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Patient Health Protection

European Medicines Agency post-authorisation procedural advice for users of the centralised procedure

This integrated version has been created for printing purposes only. Please refer to the individual question & answers as published in the post-authorisation guidance for access to the hyperlinked information.

Questions and answers are being updated continuously, and will be marked by "NEW" or "Rev." with the relevant date upon publication.

This guidance document addresses a number of questions which marketing authorisation holders (MAHs) may have on post-authorisation procedures. It provides an overview of the Agency's position on issues, which are typically addressed in discussions or meetings with MAHs in the post-authorisation phase.

It will be updated regularly to reflect new developments, to include guidance on further post-authorisation procedures and to reflect the implementation of the new European legislation. Revised topics will be marked by “New” or “Rev” upon publication.

The Agency emphasises the importance of pre-submission meetings between MAHs and the EMA/(Co-) Rapporteur. The product team is available to address any questions MAHs may have regarding a particular upcoming post-authorisation applications. Where appropriate, a pre-submission meeting could be organised at the Agency in order to obtain further procedural and regulatory/legal advice.

This guidance information and fruitful pre-submission dialogue between MAHs and the Agency should enable MAHs to submit applications, which are in conformity with the legal and regulatory requirements and which can be validated and processed promptly.

In addition, MAHs are strongly recommended to inform the Agency and (Co-) Rapporteur of all upcoming post-authorisation submissions for the following 6-12 months, in order to allow optimal planning, identification of procedural issues and handling of overlapping applications.

Note:

It should be highlighted that this document has been produced for guidance only and should be read in conjunction with "The Rules governing Medicinal Products in the European Union, Volume 2, Notice to Applicants".
MAHs must in all cases comply with the requirements of EU Legislation. Provisions, which extend to Iceland, Liechtenstein and Norway by virtue of the EEA agreement, are outlined in the relevant sections of the text.
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1. Type IA Variations

1.1. When shall I submit my Type IA/IAIN variation(s)?

Commission Regulation (EC) No 1234/2008 (‘the Variations Regulation’) and the "Commission guideline on the details of the various categories of variations" (‘the Classification Guideline’) set-out a list of changes to be considered as Type IA variations. Such minor variations have only a minimal impact or no impact at all, on the quality, safety or efficacy of the medicinal product, and do not require prior approval before implementation ("Do and Tell" procedure). The Classification Guideline clarifies the conditions which must be met in order for a change to be considered a Type IA variation.

Such minor variations are classified in two subcategories, which impact on their submission:

Type IA variations requiring immediate notification (‘IAIN’)

The Classification Guideline specifies which Type IA variations must be notified (submitted) immediately to the National Competent Authorities/European Medicines Agency (‘the Agency’) following implementation, in order to ensure the continuous supervision of the medicinal product.

Type IA variations NOT requiring immediate notification (‘IA’)

Variations which do not require immediate notification may be submitted by the marketing authorisation holder (MAH) within 12 months after implementation, or may be submitted earlier should this facilitate dossier life-cycle maintenance or when necessary e.g. to ensure that the latest product information is reflected in Certificates of Pharmaceutical Products.

The 12 months deadline to notify minor variations of Type IA allows for an ‘annual reporting’ for these variations, where a MAH submits several minor variations of Type IA which have been implemented during the previous twelve months.

Most of these Type IA variations do not impact on the product information. However, in case of an upcoming submission of a variation, extension or other regulatory procedure which will affect the product information, the MAH should also include any Type IA change(s) affecting the product information, in order to keep the product information up-to-date and to facilitate document management.

There are no recommended submission dates for Type IA. However, MAHs are encouraged to avoid submitting Type IA notifications shortly before or during the Agency holiday periods (e.g. end July and Christmas).

Meaning of “implementation” for Type IA variations

For quality changes, implementation is when the Company makes the change in its own Quality System.
This interpretation allows companies to manufacture conformance batches and generate any needed stability studies to support a Type IA_{IN} variation before making an immediate notification\(^1\) because the change will not be made in their own Quality System until these data are available.

For changes to the pharmacovigilance system (DDPS), `implementation` is when the Company makes the change in its DDPS (i.e. when it internally approves the DDPS incorporating the changes).

For product information, it is when the Company internally approves the revised product information. The revised product information will then be used in the next packaging run.

1.2. Can I group the submission of Type IA/IA_{IN} variations? Can they be grouped with other types of variations? Rev. Feb 2013

Article 7(2)(a) of the Variations Regulation sets out the possibility for a MAH to group several Type IA/IA_{IN} variations under a single notification to the same relevant authority, or to group them with other types of variations.

Possible grouping of Type IA/IA_{IN} changes only:

- Several Type IA or IA_{IN} affecting one medicinal product.
- This means for instance that a Type IA variation, which is normally not subject to immediate notification, can be included in the submission of a Type IA_{IN} variation.
- One Type IA or IA_{IN} affecting several medicinal products from the same MAH.

Possible grouping of Type IA/IA_{IN} with other types of variations:

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\(^1\) For example the type IA\(_{IN}\) for addition, deletion or replacement of components in the flavouring or colouring system requires stability data on at least two pilot scale or industrial scale batches.
Type IA/IAIN can also be grouped with other variations (e.g. Type IB, Type II, Extension, as listed in Annex III of Commission Regulation 1234/2008. Groupings not included in the aforesaid Annex should be discussed and agreed with the PTM/PTL prior to submission.

Such grouped submissions will follow the review procedure of the highest variation in the group. Please also refer to “What type of variations can be grouped?”.

It must be noted however, that when submitting Type IA/IAIN variations as part of a group, the legal deadlines for submission of each variation should be respected i.e. a Type IAIn should always be submitted immediately, whether or not it is grouped with other variations, and any Type IA variation should always be submitted within 12 months following its implementation.

1.3. Is the (Co-) Rapporteur involved in the review of Type IA/IAIN Variations Rev Oct 2010

The Agency will review the notification within 30 days following receipt, without involvement of the Rapporteur or Co-Rapporteur.

However, a copy of the complete Type IA/IAIn notification must be submitted to the Rapporteur (See also “How shall I present and submit my Type IA/IAIn Variation”).

The same principle applies whether a single or a group of Type IA/IAIn variations is being submitted. However, if the Type IA/IAIn Variations are grouped with other variations (Type IB, Type II, Extension), the grouped submission will follow the review procedure and timelines of the highest variation in the group and the Rapporteur will provide an assessment report for the group. Although the Rapporteur is not expected to assess the Type IA/IAIn variations in the group the Rapporteur will confirm in the assessment report whether non-acceptance of (part of) the change(s) in the group leads to non-acceptance of the Type IA/IAIn changes in the group.

1.4. How shall I present and submit my Type IA/IAIn Variation(s)? Rev. March 2013

A Type IA/IAIN variation notification should contain the elements listed in Annex IV of the Variations Regulation and should be presented in accordance with the appropriate headings and numbering of the EU-CTD format. The Commission “Guideline on the operation of the procedures laid down in Chapters II, III and IV of Commission Regulation (EC) No 1234/2008” (”the Procedural Guideline”) further specifies which elements should be included in a Type IA/IAIN variation notification.

In order to help MAHs ensuring that their Type IA/IAIN variations are complete and correct before submitting them to the Agency, it is strongly recommended to use the pre-notification checklist before submission of any Type IA or Type IAIN variation.

Type IA variations are intended to provide for a simple, rapid and efficient procedure for minor changes. The MAH should be aware that the submission of redundant information or a confusing dossier presentation will not facilitate such procedures. Similarly, deficient and missing documentation can lead to rejection of the variation. However, in exceptional cases the Agency may issue a request for supplementary information, for which a response should be provided within 4 working days in the mandatory eCTD format for electronic submissions. Failure to provide the requested information, or submission of incomplete and/or unsatisfactory responses within 4 working days may lead to an unfavourable outcome.
The following elements should be included in a Type IA/IA\textsubscript{IN} variation notification, as specified in the Procedural Guideline:

- Cover letter (for groupings, include a short overview of the nature of the changes). The cover letter should contain the template table to facilitate submission and registration.

- The completed electronic EU variation application form (eAF) or the application form (as published on the Commission’s website in Volume 2C of the Notice to applicants), including the details of the marketing authorisation(s) concerned, as well as a description of all variations submitted together with their date of implementation. The EMA strongly recommends the use of the equivalent Electronic Application Form that is using structured data. Where a variation leads to or is the consequence of other variations, a description of the relation between these variations should be provided in the appropriate section of the application form.

- MAHs are reminded that the variation application form should be signed by the official contact person as specified in section 2.4.3 of Part IA/Module 1. Should the official contact person not be available, an official letter of authorisation confirming the delegation of signature to a different person should be enclosed. For a grouping affecting several medicinal products, MAHs are reminded to confirm in the application form under "Declaration of the applicant" that the MAs concerned belong to the same MAH and that the main signatory confirms authorisation to sign on behalf of the designated contacts.

- Reference to the part of the Classification guideline, indicating that all conditions and documentation requirements are met, or reference to the published Article 5 Recommendation, if applicable, used for the relevant application. Applicable conditions and documentation should be clearly ticked on the extract provided, or marked as n/a. if that is the case. If a condition and or documentation is n/a. a justification for its absence should be provided.

- Relevant documentation in support of the proposed variation, including all documentation as specified in the Commission Classification Guideline.

- If applicable, the revised summary of product characteristics (SmPC or Annex I), annex II, labelling (Annex IIIA) and/or package leaflet (Annex IIIB) as a full set of annexes. If the change applied for affects Annex A, this should be provided as a separate set of one document per EU language. (See also 10. When do I have to submit revised product information? In all languages?) Additional information on how to comply with this in a required technical format can be found in the TIGes Harmonised Guidance.

- Where the overall design and readability of the outer and immediate packaging and/or package leaflet is affected, the need for the provision of mock-ups or specimens should be discussed with the Agency Medical Information Sector on a case-by-case basis.

**Grouped Type IA/IA\textsubscript{IN} variations**

For grouped Type IA/IA\textsubscript{IN} variations concerning one marketing authorisation, all Type IA variations must be declared in the variation application form. The supportive documentation for all variations concerned should be submitted as one integrated package (i.e. there is no need to submit a separate documentation package for each variation). However, the present-proposed section of the application form should clearly identify the relevant CTD sections in support of each variation.

For a (group of) Type IA/IA\textsubscript{IN} variation(s) concerning several marketing authorisations, one eCTD sequence per medicinal product should be submitted. This will include a common cover letter and common application form referring to all medicinal products and variations concerned. In addition, for each medicinal product the relevant supportive documentation and revised product information (if
applicable) should be provided, in order to allow the Agency to update the dossier of each marketing
authorisation with the relevant updated/new information. Cross-references to any documentation
submitted for another medicinal product can therefore not be accepted. For further details, please refer
to "How shall I present a grouped variations application?" and to TIGes Harmonised Guidance.

It should be noted that the responsibility for the quality of the submitted documentation lies with the
MAH and is crucial to the overall process. The MAH is responsible for ensuring that the Type IA
variation complies fully with the conditions and documentation requirements as specified in the
Classification guideline.

For more detailed queries on technical matters please contact the PA-BUS department (PA-
BUS@ema.europa.eu). For procedural matters related to a Type IA/ IAIN Variation for a specific
product and in order to avoid rejection, please contact the relevant Product Team Member for your
product in the Quality Sector.

