period. The requirements for full documentation are listed in Annex 3.

Within the standard renewal procedure, no changes to the MA particulars can be made. Only in exceptional cases, with the approval of the reference Member State (RMS) and concerned Member States (CMS), certain changes to the MA particulars may be made within an expanded renewal (see section 3.7), and these changes shall not trigger a variation procedure. However, none of the SmPC changes introduced at renewal should substitute for the MAH obligation to update the MA throughout the life of the product by the appropriate variation procedure as data emerge. The MAH has an obligation to ensure that the product information is kept up to date with current scientific knowledge including the conclusions of assessments and recommendations made publicly available by means of the European medicines web-portal.

3.6.1. Administrative Information

To facilitate the procedure, the application should be accompanied by a cover letter following the CMDh template http://www.hma.eu/562.html.

The cover letter should include confirmation that no new data are available that changes, or would result in a re-evaluation of the benefit/risk balance, and that the product information is up to date with current scientific knowledge (or otherwise a commitment to update the product information by the appropriate variation within 3 months of the finalisation of the renewal should be provided).

The European electronic renewal application form should be completed. The form is available at the eSubmission website: https://esubmission.ema.europa.eu/eaf.

The renewal application form 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.

The MAH is responsible for ensuring that the dossier is kept up to date throughout the life of the product by way of the variation process.

3.6.2. Risk Management Plan (RMP)

No changes to the RMP can be proposed by the MAH within the framework of the renewal procedure. However, when there are adequate and objective reasons not to renew the MA in its existing terms (as assessed within an expanded renewal procedure) and changes are necessary to the RMP arising from the evaluation or other information, the MAH may submit an amended RMP as part of the renewal process to address the concerns raised. This will not initiate a separate variation procedure.

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

By default, no addendums to the clinical, non-clinical or quality overviews have to be submitted with the renewal application.

For full renewal documentation, the addendums should be compiled in accordance with the below:

Addendum to the Clinical Overview/Clinical Expert Statement:

The addendum should consist of a clear conclusive statement from the clinical expert that the product can be safely renewed at the end of the 5-year period for an unlimited period or any action recommended or initiated, for example, recommendation for further review in 5 years-time should be specified and justified. The expert should ensure that the updated benefit/ risk evaluation has been addressed adequately, taking account of the consolidated version of the file and all relevant new information.

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

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

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

Addendum to the Quality Overall Summary/Quality Expert Statement:

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

The addendum should include a declaration of compliance with Article 23 of Directive 2001/83/EC, which obliges MAHs to "…take account of technical and scientific progress and introduce any changes..." The addendum should include confirmation that all changes relating to the quality of the product have been made following applications for variations and that the product conforms to current CHMP quality guidelines where relevant. The currently authorised specifications for the active substance and the finished product and the qualitative and quantitative composition in terms of the active substance(s) and the excipient(s) should also be included.

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

The MAH will continue to monitor the stability of the product in accordance with agreed stability protocols but needs only to inform competent authorities should a problem arise together with a recommended course of action. A certificate of compliance with Good Manufacturing Practice (GMP), which is not older than 3 years, for the manufacturer(s) of the medicinal product listed in the application, should be submitted within the full renewal documentation. (A reference to the Community EudraGMDP database, if available, will suffice.) For manufacturing sites of the medicinal product not located in the EEA or in the territory of an MRA partner, a list should be provided of the most recent GMP inspections carried out indicating the date, inspection team and outcome.

The full renewal documentation should also include declarations by the Qualified Person(s) of the manufacturing authorisation holder(s) listed in the application as responsible for batch release. In addition, such declarations should also be provided for Manufacturing Authorisation Holders, where the active substance is used as a starting material stating that the active substance manufacturer(s) referred to in the application operate in compliance with the detailed guidelines on good manufacturing practice for starting materials.

Addendum to Non-Clinical Overview

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

3.7. Expanded renewal procedure with full documentation

In exceptional cases, due to circumstances surrounding the individual MA, there may be grounds for a more comprehensive renewal evaluation, based on full documentation and with an expanded timetable. These cases should mainly be related to concerns regarding the benefit/risk balance of the medicinal product.

If an additional renewal has been requested on pharmacovigilance grounds after a previous renewal procedure, a renewal application with full documentation is expected from the MAH and the expanded renewal procedure will be followed.

If the RMS is of the opinion that the standard renewal cannot be accepted, the RMS will request full documentation from the MAH (in accordance with Annex 3) during validation and notify the CMS. The renewal procedure will follow the expanded timetable in Annex 2.