Submission of Type IA/ IAIN Variation Notifications

The EMA strongly recommends using the eSubmission Gateway or the eSubmission Web Client as the
preferred submission method for all eCTD submissions. More information on how to register and
connect to the Gateway / Web Client can be found in the eSubmission website and detailed information
on the required naming conventions and file formats can be found in the eSubmission Gateway Q&A
document and the Web Client Q&A. Applicants must not send duplicate submissions electronically or
via CD-ROM or DVD as this might lead to delays in the handling of applications.

Applications that are sent using the eSubmission Gateway and eSubmission Web Client will receive an
automated ‘acknowledgement’, confirming whether the submission has passed the relevant technical
validation criteria and whether it has been uploaded to the agency’s review tool. There is no need to
send any separate paper cover letters for these submissions, as the cover letter will be in the relevant
part of eCTD module 1 in PDF format.

MAHs not yet using the eSubmission Gateway or the Web Client solution should send their Type IA/
IAIN variation notifications as CD-ROM or DVD to the attention of the Product and Application Business
Support (PA-BUS) at the following address:

Product and Application Business Support (PA-BUS)
European Medicines Agency
Loading Dock
Ontario Way
Canary Wharf
UK - London, E14 4HB

Only one CD-ROM or DVD of the Variation Notification presented in eCTD format should be submitted
to the Agency, together with one original, signed paper cover letter when using this format of
submission. The Product Team Leader should be indicated in copy “cc” on the cover letter (no
additional copy needed).

Where applicable, revised product information Annexes (including Annex A, if applicable) should be
included in electronic (Word and PDF) format (see also Type IA variations - “When do I have to submit
revised product information? In all languages?”) in the same eSubmission Gateway and eSubmission
Web Client package or CD-ROM or DVD within a folder called ‘working documents’.

One electronic copy should also be sent to the CHMP (Co-) Rapporteur and other CHMP members at
the time of submission (for information) to maintain the life cycle of the eCTD dossier. It is essential
that identical eCTD sequences are circulated to Committee Members. Any minor changes that affect the "md5 checksum" will lead to inconsistency and possibly result in future technical invalidity.

It is essential that identical eCTD sequences are circulated to Committee Members. Any minor changes that affect the "md5 checksum" will lead to inconsistency and possibly result in future technical invalidity.

Where applications are amended during the agency’s review, such as e.g. responses to a request for supplementary information or a withdrawal, new or consolidated eCTD sequence should be provided in order to maintain the eCTD life-cycle. The same applies in case the outcome of the variation application review is unfavourable for one or more changes applied for (mixed outcome). Please refer to the TIGes Harmonised Guidance and to the Question and Answer document under the New Variation Regulation and eCTD for specific advice.

For a full overview of dossier requirements for National Competent Authorities of CHMP (Co-)Rapporteur and Committee members, including delivery addresses, please refer to the following document: Dossier requirements for Centrally Authorised Products (CAPs).

Please note that the EMA only accepts submissions made in a mandatory eCTD format.

For practical aspects of eCTD dossier submission under the Variation Regulation (EC) No 1234/2008, please refer to the ‘Q&A - eCTD Variations’ published on the Agency e-submission website and to the TIGes Harmonised Guidance for eCTD Submissions in the EU.

Information on the electronic Application Form for variations can be found in the eSubmissions eAF webpage.

References

• Commission Regulation (EC) No 1234/2008
• Electronic Variation application form / Variation application form, The Rules governing Medicinal Products in the European Union, Notice to Applicants, Volume 2C
• Pre-notification checklist for Type IA variations
• Template for cover letter
• Dossier requirements for Centrally Authorised Products (CAPs)
• Classification Guideline
• Article 5 Recommendation
• TIGes Harmonised Guidance for eCTD Submissions in the EUeSubmission webpage
• eSubmission website
• eSubmission Gateway Q&A
• eSubmission Gateway Web Client Q&A

1.5. How shall my Type IA/ IA_in variation be handled (timetable)? Rev Oct 2012

The Agency will review the (grouped) Type IA/ IA_in variation(s) within 30 calendar days following receipt. The Agency will check the correctness of the application form, the presence of the required
documentation and compliance with the required conditions, in accordance with the Classification guideline.

Receipt of Type IA/ IAIN variation notification Day 0
Start of Agency check Day 1
Favourable/Unfavourable review outcome by Day 30

By day 30, the Agency will inform by Eudralink the MAH about the outcome of the review.

Where the outcome of the procedure is favourable and the Commission Decision granting the Marketing Authorisation requires amendments, the Agency will inform the Commission accordingly.

Where one or several Type IA/ IAIN variations are submitted as part of one notification, the Agency will clearly inform the MAH about which variation(s) have been accepted or rejected following its review.

Type IA/ IAIN changes can be implemented prior to submission of the notification. However, in case of unfavourable outcome, the Variations Regulation requires the MAH to immediately cease applying the rejected variation(s). Please refer to “What should I do in case of an unfavourable review outcome for my type IA/ IAIN variation?” for further details.

It is still possible for MAHs to submit Type IA notifications prior to its implementation, particularly when the proposed changes are related to other notifications/variations requiring prior approval.

### 1.6. Can my Type IA/ IAIN be part of worksharing? Rev Oct 2010

In accordance with the provisions of Article 20 of the Variations Regulation, the worksharing procedure does not apply to Type IA/ IAIN variations.

However, the submission of one or several Type IA/ IAIN variations affecting more than one marketing authorisation of the same MAH, in one notification to the same relevant authority (similar to worksharing) is possible under Article 7(2) of the Regulation – see also “Can I group the submission of Type IA/ IAIN variations? Can they be grouped with other types of variations?”

In addition, it is also possible to group a Type IA/ IAIN variation(s) with a Type IB or Type II variation, which is submitted for a worksharing procedure. In such case, the Rapporteur will be asked to confirm whether the non-acceptance of (part of) the change(s) leads to non-acceptance of Type IA/IAIN in the group.

### 1.7. What should I do in case of an unfavourable outcome for my Type IA/ IAIN variation(s)? Rev Feb 2013

A Type IA/ IAIN variation will be rejected when:

- The classification of the proposed change(s) in incorrect
- not all of the conditions for the Type IA/ IAIN variation are met
- the submitted documentation as required by the Classification Guideline is deficient or inaccurate, including provision of the product information Annexes and Annex A, if affected by the change(s) applied for.

In such case, the MAH shall immediately cease to apply the rejected changes.
In the case of a negative outcome of a Type IA application because the conditions for Type IA variation(s) are not met and consequently a resubmission (as a Type IB, Type II variation or Extension) is needed or because documentation is deficient, it is the MAH responsibility to judge whether the rejected Type IA variation has an impact on the quality, safety or efficacy of the medicinal product. If this is the case, the MAH has to take appropriate action.

The Agency may ask the MAH to complete a suspected quality defect notification form and provide a Risk Assessment report on the impact of the product on the market via e-mail to qdefect@ema.europa.eu within 7 calendar days from the date of the rejection letter. Such requests are expected to be very exceptional. The MAH has to follow the instructions under Notifying Quality Defects or Product Recalls.

**1.8. What fee do I have to pay for a Type IA/ IA\textsubscript{IN} variation? Rev Feb 2013**

For information on the fee applicable for Type IA/ IA\textsubscript{IN} variations, please refer to the explanatory note on fees payable to the European Medicines Agency. Such fee covers all authorised strengths, pharmaceutical forms and presentations of a given medicinal product.

For variations introducing additional presentation(s)/pack-size(s), each additional presentation/pack-size attracts separate fees (‘x’ additional presentations = ‘x’ separate fees). Each presentation/pack-size should therefore be declared as a separate variation on the variation application form under the section ‘Variations included in this application’.

Grouped Type IA/ IA\textsubscript{IN} variations, whether consequential or not, will each attract a separate Type IA fee.

The fee will become due on the date of receipt of Type IA/ IA\textsubscript{IN} variation notification and fees will be payable within 45 calendar days of the date of the said notification. After approximately 15 days an invoice will be sent to the applicants billing address held on the Agency’s file.

The invoice will contain details of the product and type of procedure involved, the fee amount, the customer purchase order number associated with the procedures invoiced and financial information.

Applicants requiring a purchase order number or similar references on the invoice are requested to clearly indicate it on the cover letter or application for accompanying the dossier. The Agency does not accept stand-alone notifications of purchase order numbers that are not associated with a dossier. Applicants not requiring a purchase order number on the invoice should also clearly state this in the cover letter. Applicants are requested to provide this information in the cover letter template.

The Agency will charge the fee for type IA variations or grouped type IA variations at the start of the procedure, irrespective of its outcome (positive, negative or partial/full withdrawal).

Type IA variations which are grouped with other type of variations/extensions or which are part of worksharing procedure will continue to be charged on conclusion of the validation of the application.

Guidance on how to pay an invoice can be found on our website.

**References**

- Explanatory note on fees payable to the European Medicines Agency
1.9. Do I have to submit mock-ups and specimens? Rev Apr 2012

Mock-ups
In case the Type IA/ IAIN variation affects labelling and/or package leaflet, no mock-ups are required to be provided with the notification.

Specimens
Where the overall design and readability of the outer and immediate packaging and/or package leaflet is affected, the need for the provision of specimens should be discussed with the Agency Medical Information Sector on a case-by-case basis (e.g. specimens would be required when proposing a new container type or a new pack size smaller than the current approved range, but not e.g. when only limited new text is added in a leaflet section). In case specimens are required, in principle only one relevant example (multi-lingual if possible) would need to be sent to the Agency at the latest 15 working days before marketing. However, depending on the nature and extent of the change(s) concerned, additional specimens may be required by the Agency. The Agency will perform a general check from the viewpoint of readability within 15 working days, and will check if any previous comments on specimens have been duly implemented. The applicant will be informed about the outcome of the check.

Note:
In case the MAH wishes to receive feedback from the Agency on their proposed new packaging in advance of the specimen review, the Agency could agree with the MAH, on a case-by-case basis, to review draft mock-ups before specimen submission.

The above principles also apply to mock-ups for Iceland. The mock-ups should be sent by e-mail to mockups@ima.is. See also http://www.imca.is/IMCA/News.nr/1263

No mock-ups and specimens are required for Norway.

References
- The Revised Checking Process of Mock-Ups and Specimens of outer/immediate labelling and package leaflets of human medicinal products in the Centralised Procedure (EMEA/305821/2006)

1.10. How to obtain new EU sub-numbers for Type IAIN variation concerning an additional presentation (e.g. new pack-size)? Rev Feb 2013

In the specific case of a Type IAIN Variation for an additional presentation, the new EU marketing authorisation sub-number should be requested from the Agency before implementation.

The request should be sent together with a draft Annex A (in English only) to the Procedural office (H-QM-PRO@ema.europa.eu) with a copy to the product shared mailbox and should be made at least 5 working days in advance of the intended submission of the variation. Once a number has been allocated, this number should subsequently be included in the Annex A and product information annexes submitted together with the Variation notification.
1.11. When do I have to submit revised product information? In all languages? Rev Feb 2013

In case the Type IA/IAIN notification affects any of the annexes, i.e. annex A, SPC, annex II, labelling and/or package leaflet, the affected revised product information Annexes must be submitted as follows:

- All EU language versions: complete set of Annexes electronically only in Word format (highlighted) and in PDF (clean)

The ‘complete set of Annexes’ includes Annex A (if applicable), I, II, IIIA and IIIB i.e. all authorised presentations (if applicable), SmPC, labelling and PL texts for all strengths and pharmaceutical forms of the product concerned, as well as Annex II. The complete set of Annexes must be presented sequentially (i.e. Annex I, II, IIIA, IIIB) as one document for each official EU language. Page numbering should start with "1" (bottom, centre) on the title page of Annex I. If annex A is affected, the document should also be provided in all EU official languages as a separate set. The ‘QRD Convention’ published on the Agency website should be followed. When submitting the full set of Annexes in PDF format, this should be accompanied by the completed formatting checklist. A user guide on how to generate PDF versions of the product information and annexes is also available.

The electronic copy of all languages should be provided as part of the variation application on CD-ROM/DVD. Highlighted changes should be indicated via ‘Tools – Track Changes’. Clean versions should have all changes ‘accepted’.

Icelandic and Norwegian language versions must always be included.

The Annexes provided should only reflect the changes introduced by the Variation(s) concerned. However, in exceptional cases where MAHs take the opportunity to introduce minor linguistic or typographical corrections in the texts this should be clearly mentioned in the cover letter and in the scope section of the application form.

In addition, the section “present/proposed” in the application form should clearly list the minor linguistic or typographical corrections introduced for each language. Alternatively, such listing may be provided as a separate document attached to the application form. Any changes not listed, will not be considered as part of the variation application.

In such cases, and in cases where any other ongoing procedure(s) may affect the product information Annexes, the MAH is advised to contact the Agency in advance of submission or finalisation of the procedure(s) concerned.

When the Type IA/IAIN Notification concerns several medicinal products, the relevant complete set of product information Annexes should be included in the eCTD sequence for each product concerned.

For Type IA/IAIN variations affecting Annex A (e.g. introduction of a new presentation), translations of the revised Annex A in all EU languages should be provided as separate documents in clean Word and PDF format, together with the variation application. Where the variation introduces (a) new EU sub-number(s), this/these should be included in the Annex A and in the product information texts as part of the variation application (see also “How to obtain new EU sub-numbers for a Type IAIN variation concerning an additional presentation (e.g. new pack-size)”?).

Similarly, in case of a deletion of a pharmaceutical form/strength/pack-size(s), the amended Annex A and product information Annexes should be provided as part of the Variation application.
1.12. How and when will the updated product information Annexes become part of the Marketing Authorisation? Rev Oct 2012

For Type IA/IA\textsubscript{IN} variations affecting the product information Annexes to the Commission Decision, the Commission Decision will be updated within one year.

By the end of this period, the Agency will send the complete set of Annexes, based on the latest (previously) approved Annexes and reflecting the Type IA/IA\textsubscript{IN} change(s) agreed during the past year together with a line-listing of those Type IA/IA\textsubscript{IN} notification(s). The Commission will subsequently issue a Commission Decision on the Type IA/IA\textsubscript{IN} notification(s) concerned.

However, where an Opinion affecting the Annexes which is followed by an immediate Commission Decision, e.g. listed in the Article 23.1a(a), is transmitted to the Commission within this yearly period the changes of the Type IA/IA\textsubscript{IN} notification(s) concerned will already be included in the Annexes to that Opinion and will consequently be reflected in the resulting Commission Decision. This Commission Decision will therefore replace the yearly updating of the MA for the Type IA/IA\textsubscript{IN} notification(s) concerned.

At the occasion of the next Type IA/IA\textsubscript{IN} variation affecting the Annexes, the procedure outlined above will be repeated based on the new ‘Reference point’ of the next Type IA/IA\textsubscript{IN} concerned.

(See also diagram below, which illustrates the updating process.)

In addition, it is important that in case of an upcoming submission of a variation, extension or other regulatory procedure which will affect the product information, the MAH should also include as a grouping application any Type IA change(s) affecting the product information that have not been previously notified, in order to keep the product information up-to-date and to facilitate document management.

Where a Type IA/IA\textsubscript{IN} notification concerns several marketing authorisations, the Commission will update the marketing authorisation with one Decision per marketing authorisation concerned.
1.13. What should be the date of revision of the text for Type IA Variations? New Oct 2010

Type IA/IAIN variations do not require prior approval before implementation ("Do and Tell" procedure), i.e. they can be implemented and notified to the Agency either immediately for Type IA variations requiring immediate notification ("IAIN") or within 12 months for Type IA variations not requiring immediate notification ("IA").

For Type IA variations affecting the product information, the date of revision of the text to be included in section 10 of the summary of product characteristics and in the corresponding section of the package leaflet at the time of printing should be the date of implementation of the change by the Marketing Authorisation Holder.

The meaning of “implementation” is explained in question and answer 1. When shall I submit my Type IA/IAIN variation(s)?
2. Type IB variations

2.1. What changes are considered Type IB Variations? Rev Feb 2013

Commission Regulation (EC) No 1234/2008 (‘the Variations Regulation’) defines a minor variation of Type IB as a variation which is neither a Type IA variation nor a Type II variation nor an Extension. Such minor variations must be notified to the National Competent Authority/European Medicines Agency (‘the Agency’) by the Marketing Authorisation Holder (MAH) before implementation, but do not require a formal approval. Upon acknowledgement of receipt of a valid notification, the MAH must wait a period of 30 days to ensure that the notification is deemed acceptable by the National Competent Authority/the Agency before implementing the change (‘Tell, Wait and Do’ procedure).

The “Commission guideline on the details of the various categories of variations” (‘the Classification Guideline’), contains examples of changes which are considered as Type IB variations. In addition, any change which is not an Extension and whose classification is not determined taking into account the Commission Guideline and the recommendations delivered pursuant to Article 5 of the Variations Regulation is considered a Type IB variation by default.

When one or more of the conditions established in the Classification Guideline for a Type IA variation are not met, the concerned change may be submitted as a Type IB variation unless the change is specifically classified as a major variation of Type II.

For changes which are submitted as default Type IB variations, the Agency will determine during validation whether the proposed classification as Type IB variation is appropriate before the start of the evaluation procedure (see also “How shall my Type IB variation be handled?”)

References

- Classification guideline
- Procedural guideline

2.2. Is the (Co-) Rapporteur involved in Type IB Variations?

Upon validation of the notification by the Agency, the Rapporteur will be involved in the evaluation of such Type IB variations “How shall my Type IB variation be handled (timetable)?”

The Co-Rapporteur is not involved in Type IB variations. However, a copy of the complete Type IB notification must also be submitted to the Co-Rapporteur.

2.3. Can I group the submission of Type IB variations? Can they be grouped with other types of variations?

MAHs may choose to group the submission of several Type IB variations for the same product into one notification. It is also possible for a MAH to group a Type IB variation with other variation(s) for the same product (e.g. Type IA, Type II, Extension), where applicable.
Allowed groupings are listed in Annex III of the Variations Regulation. Other groupings have to be agreed in advance with the Agency. Any proposal to group clinical and quality variations should be adequately justified.

Such grouped submissions will follow the review procedure of the highest variation in the group. Please also refer to “What type of variations can be grouped?“.

Where the same minor Type IB variation(s) affect more than one marketing authorisations from the same holder, the MAH may choose to submit these variations as one application for ‘worksharing’. Please also refer to “What is worksharing and what type of variations can be subject to worksharing?“.

References

- Procedural guideline

2.4. How shall I present and submit my Type IB Variation? Rev March 2013

A Type IB variation notification should contain the elements listed in Annex IV of the Variations Regulation and should be presented in accordance with the appropriate headings and numbering of the EU-CTD format.

The Commission "Guideline on the operation of the procedures laid down in Chapters II, III and IV of Commission Regulation (EC) No 1234/2008 " ('the Procedural Guideline') further specifies which elements should be included in a Type IB variation notification:

- Cover letter (for groupings, include a short overview of the nature of the changes and indicate whether it is submitted under Article 7.2(b), i.e. it falls within one of the cases listed in Annex III of the variations regulation or it is submitted under Article 7.2(c), i.e. the grouping has been agreed with the Agency). The cover letter should contain the template table to facilitate submission and registration.
- The completed electronic EU variation application form (eAF) or the application form (as published on the Commission’s website in Volume 2C of the Notice to applicants), including the details of the marketing authorisation concerned. Where a variation is considered a Type IB by default, a detailed justification for its submission as a Type IB notification must be included. MAHs are reminded that the variation application form should be signed by the official contact person as specified in section 2.4.3 of Part IA/Module 1. Should the official contact person not be available, an official letter of authorisation confirming the delegation of signature to a different person should be enclosed.
• Reference to the part of the Classification guideline, or reference to the published Article 5 Recommendation, if applicable, used for the relevant application. Applicable documentation should be clearly ticked on the extract provided, or marked as n/a if the case. If a documentation is n/a, a justification for its absence should be provided.

• Relevant documentation in support of the proposed variation including all documentation as specified in the Commission Classification Guideline.

• For variations submitted to implement changes requested by the Agency or for generic/hybrid/biosimilar medicinal products, where no new additional data are submitted by the MAH, a copy of the request should be annexed to the cover letter.

• If applicable, the revised summary of product characteristics (SmPC or Annex I), annex II, labelling (Annex IIIA) and/or package leaflet (Annex IIIB) as a full set of annexes. If the change applied for affects Annex A, this should be provided as a separate set of document per EU language (See also 8. When do I have to submit revised product information? In all languages?). Additional information on how to comply with this in a required technical format can be found in the TIGes Harmonised Guidance.

• Where the overall design and readability of the outer and immediate packaging and/or package leaflet is affected, the need for the provision of mock-ups or specimens should be discussed with the Agency Medical Information Sector on a case-by-case basis.

**Grouped variations**

For grouped variations concerning one marketing authorisation, all variations must be declared in the variation application form. The documentation requirements for each type of variation in the group must be adhered to. However, the supportive documentation for all variations concerned should be submitted as one integrated package (i.e. there is no need to submit a separate documentation package for each variation). The present-proposed section of the application form should clearly identify the relevant CTD sections in support of each variation. For grouped variations please refer to "Can I group the submission of Type IB variations? Can they be grouped with other types of variations?". For grouped variations concerning more than one marketing authorisation please refer to "What is worksharing and what types of variations can be subject to worksharing?".

It should be noted that the responsibility for the quality of the submitted documentation lies with the MAH and is crucial to the overall process. The MAH is responsible for ensuring that the Type IB variation complies fully with the data and documentation requirements as specified in the Classification Guideline and in the Procedural Guideline. The MAH should pay particular attention to grouping of variations, for which each change should be clearly identified as well as the related supportive documentation. A confusing dossier presentation may delay the procedure.

For more detailed queries on technical matters please contact the PA-BUS department (PA_BUS@ema.europa.eu). For procedural matters related to a Type IB notification for a specific product and in order to avoid rejection, please contact the relevant Product Team Leader for your product in the Safety and Efficacy Sector for safety/efficacy related variations or the Product Team member in the Quality Sector for quality related variations.

**Submission of Type IB Notifications**

The EMA strongly recommends using the eSubmission Gateway or the eSubmission Web Client as the preferred submission method for all eCTD submissions. More information on how to register and connect to the Gateway / Web Client can be found in the eSubmission website and detailed information
on the required naming conventions and file formats can be found in the eSubmission Gateway Q&A document and the Web Client Q&A. Applicants must not send duplicate submissions electronically or via CD-ROM or DVD as this might lead to delays in the handling of applications.

Applications that are sent using the eSubmission Gateway and eSubmission Web Client will receive an automated ‘acknowledgement’, confirming whether the submission has passed the relevant technical validation criteria and whether it has been uploaded to the agency’s review tool. There is no need to send any separate paper cover letters for these submissions, as the cover letter will be in the relevant part of eCTD module 1 in PDF format.