If a CMS is of the opinion that the standard renewal cannot be accepted, the CMS will raise the issues identified to the RMS and other CMSs during validation. Provided that the RMS is in agreement that there are grounds to conduct an expanded renewal procedure, full documentation (in accordance with Annex 3) will be requested from the MAH and the renewal procedure will follow the expanded timetable in Annex 2.

4. The Renewal Procedure

4.1. Timetable

Member States have agreed the need for a timetable approach to renewals. By default, the renewal will follow a 30-day procedure with no clock stop. A timetable is given in Annex 1.

After receipt of the application, the RMS will create a case in CTS that includes only the CMS concerned by the application. The RMS will circulate a start e-mail to the (concerned) CMSs, informing about the procedure start and the timetable. CMS may comment on the application at the latest on day 20. Between day 20 and day 30, the RMS will be able to liaise with the MAH to reach an agreement on any necessary amendments to the application or need for future updates to the product information. No assessment report will be circulated. Any conditions imposed on the MA will not be reviewed and cannot be lifted during the standard renewal procedure. The RMS will close the procedure at day 30 with circulation of the End of Procedure letter for renewals to the concerned CMS (clearly stating if any updates to the product information are required through a subsequent variation procedure).

When additional documentation has been requested by a member state in accordance with section 3.6, without raising concerns in accordance with section 3.7, the RMS decides on which timetable to apply.

In the exceptional case that a renewal application with full documentation is requested in accordance with section 3.7 (expanded renewal), the use of a preliminary assessment report as well as a finalised assessment report, and a clock-off period, will allow Member States to give input to the renewal assessment as required and give MAHs the opportunity to resolve issues within the renewal process.

In these cases, a 90-day procedure is followed using the Type II variation model, with the possibility of clock-off for no more than 30 days to allow for the applicant to provide the responses required. In exceptional circumstances only, and with agreement of the RMS, the clock-off period may be extended. A timetable is given in Annex 2. If a deviation from the regular timetable is made during the procedure, this should be communicated by e-mail to alert the CMS.

4.2. Assessment

The assessment approach of the Member States will consist of a benefit/risk balance re-evaluation, based on a consolidated version of the file and confirmation by the MAH that the benefit/risk balance of the medicinal product can still be considered positive. 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.

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

The MAH should update the SmPC, package leaflet and label as necessary throughout the life of the product. In addition, it will be checked during the assessment whether the MAH has complied with obligations to keep the product information up to date in the light of current scientific knowledge taking into account conclusions of assessments and recommendations which are made public on the European medicines web-portal.

If the RMS finds that the MAH did not fulfil these obligations and major changes are required, the SmPC and PL should be updated through the appropriate variation procedure after conclusion of the renewal. The RMS may accept introduction of minor changes during an expanded renewal procedure to avoid additional submissions.

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

- If the product contains a substance listed as subject to additional monitoring;

- If RMP updates are requested that require PRAC agreement;
- If the RMS has proposed a further 5-year renewal based on pharmacovigilance grounds;

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

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

Where there are adequate and objective reasons not to renew the MA in its existing terms and changes are necessary to the product information and/or RMP arising from the evaluation or other information, the MAH may, within an expanded renewal procedure, submit amended product information and/or RMP to address the concerns raised. This will not initiate a separate variation procedure.

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

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

4.3. Outcome of the Renewal Procedure

4.3.1. Unlimited Validity

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

In cases where changes have been made to the product information, the renewal documents issued will include the SmPC, package leaflet and labelling texts as amended.

4.3.2. Further Renewal

In some circumstances, an additional 5-year renewal may be required. This should be determined on pharmacovigilance grounds. In circumstances where, for example, a new indication is granted following the renewal, other pharmacovigilance provisions are available outside the renewal process, for example, increased PSUR frequency or benefit/risk review if needed. Indeed, the MAH can be asked to perform a benefit/risk evaluation at any time. In cases where a further renewal is considered based on pharmacovigilance grounds PRAC advice may be sought.

4.3.3. Non-renewal

Members States will not renew the MA if there are serious public health issues remaining at the time of renewal. The criteria for non-renewal are specified in Article 116 of Directive 2001/83/EC, as amended. These criteria include where the product proves to be harmful in the normal conditions of use, or where its therapeutic efficacy is lacking, or where the benefit/risk balance is not positive under the normal conditions of use, or where its qualitative and quantitative composition is not as declared. Therapeutic efficacy is considered to be lacking when it is established that therapeutic results cannot

be obtained with the medicinal product. Additionally, non-renewal may be considered where the particulars supporting the application for renewal are incorrect or have not been updated, or where any conditions of the marketing authorisation have not been fulfilled, or when the controls on the manufacturing process or on the finished product have not been carried out, or when commitments have not been fulfilled.