MAHs not yet using the eSubmission Gateway or the Web Client solution should send their Type IB variation notifications as CD-ROM or DVD to the attention of the Product and Application Business Support (PA-BUS) at the following address:

Product and Application Business Support (PA-BUS)
European Medicines Agency
Loading Dock
Ontario Way
Canary Wharf
UK - London, E14 4HB

Only one CD-ROM or DVD of the Variation Notification presented in eCTD format should be submitted to the Agency, together with one original, signed cover letter when using this format of submission. The Product Team Leader should be indicated in copy “cc” on the cover letter (no additional copy needed).

Where applicable, revised product information Annexes (including Annex A, if applicable) should be provided in electronic (Word and PDF) format (see also Type IB variations - "When do I have to submit revised product information? In all languages?") in the same eSubmission Gateway and eSubmission Web Client package or CD-ROM or DVD within a folder called ‘working documents’.

One electronic copy should also be sent to the CHMP (Co-)Rapporteur and other CHMP members at the time of submission for evaluation to maintain the life cycle of the eCTD dossier. It is essential that identical eCTD sequences are circulated to Committee Members. Any minor changes that affect the ‘md5’ checksum will lead to inconsistency and possibly result in future technical invalidity.

Where applications are amended during the agency’s review, such as e.g. responses to a request for supplementary information or a withdrawal, a new or consolidated eCTD sequence should be provided in order to maintain the eCTD life-cycle. The same applies in case the outcome of the variation application review is unfavourable for one or more changes applied for (mixed outcome). Please refer to the TIGes Harmonised Guidance and the Question and Answer document under the New Variation Regulation and eCTD guidance for specific advice.

For a full overview of dossier requirements for National Competent Authorities of (Co-)Rapporteur and Committee members, including delivery addresses, please refer to the following document: Dossier requirements for Centrally Authorised Products (CAPs).

Please note that the EMA only accepts submissions made in a mandatory eCTD format.

For practical aspects of eCTD dossier submission under the Variation Regulation (EC) No 1234/2008, please refer to the ‘Q&A - eCTD Variations’ published on the Agency e-submission website and to the TIGes Harmonised Guidance for eCTD Submissions in the EU.

Information on the electronic Application Form for variations can be found in the eSubmission eAF webpage.

References
2.5. **When shall I submit my Type IB Variation? New Oct 2010**

In order to facilitate the linguistic review process of product information for certain variations which have been downgraded from Type II to Type IB, the Agency has published recommended submission dates for Type IB variations requiring linguistic review (See also “Human Medicines – Procedural timetables/Submission dates)


These submission dates are not applicable for type IB variations included in a worksharing submission or for Type IB variations submitted as part of a group including Type II variations and/or extensions.

The Agency considers that despite the downgrading of certain variations to Type IB it is important from a public health protection point of view to continue to ensure high quality and consistent product information of centrally authorised medicinal products in all Member States.

Some examples of Type IB variations where a linguistic review will be performed are listed below:

- C.I.3.a) Implementation of change(s) requested by the Agency following the assessment of an Urgent Safety Restriction, class labelling, a Periodic Safety Update report, Risk Management Plan, Follow up Measure/Specific Obligation, data submitted under Article 45/46 of Regulation (EC) No 1901/2006, or amendments to reflect a competent authority Core SPC

- Other default safety and efficacy Type IB variations affecting the product information.

Some examples of Type IB variations where a linguistic review will not be performed are:

- C.I.2.a) Change in the Summary of Product Characteristics, Labelling or Package Leaflet of a generic/hybrid/biosimilar medicinal products following assessment of the same change for the reference product

- Deletion of information from the product information

The linguistic review process will be normally performed within the 30 day timeframe for assessment of the Type IB variations on the translations submitted at the start of the procedure.

Where the CHMP requests a variation following the assessment of a PSUR, FUM or SO, data submitted under Article 45/46 of Regulation (EC) No 1901/2006, following adoption of class-labelling or
amendments to a Core SPC or requests a variation for generic/hybrid/biosimilar medicinal products following assessment of the same change for the reference product, MAHs must submit the corresponding variation application at the latest within 2 months following the adoption of the relevant assessment conclusion.

Variation applications reflecting the outcome of an Urgent Safety Restriction (USR) shall be submitted immediately and in any case no later than 15 days after the initiation of the USR to the Agency. This applies to USRs initiated by the MAH or imposed by the European Commission.

References
- The Linguistic Review Process of Product Information in the Centralised Procedure - Human

2.6. How shall my Type IB variation be handled (timetable)? Rev Oct 2012

Upon receipt of a Type IB notification, the Agency will handle the notification as follows:

a) Handling of Type IB variations included (‘foreseen’) in the Classification Guideline or covered by an Article 5 Recommendation:

The Agency will check within 5 working days whether the variation is correct and complete (‘validation’) before the start of the evaluation procedure.

<table>
<thead>
<tr>
<th>Day</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day x</td>
<td>Receipt of Type IB variation</td>
</tr>
<tr>
<td>Day x+1</td>
<td>Start of Agency validation</td>
</tr>
<tr>
<td>Day x+5</td>
<td>Agency validation</td>
</tr>
<tr>
<td></td>
<td>(in case of missing information, this period will be extended)</td>
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</tbody>
</table>

Issues identified during validation will be notified to the MAH by Eudralink.

The Agency will send to the MAH a confirmation of the positive outcome of the validation and the start date of the procedure.

<table>
<thead>
<tr>
<th>Day</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 1</td>
<td>Start of evaluation</td>
</tr>
<tr>
<td>by Day 20</td>
<td>Receipt of Assessment Report</td>
</tr>
<tr>
<td>by Day 30</td>
<td>(Non-)acceptance of the variation</td>
</tr>
</tbody>
</table>
Within 30 days following the acknowledgement of receipt of a valid notification, the Agency will notify the MAH by Eudralink of the outcome of the procedure. If the Agency has not sent the holder its opinion on the notification within 30 days, the notification shall be deemed acceptable.

In case of an unfavourable outcome the MAH may, within 30 days, amend the notification to take due account of the grounds for the non-acceptance of the variation. If the MAH does not amend the notification as requested, the notification shall be rejected.

Within 30 days of receipt of the amended notification, the Agency will inform the MAH of its final (non-)acceptance of the variation and whether the Commission Decision granting the Marketing Authorisation requires any amendments.

Where the outcome of the procedure is favourable and the Commission Decision granting the Marketing Authorisation requires amendments, the Agency will inform the Commission accordingly.

Where Type IB Variations affect the Annexes to the Marketing Authorisation, such changes can be implemented without awaiting the update of the Commission Decision and the agreed change(s) should be included in the Annexes of any subsequent Regulatory Procedure.

b) Handling of Type IB variations claimed by the MAH to be IB variations by default:

The Agency will check within 5 working days whether the proposed change can be considered a minor variation of Type IB, and whether the notification is correct and complete ('validation') before the start of the evaluation procedure. In exceptional cases, the Agency may have to consult with the Rapporteur on the appropriate classification of the variation, which may lead to a slightly longer validation period (up to 10 working days).

When the Agency is of the opinion that the proposed variation may have a significant impact on the quality, safety or efficacy of the medicinal product, the MAH will be notified that the applied change cannot be handled as a Type IB and that the variation will have to be reclassified as a Type II variation. As a consequence, the MAH will be requested to revise and supplement its variation application so that the requirements for a Type II variation application are met.

Following receipt of the valid revised variation application, a Type II assessment procedure will be initiated according to the Agency procedural timetables for Type II variation.

When the Agency is of the opinion that the proposed variation can be considered a Type IB variation, the MAH will be informed of the outcome of the validation and of the start date of the procedure. The Type IB notification will be handled as set-out in section a) above.

c) Handling of Groupings of Minor Variations (Type IB/Type IA)

For grouping of minor variations, where not all of the changes applied for can be positively validated, all valid and not valid variations will be clearly listed in the validation outcome letter.

Where a Type IB by default variation, within a group of variations, has to be reclassified as a Type II variation, the MAH will be requested to confirm whether this variation should remain in the group. If confirmed, the whole group will be handled as a Type II variation, as set out in b) above.

Where several Type IB variations are submitted as part of one notification, it will be clearly specified in the final Agency notification which variation(s) have been accepted or rejected following assessment, unless some of the variations have been withdrawn by the MAH during the procedure (see grouping Q&A).
2.7. **What fee do I have to pay for a Type IB Variation?** Rev Feb 2013

For information on the fee applicable for Type IB variations, please refer to the explanatory note on fees payable to the European Medicines Agency. Such fee covers all authorised strengths, pharmaceutical forms and presentations of a given medicinal product.

For variations introducing additional presentation(s)/pack-size(s), each additional presentation/pack-size attracts separate fees (“X” additional presentations = “x” separate fees). Each presentation/pack-size should therefore be declared as a separate variation on the variation application form under the section ‘Variations included in this application’.

Grouped Type IB variations, whether consequential or not, will each attract a separate Type IB fee.

The fee will become due on the date of the notification of the administrative validation to the applicant and fees will be payable within 45 calendar days of the date of the said notification. After approximately 15 days an invoice will be sent to the applicants billing address held on the Agency’s file.

The invoice will contain details of the product and type of procedure involved, the fee amount, the customer purchase order number associated with the procedures invoiced and financial information.

Applicants requiring a purchase order number or similar references on the invoice are requested to clearly indicate it on the cover letter or application form accompanying the dossier. The Agency does not accept stand-alone notifications of purchase order numbers that are not associated with a dossier. Applicants not requiring a purchase order number on the invoice should also clearly state this in the cover letter. Applicants are requested to provide this information in the cover letter template.

Guidance on how to pay an invoice can be found on our website.

**References**

- Fees payable to the European Medicines Agency

2.8. **Do I have to submit mock-ups and specimens?** Rev Apr 2012

**Mock-ups**

In case the Type IB variation affects labelling and/or package leaflet, no mock-ups are required to be provided with the notification.

**Specimens**

Where the overall design and readability of the outer and immediate packaging and/or package leaflet is affected, the need for the provision of specimens should be discussed with the Agency Medical Information Sector on a case-by-case basis (e.g. specimens would be required when proposing a new container type or a new pack size smaller than the current approved range, but not e.g. when only limited new text is added in a leaflet section). In case specimens are required, in principle only one relevant example (multi-lingual if possible) would need to be sent to the Agency at the latest 15 working days before marketing. However, depending on the nature and extent of the change(s) concerned, additional specimens may be required by the Agency. The Agency will perform a general check from the viewpoint of readability within 15 working days, and will check if any previous
comments on specimens have been duly implemented. The applicant will be informed about the outcome of the check.

**Note:**

In case the MAH wishes to receive feedback from the Agency on their proposed new packaging in advance of the specimen review, the Agency could agree with the MAH on a case-by-case basis, to review draft mock-ups before specimen submission.

The above principles also apply to mock-ups for Iceland. The mock-ups should be sent by e-mail to mockups@ima.is. See also http://www.imca.is/IMCA/News/nr/1263

No mock-ups and specimens are required for Norway.

**References**

- The Revised Checking Process of Mock-Ups and Specimens of outer/immediate labelling and package leaflets of human medicinal products in the Centralised Procedure (EMEA/305821/2006)

**2.9. When do I have to submit revised product information? In all languages? Rev Oct 2010**

In case the Type IB notification affects any of the annexes, i.e. annex A, SPC, annex II, labelling and/or package leaflet, the affected revised product information Annexes must be submitted as follows:

- All EEA language versions: complete set of Annexes electronically only in Word format (highlighted) and in PDF (clean)²

The ‘complete set of Annexes’ includes Annex A (if applicable), I, II, IIIA and IIIB i.e. all authorised presentations (if applicable), SPC, labelling and PL texts for all strengths and pharmaceutical forms of the product concerned, as well as Annex II. The complete set of Annexes must be presented sequentially (i.e. Annex I, II, IIIA, IIIB) as one document for each official EU language. Page numbering should start with "1" (bottom, centre) on the title page of Annex I. If annex A is affected, the document should also be provided in all EU official languages as a separate set. The ‘QRD Convention’ published on the Agency website should be followed. When submitting the full set of Annexes in PDF format, this should be accompanied by the completed formatting checklist which provides guidance on how to correctly prepare the PDF versions.

The electronic copy of all languages should be provided as part of the variation application on CD-ROM/DVD. Highlighted changes should be indicated via ‘Tools – Track Changes’. Clean versions should have all changes ‘accepted’.

Icelandic and Norwegian language versions must always be included.

The Annexes provided should only reflect the changes introduced by the Variation(s) concerned. However, in exceptional cases where MAHs take the opportunity to introduce minor linguistic amendments in the texts this should be clearly mentioned in the cover letter and in the scope section of the application form.

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² PDF clean versions are only required at the time of submission if there is no linguistic review of the product information (see question 5)
In addition, the section “present/proposed” in the application form should clearly list the minor linguistic amendments introduced for each language. Alternatively, such listing may be provided as a separate document attached to the application form. Any changes not listed, will not be considered as part of the variation application.

In such cases, and in cases where any other ongoing procedure(s) may affect the product information Annexes, the MAH is advised to contact the Agency in advance of submission or finalisation of the procedure(s) concerned.

For Type IB variations affecting Annex A (e.g. introduction of a new presentation), translations of the revised Annex A in all EU languages should be provided as separate documents in clean Word and PDF format, together with the variation application. Where the variation introduces a new EU sub-number, the sub-number should be included in the Annex A and in the product information texts as part of the variation application (see also “How to obtain new EU sub-numbers for a Type IB variation concerning an additional presentation? (e.g. new pack-size)?”).

Similarly, in case of a deletion of a pharmaceutical form/strength(s), the amended Annex A and product information Annexes should be provided as part of the Variation application.

**2.10. How to obtain new EU sub-numbers for a Type IB variation concerning an additional presentation (e.g. new pack-size)? Rev Mar 2011**

In the specific case of a Type IB Variation for an additional presentation, the new EU marketing authorisation sub-number should be requested from the Agency before submission.

The request should be sent together with a draft Annex A (in English only) to the Procedural office (H-QM-PRO@ema.europa.eu) with a copy to the product shared mailbox and should be made at least 5 working days in advance of the intended submission of the variation. Once a number has been allocated, this number should subsequently be included in the Annex A and Product Information Annexes submitted together with the Variation notification.

**2.11. How and when will the updated Annexes become part of the Marketing Authorisation? Rev Oct 2012**

For type IB variations affecting the annexes to the Commission Decision, the Commission Decision will generally be updated within one year, unless the Type IB variation concerns any of the changes listed in Article 23.1a(a) whereby the Commission Decision will be updated within two months. This would include variations related to the addition of a new therapeutic indication or modification of an existing one, addition of a new contraindication or change in posology. It is expected that such variations would be processed as Type IB variations mainly in the framework of generics/hybrids following changes to the product information of the reference medicinal product.

However, all Type IB variations affecting the annexes can be implemented without awaiting the update of the marketing authorisation and the agreed Type IB changes should be included in the Annexes of any subsequent Regulatory Procedure.

For type IB variations subject to yearly update of the respective Commission decision, at the end of this yearly period, the Agency will send the complete set of Annexes, based on the latest approved Annexes and reflecting the Type IB change(s) introduced during the past year as well as a line-listing of those variations pending update of the Commission decision.
Where a notification contained several Type IB variations concerning one marketing authorisation, the Commission will update the marketing authorisation with one single decision to cover all the approved minor variations.

However, where a notification/opinion affecting the Annexes which is followed by an immediate Commission decision, is transmitted to the Commission within this yearly period, the changes of the Type IB notification(s) concerned will already be included in the Annexes to the notification/opinion and will consequently be reflected in the resulting Commission Decision. This Commission Decision will therefore replace the yearly updating of the MA for the Type IB notification(s) concerned.

At the occasion of a next Type IB variation affecting the Annexes, the procedure outlined above will be repeated based on the new 'Reference point' of the next Type IB concerned.

(see also diagram below)
3. Type II variations

3.1. What changes are considered Type II Variations?

Commission Regulation (EC) No 1234/2008 (‘the Variations Regulation’) defines a major variation of Type II as a variation which is not an extension and which may have a significant impact on the Quality, Safety or Efficacy of a medicinal product.

The Variations Regulation and the Classification Guideline set out a list of changes to be considered as Type II variations. In addition, any other change which may have a significant impact on the quality, safety or efficacy of the medicinal product must be submitted as a Type II variation. Please refer also to “When will my variation application be considered a Type II variation or an extension application?”. During validation of an ‘unforeseen’ variation, submitted by the MAH as a Type IB variation, the Agency may consider that the proposed variation may have a significant impact on the quality, safety or efficacy of the medicinal product. In such case, the marketing authorisation holder will be requested to revise and supplement its variation application so that the requirements for a Type II variation application are met (see also “How shall my Type IB variations be handled (timetable)?”).

References

- Procedural guideline
- Classification guideline

3.2. Is the Co-Rapporteur involved in Type II Variations? Rev. March 2013

The CHMP Co-Rapporteur is normally not involved in the assessment of a Type II variation application concerning quality, pre-clinical and most of the clinical SPC changes.

The involvement of the CHMP Co-Rapporteur is however deemed necessary for new indications.

The MAH should therefore inform the Agency of an upcoming Type II application for a new indication at least 2 months before submission, so that the CHMP can agree on the Co-Rapporteur’s involvement and be informed of the future submission.

The involvement of the CHMP Co-Rapporteur in other Type II variations will be decided by the CHMP on a case-by-case basis.

Furthermore a PRAC Rapporteur may be involved, where applicable.

The Agency will inform the MAH accordingly.

Regarding the submission of a Type II variation application to the (Co-) Rapporteurs, please see also “How and to whom shall I submit my Type II Variation application”.

3.3. **Can I group the submission of Type II variations? Can they be grouped with other types of variations?**

Marketing authorisation holders may choose to group the submission of several Type II variations for the same product into one application, provided that this corresponds to one of the cases listed in Annex III of the Variations Regulation or when this has been agreed upfront with the Agency.

It is also possible for a marketing authorisation holder to group a Type II variation with other variation(s) submission (e.g. Extension, Type IB or IA variations), where applicable. Such grouped submissions will follow the review procedure of the highest variation in the group. Please also refer to "What types of variations can be grouped?".

Where the same Type II variation(s) affect one or more marketing authorisations from the same holder, the marketing authorisation holder may choose to submit these variations as one application for 'worksharing'. Please also refer to “What is worksharing and what types of variations can be subject to worksharing?”.

**References**

- Procedural guideline

3.4. **How shall I present my Type II Variation application? Rev Feb 2013**

A Type II variation application should contain the elements listed in Annex IV of the Variations Regulation and should be presented in accordance with the appropriate headings and numbering of the EU-CTD format.

The Commission "Guideline on the operation of the procedures laid down in Chapters II, III and IV of Commission Regulation (EC) No 1234/2008 “ (’the Procedural Guideline’) further specifies which elements should be included in a Type II variation application:

- Cover letter (for groupings, include a short overview of the nature of the changes and indicate whether it is submitted under Article 7.2(b), i.e. it falls within one of the cases listed in Annex III of the variations regulation or it is submitted under Article 7.2.(c), i.e. the grouping has been agreed with the Agency). The cover letter should contain the template table to facilitate submission and registration.

- The completed electronic EU variation application form (eAF) or the application form, including the details of the marketing authorisation concerned. Where a variation leads to or is the consequence of other variations, a description of the relation between these variations should be provided in the appropriate section of the application form. All proposed changes should be declared in the 'Type of changes' section of the form, and be clearly described in the “scope” section of the form.

- Reference to the part of the Commission Classification Guideline or reference to the published Article 5 Recommendation, if applicable, used for the relevant application.

- Supporting data relating to the proposed variation(s).

- Update or Addendum to quality summaries, non-clinical overviews and clinical overviews, as relevant. When non-clinical or clinical study reports are submitted, even if only one, their relevant summary(ies) should be included in Module 2.
For variations submitted to implement changes requested by the Agency or for
generic/hybrid/biosimilar medicinal products, a copy of the request should be annexed to the cover
letter.

In case that the changes affect SPC, labelling and/or package leaflet, the revised product
information Annexes must be submitted (see also: Type II variations - "When do I have to submit
revised product information? In all languages?").

It should be noted that the responsibility for the quality of the submitted documentation lies with the
MAH and is crucial to the overall process.

For queries relating to the presentation of the application, please contact the Agency.

References

- Procedural guideline
- Electronic Variation application form / Variation application form
- Template for cover letter

3.5. How and to whom shall I submit my Type II Variation application?

Revised March 2013

The EMA strongly recommends using the eSubmission Gateway or the eSubmission Web Client as the
preferred submission method for all eCTD submissions. More information on how to register and
connect to the Gateway / Web Client can be found in the eSubmission website and detailed information
on the required naming conventions and file formats can be found in the eSubmission Gateway Q&A
document and the Web Client Q&A. Applicants must not send duplicate submissions electronically or
via CD-ROM or DVD as this might lead to delays in the handling of applications.

Applications that are sent using the eSubmission Gateway and eSubmission Web Client will receive an
automated ‘acknowledgement’, confirming whether the submission has passed the relevant technical
validation criteria and whether it has been uploaded to the agency’s review tool. There is no need to
send any separate paper cover letters for these submissions, as the cover letter will be in the relevant
part of eCTD module 1 in PDF format.

MAHs not yet using the eSubmission Gateway or the Web Client solution should send their Type II
variation applications as CD-ROM or DVD to the attention of the Product and Application Business
Support (PA-BUS) at the following address:

Product and Application Business Support (PA-BUS)
European Medicines Agency
Loading Dock
Ontario Way
Canary Wharf
UK - London, E14 4HB

Only one CD-ROM or DVD of the Variation application presented in eCTD format should be submitted to
the Agency, together with one original, signed cover letter when using this format of submission. The
Product Team Leader should be indicated in copy ("cc") on the cover letter (no additional copy
needed).
Where applicable, revised product information Annexes (including Annex A, if applicable) should be included in electronic (Word and PDF) format (see also Type II variations - “When do I have to submit revised product information? In all languages?”) in the same eSubmission Gateway and eSubmission Web Client package in CD-ROM or DVD within a folder called ‘working documents’

One electronic copy of the electronic Variation application form or the Variation application form and supportive documentation should be submitted to the (Co-)Rapporteurs after the eSubmission Gateway / Web Client confirmation of a technically valid submission. When submitted as CD-ROM or DVD the applicant should dispatch an electronic copy to the (Co)-Rapporteur at the same time as dispatching to the EMA.

Any additional information/documentation requested by Agency prior to the start of the procedure should be equally provided to (Co-)Rapporteurs.

Upon validation by the Agency, the MAH should forthwith send one electronic copy of the Type II variation application to the other Committee members, including any additional data or information supplied during the validation phase (as appropriate).

It is essential that identical eCTD sequences are circulated to Committee Members. Any minor changes that affect the “md5 checksum” will lead to inconsistency and possibly result in future technical invalidity.

Where applications are amended during the agency’s review, such as e.g. responses to a request for supplementary information or a withdrawal, new or consolidated eCTD sequence should be provided in order to maintain the eCTD life-cycle. The same applies in case the outcome of the variation application review is unfavourable for one or more changes applied for (mixed outcome). Please refer to the TIGes Harmonised Guidance and to the Question and Answer document under the New Variation Regulation and eCTD for specific advice.