Additionally, Member States will consider non-renewal if the MAH fails to respond to the issues raised during assessment within the timescale given and where no adequate justification or explanation is given.

By analogy to the procedure for mutual recognition/decentralised applications, use will be made of the Co-ordination Group for Mutual Recognition and Decentralised – human (CMDh) where Member States have divergent opinions.

In cases where there is a divergent view amongst Member States at the end of the 90-day renewal procedure, by analogy with Articles 28-29 of Directive 2001/83/EC, as amended, there will follow a 60-day referral process to CMDh. If by the new Day 60 CMDh has not achieved a common position, a scientific evaluation of the matter would be undertaken by the Committee for Medicinal Products for Human Use (CHMP). In the case of no agreement in the renewal procedure the formal referral to arbitration should be made by the RMS.

ANNEX 1 – Standard renewal timetable

Starting the procedure

There should be an automatic validation process for starting the procedure. The validation period is 14 calendar days from receipt of the application. The RMS will start the procedure based on the assumption that renewal applications have been submitted to all CMS listed in the application form, i.e. there is no requirement for acknowledgement of receipt from CMS. Positive validation should only be indicated in CTS, not via e-mail. If a CMS has informed the RMS that the application is not valid, the procedure will not be started until that CMS confirms to the RMS that the issues have been resolved and the application is valid.

Day 0	Start of procedure. The concerned CMSs are informed via e-mail of the start of the procedure and the timetable.
Day 20	CMS to advise acceptance/non-acceptance of the application. Between day 20 and 30 agreement should be made on any necessary amendments to the application or need for future updates to the product information via variation.
Day 30[1]	RMS to issue End of Procedure letter.

[1] Allow 30 days for national approval.

ANNEX 2 – Expanded renewal timetable

Starting the procedure

There should be an automatic validation process for starting the procedure. The validation period is 14 calendar days from receipt of the application. The RMS will start the procedure based on the assumption that renewal applications have been submitted to all CMS listed in the application form, i.e. there is no requirement for acknowledgement of receipt from CMS. Positive validation should only be indicated in CTS, not via e-mail. If a CMS has informed the RMS that the application is not valid, the procedure will not be started until that CMS confirms to the RMS that the issues have been resolved and the application is valid.

Day 0	Start of procedure. The concerned CMSs are informed via e-mail of the start of the procedure and the timetable.
Day 40	RMS to circulate preliminary renewal assessment report to CMS The preliminary report may also be circulated to PRAC members if appropriate (see section 4.2).
Day 55	Receive comments from CMS (and PRAC members if appropriate).
Day 59	RMS to send request for supplementary information to MAH and CMS via e-mail (if necessary). Clock-off up to 30 days (opportunity to prolong in exceptional circumstances only with agreement of RMS).
Day 60	RMS to circulate finalised renewal assessment report with draft decision.
Day 80	CMS to advise acceptance/non-acceptance of decision.
Day 90[2]	Issue renewal or refer to CMDh for 60-day referral procedure RMS to issue End of the procedure letter. If the MAH had proposed changes to the SmPC, labelling and package leaflet and/or additional changes had been agreed during the procedure; the RMS checks the highlighted track-change versions, provided by the MAH in electronic format. The RMS circulates the clean and track-change versions with a statement that it has endorsed the changes made to the MAH and CMSs. The clean documents have to be uploaded to CTS for transfer to the MRI Product Index. The MAH will provide the CMSs with the relevant amended translations of the SmPC, labelling and package leaflet within 7 days of the end of procedure.
Within 30 days start referral, Day 0	
New Day 0 – 60	Follow procedure in CMDh SOP Disagreement in Procedures – Referral to CMDh.
New Day 60[2]	Issue renewal or refer to CHMP.

[2] Allow 30 days for national approval.

ANNEX 3 - Renewal documentation

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

By default, the consolidated file may be reduced to a cover letter from the MAH accompanied by an application form (without annexes). The cover letter should include confirmation that no new data are available that changes, or would result in a re-evaluation of, the benefit/risk balance and that the product information is up to date with current scientific knowledge (or otherwise a commitment to update the product information by the appropriate variation within 3-months of the finalisation of the renewal), and a declaration that full documentation is available for submission on request of a CMS.