For a full overview of dossier requirements for National Competent Authorities of (Co-)Rapporteur and Committee members, including delivery addresses, please refer to the following document: Dossier requirements for Centrally Authorised Products (CAPs).

Please note that the EMA only accepts submissions made in a mandatory eCTD format.

For practical aspects of eCTD dossier submission under the Variation Regulation (EC) No 1234/2008, please refer to the ‘Q&A - eCTD Variations’ published on the Agency e-submission website and to the TIGes Harmonised Guidance for eCTD Submissions in the EU.

Information on the electronic Application Form for variations can be found in the eSubmissions eAF webpage.

References

- Commission Regulation (EC) No 1234/2008
- Electronic Variation application form / Variation application form, The Rules governing Medicinal Products in the European Union, Notice to Applicants, Volume 2C
- Template for cover letter
- Dossier requirements for Centrally Authorised Products (CAPs)
- Classification Guideline
- Article 5 Recommendation
- TIGes Harmonised Guidance for eCTD Submissions in the EU
3.6. **When shall I submit my Type II Variation application? Rev Oct 2012**

The MAH shall submit Type II application(s) at the latest by the recommended submission dates published on the Agency’s website (See also “Human Medicines – Procedural Timetables / Submission dates”).

MAHs are reminded, especially for safety issues, that once new information becomes available which might entail the variation of the MA, MAHs should submit any variation application resulting from the fulfilment of the post-authorisation measures (PAMs) and/or Specific Obligations (SOs) at the same time as the fulfilment of the PAM/ SO, rather than awaiting the assessment of those data by CHMP.

Where the CHMP requests the submission of a variation following the assessment of a PAM or SO, or following adoption of class-labelling, MAHs must submit the corresponding variation application at the latest within 2 months following the adoption of the relevant assessment conclusion.

Variation applications reflecting the outcome of an Urgent Safety Restriction (USR) shall be submitted immediately and in any case no later than 15 days after the initiation of the USR to the Agency. This applies to USRs initiated by the MAH or imposed by the European Commission.

Implementation of agreed wording changes following the above mentioned procedures for which no additional data are submitted by the MAH will follow a Type IB variation procedure.

References

- Classification Guideline

3.7. **How shall my Type II application be handled (timetable)? Rev. March 2013**

The Agency will acknowledge receipt of a valid application of a Type II variation and shall start the procedure in accordance with the official starting dates published on the EMA website.

The submission deadlines and full procedural detailed timetables are published as a generic calendar on the EMA website (see: "submission deadlines and full procedural timetables").

The published timetables identify the submission, start and finish dates of the procedures as well as other interim dates/milestones that occur during the procedure.

One of the following timetables (TT) shall apply:
For a 60 day TT (= standard timetable):

Condition:
- All standard Type II variations; i.e. excluding those qualifying for a 30- or 90-day TT (see below)

<table>
<thead>
<tr>
<th>Day</th>
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<tr>
<td>Day 1</td>
<td>Start of evaluation</td>
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<tr>
<td>Day 30</td>
<td>Receipt of (Co-) Rapporteur Assessment Report</td>
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<tr>
<td>Day 50</td>
<td>Comments by other CHMP members</td>
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<tr>
<td>Day 60</td>
<td>Adoption of the CHMP Opinion</td>
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<td>[or Request for supplementary information]</td>
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For a 30 day TT:

Condition:
- Changes, which in the opinion of the Committee, would benefit from a shortened assessment, having regard to the urgency of the matter, in particular for safety issues.

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<th>Action</th>
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<tbody>
<tr>
<td>Day 1</td>
<td>Start of evaluation</td>
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<tr>
<td>Day 17</td>
<td>Receipt of Rapporteur Assessment Report</td>
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<tr>
<td>Day 25</td>
<td>Comments by other CHMP members</td>
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<tr>
<td>Day 30</td>
<td>Adoption of the CHMP Opinion</td>
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<td></td>
<td>[or Request for supplementary info]</td>
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In exceptional cases, this timetable could even be shortened.

For a 90 day TT:

Condition:
- For variations concerning changes to or addition of therapeutic indications

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<th>Action</th>
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<tr>
<td>Day 1</td>
<td>Start of evaluation</td>
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<tr>
<td>Day 55</td>
<td>Receipt of (Co-) Rapporteur Assessment Report</td>
</tr>
<tr>
<td>Day 80</td>
<td>Comments by other CHMP members</td>
</tr>
<tr>
<td>Day 90</td>
<td>Adoption of the CHMP Opinion</td>
</tr>
<tr>
<td></td>
<td>[or Request for supplementary info]</td>
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</table>
In cases where the PRAC is involved in the assessment of a type II variation, e.g. when a RMP is submitted within the variation, the following time tables with PRAC milestones will apply:

- **60 day TT (= standard timetable) with PRAC involvement:**

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<tr>
<td>Day 1</td>
<td>Start of evaluation</td>
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<tr>
<td>Day 30</td>
<td>Receipt of (Co-) Rapporteur Assessment Report</td>
</tr>
<tr>
<td>Day 37</td>
<td>Draft PRAC Rapporteur AR</td>
</tr>
<tr>
<td>Day 47</td>
<td>Adoption of PRAC advice</td>
</tr>
<tr>
<td>Day 51</td>
<td>Comments by other CHMP members</td>
</tr>
<tr>
<td>Day 60</td>
<td>Adoption of the CHMP Opinion</td>
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<td>[or Request for supplementary information]</td>
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- **30 day TT with PRAC involvement:**

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<th>Day</th>
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<tr>
<td>Day 1</td>
<td>Start of evaluation</td>
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<tr>
<td>Day 9</td>
<td>Receipt of Rapporteur Assessment Report</td>
</tr>
<tr>
<td>Day 13</td>
<td>Draft PRAC Rapporteur AR</td>
</tr>
<tr>
<td>Day 17</td>
<td>Adoption of PRAC advice</td>
</tr>
<tr>
<td>Day 20</td>
<td>Comments by other CHMP members</td>
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<tr>
<td>Day 30</td>
<td>Adoption of the CHMP Opinion</td>
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<td></td>
<td>[or Request for supplementary info]</td>
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- **90 day TT with PRAC involvement:**

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<th>Day</th>
<th>Action</th>
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<tbody>
<tr>
<td>Day 1</td>
<td>Start of evaluation</td>
</tr>
<tr>
<td>Day 53</td>
<td>Receipt of (Co-) Rapporteur Assessment Report</td>
</tr>
<tr>
<td>Day 67</td>
<td>Draft PRAC Rapporteur AR</td>
</tr>
<tr>
<td>Day 76</td>
<td>Adoption of PRAC advice</td>
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<tr>
<td>Day 80</td>
<td>Comments by other CHMP members</td>
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<tr>
<td>Day 90</td>
<td>Adoption of the CHMP Opinion</td>
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<tr>
<td></td>
<td>[or Request for supplementary info]</td>
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</table>
MAHs are encouraged to contact the Agency in advance of the submission, in case clarification on the timetable for a specific variation is needed.

The MAH will be informed of the adopted timetable at the start of the procedure.

In case issues are identified which prevent the adoption of an Opinion, the CHMP will adopt a request for supplementary information together with a timetable stating the date by when the MAH must submit the requested data. The clock will be stopped until the receipt of the supplementary information.

Any response to a request for supplementary information must be sent directly to the Agency, all CHMP members and the (Co-) Rapporteur.

As a general rule, a clock-stop of up to 1 month will apply. For clock-stops longer than 1 month the MAH should send a justified request to the EMA for agreement by CHMP. Such requests should be sent after receipt of the Assessment Report, and at the latest before the CHMP meeting at which the request for supplementary information will be adopted. In exceptional cases (e.g. in the case of new indications or where the variation requires an inspection) a clock-stop of up to a maximum of 6 months may be applied.

For any follow-on request for supplementary information, an additional clock-stop of up to 1 month will be applied in general; a maximum of 2 months may be applied when justified.

The MAH will receive the adopted timetable together with the request for supplementary information or follow-on request.

The CHMP assessment of responses will take up to 30 or 60 days depending on the complexity and amount of data provided by the MAH.

An oral explanation to the CHMP can be held at the request of the CHMP or the MAH, where appropriate.

References

- Procedural guideline

3.8. Which post-opinion steps apply to my Type II variation and when can I implement the approved changes? Rev Feb 2013

Upon adoption of the CHMP opinion, the Agency will inform the MAH within 15 days as to whether the CHMP opinion is favourable or unfavourable (including the grounds for the unfavourable outcome), as well as whether the Commission Decision granting the marketing authorisation requires any amendments.

Where the outcome of the procedure is favourable and the Commission Decision granting the Marketing Authorisation requires amendments, the Agency will inform the Commission accordingly.
Re-examination

Art. 9(2) of Regulation (EC) No 726/2004, also applies to CHMP Opinions adopted for Type II variation applications. This means that the MAH may give written notice to the Agency/CHMP that he wishes to request a re-examination within 15 days of receipt of the opinion (after which, if he does not appeal, the opinion shall be considered as final). The grounds for the re-examination request must be forwarded to the Agency within 60 days of receipt of the opinion. In case the MAH requests that the committee consults a SAG in connection with the re-examination, the applicant should inform the CHMP as soon as possible of this request.

The CHMP will appoint a different (Co-) Rapporteur, to co-ordinate the re-examination procedure. Within 60 days from the receipt of the grounds for re-examination, the CHMP will consider whether its opinion is to be revised. If considered necessary, an oral explanation can be held within this 60 days timeframe.

Decision-Making Process

Upon receipt of a favourable CHMP opinion which requires amendments to the decision granting the marketing authorisation, the Commission shall amend the marketing authorisation to reflect the variation within 2 months, for the variations listed under Article 23(1a)(a) or within one year for the other type II variations.

Article 23(1a)(a) provides for a two month timeframe for amending the decision granting the marketing authorisation for the following variations:

- Variations related to the addition of a new therapeutic indication or to the modifications of an existing one;
- Variations related to the addition of a new contra-indication;
- Variations related to a change in posology;
- Variations related to changes to the active substance of a seasonal, pre-pandemic or pandemic vaccine against human influenza;
- Other Type II variations that are intended to implement changes to the decision granting the marketing authorisation due to a significant public health concern or significant animal health or environmental concern in the case of veterinary medicinal products.
All the other type II variations will follow a yearly timeframe for update of the respective Commission decision.

**Timeline for Variations**

*Post Opinion*

- **Product information v.1 (MAH)**
- **Member State Review (QRD/CHMP)**
- **Product information v.2 (MAH) + Form 2**
  - PIQ final check (implemented comments)
- **Product information v.3 (AGENCY)**

Day

0 Opinion

+ 5

+ 19 Comments from MS

+ 25

+ 27** Transmission to Commission

+ 29 **Commission: Start adoption process**

+ 75 **Final Commission Decision (2 month DMP timeframe**)**

**applicable only to Type II variations listed under Art. 23.1a(e) of Commission Regulation (EC) No 1234/2008**
Where a group of variations to the terms of one marketing authorisation submitted as part of one variation have been approved, the Commission will update the marketing authorisation with one single decision to cover all the approved variations.

**Implementation**

Type II variations listed in Article 23(1a)(a) may only be implemented once the Commission has amended the marketing authorisation and has notified the MAH accordingly. Variations related to safety issues, including urgent safety restrictions, must be implemented within a time-frame agreed by the Marketing Authorisation Holder and the Agency.

Type II variations which do not require any amendment of the marketing authorisation or which follow a yearly update of the respective Commission Decision can be implemented once the MAH has been informed of the favourable outcome by the Agency. However, it is expected that where the variation includes changes to the product information, the MAH waits for the finalisation of the linguistic review process by the Agency before implementing the variation, as appropriately checked translations are considered essential for a correct implementation of the variation.

The agreed change(s) should be included in the Annexes of any subsequent regulatory procedure.

**Date of revision of the text**

The date of revision of the text to be included in section 10 of the SmPC and corresponding section of the package leaflet for variations affecting the product information should be as follows:

- For type II variations listed in Article 23(1a)(a) this should be the date of the Commission Decision amending the marketing authorisation;

- For type II variations not listed in Article 23(1a)(a), which follow a yearly timeframe for update of the respective Commission decision, this should be the date of the adoption of the positive CHMP opinion on the variation to the terms of the marketing authorisation.

**References**

- Procedural guideline
- Re-examination guideline
- The Linguistic Review Process of Product Information in the Centralised Procedure – Human

**3.9. What fee do I have to pay for a Type II Variation? Rev Feb 2013**

For information on the fee applicable for Type II variations, please refer to the explanatory note on fees payable to the European Medicines Agency. Such fee covers all authorised strengths, pharmaceutical forms and presentations of a given medicinal product. Reduced Type II fees may apply to certain variations, as specified in the Explanatory note on fees payable to the EMA.

For Type II variations which introduce additional presentation/pack-size(s), each additional presentation/pack-size attracts separate fees (x additional presentations x separate fees). Each
presentation/pack-size should therefore be declared as a separate variation on the variation application form.

Grouped Type II variations, whether consequential or not, will each attract a separate Type II fee.

The fee will become due on the date of the notification of the administrative validation to the applicant and fees will be payable within 45 calendar days of the date of the said notification. After approximately 15 days an invoice will be sent to the applicants billing address held on the Agency’s file.

The invoice will contain details of the product and type of procedure involved, the fee amount, the customer purchase order number associated with the procedures invoiced and financial information.

Applicants requiring a purchase order number or similar references on the invoice are requested to clearly indicate it on the cover letter or application form accompanying the dossier. The Agency does not accept stand-alone notifications of purchase order numbers that are not associated with a dossier. Applicants not requiring a purchase order number on the invoice should also clearly state this in the cover letter. Applicants are requested to provide this information in the cover letter template.

Guidance on how to pay an invoice can be found on our website.

For Type II variations, if the variation is considered 'invalid' (i.e. an assessment process cannot be started), an administrative fee will be charged by the Agency (see also Explanatory note on fees payable to the EMA).

In case an inspection is required, please note that in addition an inspection fee will be requested (see also Pre-submission Guidance – "What is the fee for a GMP inspection?").

References

- Fees payable to the European Medicines Agency

3.10. Do I have to submit mock-ups and specimens? Rev Apr 2012

Mock-ups

In case the Type II variation affects labelling and/or package leaflet, no mock-ups are required to be provided with the variation application.

Specimens

Where the overall design and readability of the outer and immediate packaging and/or package leaflet is affected, the need for the provision of specimens should be discussed with the EMA Medical Information Sector on a case-by-case basis (e.g. specimens would be required when proposing a new corporate design of packs, a new container type, major changes in lay-out, but not e.g. when only limited new text is added in a leaflet section). In case specimens are required, in principle only one relevant example (multi-lingual if possible) would need to be sent to the Agency at the latest 15 working days before marketing. However, depending on the nature and extent of the change(s) concerned, additional specimens may be required by the Agency. The Agency will perform a general check from the viewpoint of readability within 15 working days, and will check if any previous
comments on specimens have been duly implemented. The applicant will be informed about the outcome of the check.

**Note:**

In case the MAH wishes to receive EMA feedback on their proposed new packaging in advance of the specimen review, EMA could agree with the MAH on a case-by-case basis, to review draft mock-ups before specimen submission.

The above principles also apply to mock-ups for Iceland. The mock-ups should be sent to mockups@ima.is. See also http://www.imca.is/IMCA/News/nr/1263.

No mock-ups and specimens are required for Norway.

**References**

- The Revised Checking Process of Mock-Ups and Specimens of outer/immediate labelling and package leaflets of human medicinal products in the Centralised Procedure (EMEA/305821/2006)

**3.11. When do I have to submit revised product information? In all languages? Rev Oct 2012**

In case the Type II Variation affects SPC, labelling and/or package leaflet, the revised product information Annexes must be submitted as follows:

**At submission (Day 0)**
- English language: complete set of Annexes electronically only in Word format (highlighted)

**After CXMP Opinion (Day +5)**
- All EU languages (incl. NO+IS): complete set of annexes electronically only in Word format (highlighted)

**After Linguistic check (Day +25)**
- All EU languages (incl. NO+IS): complete set of annexes electronically only in Word format (highlighted) and in PDF (clean)

**Overview:**

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<tr>
<th>Day</th>
<th>Lang.*</th>
<th>Post-opinion linguistic review Timetable</th>
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<td>Word format (highlighted)</td>
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</tbody>
</table>

* = complete set of Annexes i.e. Annex I, II, IIIA and IIIB submitted as one document per language
The ‘complete set of Annexes’ includes Annex, I, II, IIIA and IIIB i.e. all SPC, labelling and PL texts for all strengths and pharmaceutical forms of the product concerned, as well as Annex II.

The complete set of Annexes must be presented sequentially (i.e. Annex I, II, IIIA, IIIB) as one document for each official EU language. Page numbering should start with “1” (bottom, centre) on the title page of Annex I. The ‘QRD Convention’ published on the Agency’s website should be followed. When submitting the full set of Annexes in PDF format, this should be accompanied by the completed formatting checklist which provides guidance on how to correctly prepare the PDF versions.

The electronic copy of all languages should be provided as part of the variation application on the Gateway / Web Client package / CD-ROM/DVD. Highlighted changes should be indicated via ‘Tools – Track changes’. Clean versions should have all changes ‘accepted’.

Icelandic and Norwegian language versions must always be included.

The Annexes provided should only reflect the changes introduced by the Variation concerned. However, in exceptional cases where MAHs take the opportunity to introduce minor linguistic amendments in the texts (e.g. further to a specimen check) this should be clearly mentioned in the cover letter and in the scope section of the application form.

In addition, the section “present/proposed” in the application form should clearly list the minor linguistic amendments introduced for each language. Alternatively, such listing may be provided as a separate document attached to the application form. Any changes not listed, will not be considered as part of the variation application.

In such cases and in cases where any other ongoing procedures may affect the product information Annexes, the MAH is advised to contact the Agency in advance of submission or finalisation of the procedure(s) concerned.

For those variations which affect the Annex A (e.g. introduction of a new presentation), the following principles apply:

Upon adoption of the opinion, the Agency will prepare and send to the MAH the revised English Annex A reflecting the new/amended presentation.

After CHMP Opinion (Day +5), the MAH provides the Agency with the electronic versions of the complete set of Annexes in all languages as well as the translations of the revised Annex A as a separate word document.

3.12. What is the procedure for assignment of new European Union sub-numbers for a type II variation concerning additional presentation(s)? New Nov 2012

At the time of the adoption of a CHMP opinion for a type II variation which includes additional presentation(s), the Agency will assign the new EU sub-numbers and include them in the revised Annex A of the medicinal product, which will be transmitted to the Marketing Authorisation Holder together with the CHMP Opinion and respective annexes.

The Marketing Authorisation Holder should include the newly assigned numbers in all language versions of the Annex A and in all applicable sections of the product information, which are submitted following the CHMP opinion for linguistic review.
3.13. Will there be any publication on the outcome of my Type II Variation? Rev Oct 2012

The meeting highlights following each CHMP meeting give information on opinions in relation to new indications, changes to an existing indication, addition, change or removal of a contraindication. This will include the name of the product, the name of the MAH, the indication(s). Where applicable, the CHMP gives also an update on safety information.

3.14. What specific requirements apply to my Type II variation for a new orphan indication?

Type II variations for a new indication, which is the same as the indication of an authorised Orphan Medicinal Product, should include relevant information in Module 1.7 of the application, based on the following considerations:

In accordance with Article 8.1 of Regulation (EC) No 141/2000, where a marketing authorisation in respect of an orphan medicinal product has been granted in all Members States, the Community and the Member States shall not, for a period of 10 years, accept another application for marketing authorisation, or grant a marketing authorisation or accept an application to extend an existing marketing authorisation, for the same therapeutic indication, in respect of a similar medicinal product.

Where a designated orphan medicinal product has been authorised for the condition which covers the proposed therapeutic indication being applied for, and a period of market exclusivity is in force, the MAH must submit a report addressing the possible "similarity" with the authorised orphan medicinal product (even if the concerned product does not have orphan designation).

If the medicinal product is deemed to be "similar" to an authorised orphan medicinal product, the MAH must furthermore provide justification that one of the derogations laid down in Article 8.3, paragraphs (a) to (c) of the same Regulation applies, namely:

(a) the holder of the marketing authorisation for the original orphan medicinal product has given his consent to the second applicant, or

(b) the holder of the marketing authorisation for the original orphan medicinal product is unable to supply sufficient quantities of the medicinal product, or

(c) the second applicant can establish in the application that the second medicinal product, although similar to the orphan medicinal product already authorised, is safer, more effective or otherwise clinically superior.

Further details can be found in the European Commission “Guideline on aspects of the application of Article 8(1) and (3) of Regulation (EC) No 141/2000: Assessing similarity of medicinal products versus authorised orphan medicinal products benefiting from market exclusivity and applying derogations from that market exclusivity.”

Even if the variation does not concern an orphan designated product, all MAHs should still check whether their claimed new indication would potentially overlap with the indication of authorised orphan medicinal products, as listed on the Commission Website in the “Community register” of designated orphan medicinal products and include the relevant documentation in their variation application as set-out above.
3.15. What should I consider in case I wish to add a new non-orphan therapeutic indication to my orphan medicinal product? New Feb 2013

As it is not possible to combine within the same marketing authorisation orphan and non-orphan indications, as provided for in Article 7(3) of the Orphan Regulation, in case you wish to extend the therapeutic indications of your orphan medicinal product to include additional non-orphan therapeutic indications, you will have to consider the following options:

- To apply for a separate application for marketing authorisation covering the therapeutic indications which are outside the scope of the Orphan Regulation; in this case you will have to consider the procedure to request the submission of a multiple application to the European Commission, as explained in the Q&A "If I intend to submit multiple applications for the same medicinal product?"
- To request the withdrawal of the orphan designation for your medicinal product, which should be removed from the Community register of orphan designated medicinal products prior to the submission of your variation for the new non-orphan therapeutic indication.

3.16. Do I need to address any paediatric requirements in my type II variation application? Rev. Apr 2012

Regulation (EC) No 1901/2006, as amended (the 'Paediatric Regulation') lays down obligations, rewards and incentives for the development and placing on the market of medicines for use in children. The Paediatric Regulation places some obligations for the applicant when developing a new medicinal product as well as new uses of an authorised product, in order to ensure that medicines to treat children are subject to ethical research of high quality and are appropriately authorised for use in children, and to improve collection of information on the use of medicines in the various subsets of the paediatric population. The paediatric population is defined as the population between birth and the age of 18 years (meaning up to but not including 18-years).