When requested, the full renewal documentation should be presented as follows in accordance with the appropriate headings and numbering of the EU-CTD format:

Module 1:

1.0 Cover letter

1.1 Comprehensive table of contents

1.2 Renewal Application form with the following annexes:

- List of all authorised product presentations for which renewal is sought, in tabular format;
- Details of contact persons:
  - Qualified person in the EEA for pharmacovigilance;
  - Contact person in the EEA with the overall responsibility for product defects and recalls
  - Contact person for scientific service in the EEA in charge of information about the medicinal product;
- List of EU Member States/Norway/Iceland where the product is on the market and indicating for each country which presentations are marketed and the launch date;
- Chronological list of all post-authorisation submissions since grant of the MA or last renewal: a list of all approved or pending Type IA & Type IA_{IN}, Type IB and Type II variations, Extensions, Art 61(3) Notifications, and PSURs giving the procedure number (where applicable), date of submission, date of approval (if approved) and brief description of the change;
- Chronological list of conditions/post-authorisation commitments submitted since the granting of the MA or the last renewal indicating scope, status, date of submission and date when issue resolved (where applicable);
- A revised list of all remaining conditions (where applicable);
- A 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 EudraGMDP database, if available, will suffice.
- For manufacturing sites of the medicinal product not located in the EEA or in the territory of an MRA partner, a list of the most recent GMP inspections carried out indicating the date, inspection team and outcome.

Module 1:

- In accordance with Article 46(f) of Directive 2001/83/EC manufacturing authorisation holders (i.e. located in the EEA) are required to use as starting materials only active substances which have been manufactured in accordance with the detailed guidelines on good manufacturing practice for starting materials as adopted by the Union. The following declarations are required:
  - A declaration by the Qualified Person (QP) of each of the manufacturing authorisation holders listed in the application form where the active substance is used as a starting material.
  - A declaration by the Qualified Person (QP) of the manufacturing authorisation holder(s) listed in the application as responsible for batch release.

  These declarations should state that all the active substance manufacturer(s)[3] referred to in the application form operate in compliance with the detailed guidelines on good manufacturing practice for starting materials[4].

1.3 Summary of Product Characteristics, Labelling and Package Leaflet
A relevant example of the proposed texts for SmPC, outer and inner labelling and Package Leaflet in English must be provided with any proposed changes (highlighted).

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

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

1.4.2 Information about the Expert – Non-Clinical (incl. signature + CV) – if applicable.

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

1.8.2 Updated Risk Management Plan (if requested by the RMS).

Module 2:

2.3 ***Addendum to the Quality Overall Summary***

The Quality Expert should include a declaration of compliance with Directive 2001/83/EC which obliges the MAH to take account of technical and scientific progress and introduce any changes that may be required to enable the medicinal product to be manufactured and checked by means of generally accepted scientific methods.
The Addendum to the Quality Overall Summary should also include:

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

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

[4] Starting materials manufactured from blood or blood components are excluded from this requirement

Module 2:

2.4 *Addendum to the Non-Clinical Overview*

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

2.5 *Addendum to the Clinical Overview*

The addendum should consist of an expert statement, where the Clinical Expert should:

- Confirm that no new clinical (or pre-clinical data in the absence of a non-clinical overview) are available which changes or results in a new benefit/risk evaluation. Where there are new pre-clinical data, the MAH should submit a non-clinical expert report as appropriate.
- Confirm that the product can be safely renewed at the end of a 5-year period for an unlimited period, or any action recommended or initiated should be specified and justified.
- Confirm that the authorities have been kept informed of any additional data significant for the assessment of the benefit/risk balance of the product concerned.
- Confirm that the product information is up to date with current scientific knowledge including the conclusions of assessments and recommendations made publicly available on the European medicines web-portal.

In cases where the benefit/risk balance of the medicinal product is questioned by the member states, additional clinical documentation can be required. The addendum should in such cases contain a critical discussion addressing the current benefit/risk balance for the product based on the consolidated version of safety/efficacy data accumulated since the granting of the initial MA or the last renewal, taking account of PSUR data (if applicable), suspected adverse reaction reports, additional pharmacovigilance activities and the effectiveness of risk minimisation measures contained in the RMP. In addition, it should make reference to any relevant new information in the public domain e.g. literature references, clinical trials and clinical experience, new treatments available, which may change the benefit/risk evaluation made at the time of the original authorisation or last renewal.