As set out in Article 8 of the Paediatric Regulation, applications for new indication(s), new pharmaceutical form(s) and/or new route(s) of administration concerning an authorised medicinal product protected either by a supplementary protection certificate or by a patent which qualifies for the granting of such a certificate must include one of the following documents/data in order to be considered 'valid':

References

- Regulation (EC) No 141/2000 on orphan medicinal products
• The results of all studies performed and details of all information collected in compliance with an agreed Paediatric Investigation Plan (PIP).

This means that the application will have to include the PIP decision but also the results in accordance with the agreed PIP.

• A decision of the EMA on a PIP including the granting of a deferral

This means that the application will have to include the PIP decision including the deferral granted and if applicable, any completed studies.

• A decision of the EMA granting a product-specific waiver

• A decision of the EMA granting a class waiver (together with the Agency’s confirmation letter of applicability if requested by the MAH)

This requirement applies irrespective of the type of application submitted for such a change(s) i.e. variation or extension (or new marketing authorisation application) and irrespective of whether the change is related to adult or paediatric use.

To define what is a ‘new indication’ for the purpose of the application of Article 8, please refer to the question 17 on the paediatric webpage: ‘What is a new indication in the context of Article 8?’

Where results of PIP studies for an authorised medicinal product which do not support a paediatric indication, and the corresponding proposal for amending the SmPC and, if appropriate the Package Leaflet Product Information may be submitted as part of a variation C.I.4 as per the guideline on the details of the various categories of variations – ‘Variations related to significant modifications to the SmPC’. Applicants are requested to mention in the application form of the variation including the paediatric results and in the cover letter the following statement in the section ‘Precise scope and background for change’: ‘Submission of paediatric study results performed in compliance with a <completed> paediatric investigation plan which do not support a paediatric indication’.

Applicants should include in the clinical overview a rationale supporting the proposed changes to the Product Information. In particular, if the PIP is completed and the results of all studies are available, the applicant should discuss whether the generated data support or not the intended paediatric indication(s) stated in the PIP.

Inclusion of the results of all studies performed in compliance with an agreed Paediatric Investigation Plan requirement in the Product Information is a prerequisite for benefiting from the paediatric reward (Article 36(1) of Regulation (EC) No 1901/2006).

As for all applications including results of studies performed in compliance with an agreed PIP, the applicant should also include in Module 1.10 an overview table of the PIP results, indicating in which application(s) they were/are going to be submitted, status of the application(s), as well as their location in the present application.

In addition, in accordance with Article 8, the PIP or Waiver application and the related decision should cover both the new and existing indications, routes of administration and pharmaceutical forms of the authorised medicinal product, taking into account the Global Marketing Authorisation (GMA) concept together with the notion of ‘same marketing authorisation holder’. Further information can be found in the Procedural Advice document on “applications for PIPs, Waivers and Modifications” which is available on the Agency’s website under ‘Medicines for children’.

Those required data/documents should be included in Module 1.10 of the EU-CTD dossier.

The following types of application are exempted from the application of Article 8:
• Generics medicinal products (Art 10(1) of Directive 2001/83/EC)
• Hybrid medicinal products (Art 10(3) of Directive 2001/83/EC)
• Similar biological medicinal products (Art 10(4) of Directive 2001/83/EC)
• Medicinal products containing active substance(s) of well-established medicinal use (Art 10a of Directive 2001/83/EC)

Furthermore, when planning submission of their marketing authorisation application, the applicant has to take into account also the need for a “PIP” compliance check to be done.

Such compliance check consists of verifying that the fulfilments of the measures as mentioned in the PIP decision including the timelines for the conduct of the studies or collection of the data are fulfilled. The compliance check procedure is explained in the document Questions and answers on the procedure of paediatric investigation plan compliance verification at the European Medicines Agency. Applicants are strongly recommended to apply for the compliance check before submission of the marketing authorisation application to not delay the validation phase.

Further details on the format, timing and content of PIP or waiver applications as well as on the compliance check can be found in the Commission guideline. In addition, deadlines for submission of PIP or Waiver applications, application templates as well as Procedural Advice documents respectively regarding applications for PIPs, Waivers and Modifications and validation of new MAA, Variation/Extension applications and compliance check with an agreed PIP are available on the Agency’s website in section “Medicines for children”.

References

• Regulation (EC) No 1901/2006
• Commission Guideline on “The format and content of applications for agreement or modification of a paediatric investigation plan and request for waivers or deferrals and concerning the operation of the compliance check and on criteria for assessing significant studies”
• Procedural Advice document related to Paediatric investigation plans (PIPs), waivers and modifications
• Questions and answers on the procedure of paediatric investigation plan compliance verification at the European Medicines Agency
• EMA website, section “Special Topics - Medicines for children”
4. Type II variations/Extension applications

4.1. When will my variation application be considered a Type II variation or an Extension application? Rev. Jul 2012

Commission Regulation (EC) No 1234/2008 defines a Type II variation as a ‘major variation’ which may have a significant impact on the Quality, Safety or Efficacy of the medicinal product.

The Variations Regulation and the Classification Guideline set out a list of changes to be considered as Type II variations. In addition, any other change which may have a significant impact on the quality, safety or efficacy of the medicinal product must be submitted as a Type II variation.

Certain changes to a Marketing Authorisation, however, have to be considered to fundamentally alter the terms of this authorisation and therefore cannot be granted following a variation procedure. These changes are to be submitted as an ‘Extension application’ and are listed in Annex I of the Variations Regulation.

This Annex lists three main categories of “changes requiring an extension application”:

1. Changes to the active substance(s)
2. Changes to strength, pharmaceutical form and route of administration
3. Other changes specific to veterinary medicinal products to be administered to food-producing animals; change or addition of target species

As the case may be, an authorisation or a modification to the existing Marketing Authorisation will have to be issued by the Commission.

The European Commission has published a guideline in order to clarify these terms pharmaceutical form and strength and to include relevant examples for such classification. (See also Guideline on the categorisation of New Applications (NA) versus Variations Applications (V), January 2002).

This guideline on categorization should be read in conjunction with the EDQM guidance on the Standard Terms, Regulation (EC) No 1234/2008 and Regulation (EC) No 1901/2006 and understood as follows:

Changes to a centralised marketing authorisation listed below should be submitted as variation(s) according to the guideline on the details of the various categories of variations to the terms of marketing authorisations:

- Addition or replacement of a presentation for a solution for injection with a different immediate container (e.g. vial, syringe, pre-filled pen, cartridge, ampoule...)
- Addition or replacement of a presentation for an eye drops solution with a different immediate container.

These changes would not fall into the scope of Article 8 of Regulation (EC) No 1901/2006 (please refer to 18. What is a ‘new pharmaceutical form’ in the context of Article 8?)

In cases of doubt, the MAH is advised to contact the Agency in advance of the submission.

References

4.2. Extension Applications - Will my invented name change?

The invented name of the medicinal product will be the same for the “extension” as it is for the existing Marketing Authorisation of the medicinal product.

It should be clear that the complete name of the medicinal product is commonly composed of the “invented name, followed by the strength, pharmaceutical form”. The pharmaceutical form should be described by the European Pharmacopoeia’s full standard term. If the appropriate standard term does not exist, a new term may be constructed from a combination of standard terms (should this not be possible, the Competent Authority should be asked to request a new standard term from the European Directorate for Quality of Medicines (EDQM) of the Council of Europe).

References

- “Guideline on the acceptability of invented names for human medicinal products processed through the centralised procedure (CHMP/328/98)”
- Standard Terms, Council of Europe

4.3. Is the (Co-) Rapporteur involved in Extension Applications? Rev. March 2013

The CHMP Co-Rapporteur is normally not involved in the assessment of an Extension Application.

However, in case the Extension application would be grouped with a Type II variation for a new indication, the CHMP Co-Rapporteur would normally be involved.

Furthermore a PRAC Rapporteur may be involved, where applicable.


Extension applications should be presented as follows in accordance with the appropriate headings and numbering of the EU-CTD format:

- Cover letter (for groupings, include a short overview of the nature of the changes and indicate whether it is submitted under Article 7.2(b), i.e. it falls within one of the cases listed in Annex III of the variations regulation or it is submitted under Article 7.2(c), i.e. the grouping has been
agreed with the Agency). The cover letter should contain the template table to facilitate submission and registration.

- The completed electronic EU application form or the application form dated and signed by the official contact person as specified in Section 2.4.3. The MAH should carefully fill-in the following sections of the application form i.e.:
  - In case of an extension of application, section 1.3 "Yes" should be ticked;
  - The precise scope of the change needs also to be filled-in;
  - The legal basis for an extension application corresponds to the legal basis of the initial application for the medicinal product. Therefore, relevant boxes of section 1.4 should be ticked.

  Note: If the extension application is grouped with other variation(s), the variation application form should be appended to this application form. See also “What type of variations can be grouped?”

- Supporting data relating to the proposed extension must be submitted. Some guidance on the appropriate additional studies required for applications under Article 10 of Directive 2001/83/EC or Extension Applications (also called “Annex I applications”) are available in Annex IV to Chapter 1 of the Notice to Applicants

- A full Module 1 should be provided, with justifications for absence of data/documents included in the relevant section(s) of Module 1 (e.g. in case ‘user testing’ is considered not necessary by the MAH, a justification should be included in section 1.3.4).

- Update/Addendum to quality summaries/non-clinical overviews and clinical overviews, if appropriate, must be submitted using the appropriate headings and numbering of the EU-CTD format. When (a) non-clinical/clinical study report(s) are submitted, even if only one, their relevant summaries should be included in Module 2.

- Module 3 of the application should only contain the relevant quality information related to the proposed extension, unless the extension is part of a group.

In case that the changes affect the SPC, labelling and/or package leaflet, the revised product information Annexes must be submitted (see also: Extension applications - "When do I have to submit revised product information? In all languages?").

It should be noted that the responsibility for the quality of the submitted documentation lies with the MAH and is crucial to the overall process.

For queries related to the presentation of the application, please contact the Agency. Alternatively, MAHs may request a pre-submission meeting with the Agency to clarify any outstanding points.

References

- Presentation and content of the dossier - Part 1, Summary of the dossier Part 1A or Module 1: Administrative information application form, The Rules governing Medicinal Products in the European Union, Notice to Applicants, Volume 2B
- Procedures for Marketing Authorisation, The Rules governing Medicinal Products in the European Union, Notice to Applicants, Volume 2A, Chapter 1
- Template for cover letter
- Electronic Variation application form / Variation application form
4.5. **What aspects should I consider at time of submission of an extension application if there are orphan medicinal products designated or authorised for a condition related to my proposed therapeutic indication? New Feb 13**

Article 8(1) of the Regulation (EC) No 141/2000 (“Orphan Regulation”) prevents the Agency and the Member States from accepting, for a period of 10 years, another application for a marketing authorisation, or granting a marketing authorisation or accepting an application to extend an existing marketing authorisation, for the same therapeutic indication, in respect of a similar medicinal product.

Therefore, if your application concerns an extension of a marketing authorisation, as defined in Annex I of the Regulation (EC) No 1234/2008 (“Variations Regulation”), e.g. a new pharmaceutical form or route of administration, you will have to indicate in the respective application form if any medicinal product has been designated as an orphan medicinal product for a condition relating to the therapeutic indication proposed in your application.

In advance of submission of your application for an extension of your marketing authorisation, irrespective of whether your medicinal product has been designated as orphan or not, you are advised to check the Community register of orphan medicinal products, for information on medicinal products designated as orphan.

If any of the designated orphan medicinal products has been granted a marketing authorisation in the Union, and a period of market exclusivity is in force, you will have to provide in Module 1.7.1 a similarity report addressing the possible similarity between your medicinal products and the orphan medicinal product(s) which have received a marketing authorisation.

The assessment of similarity between two medicinal products takes into consideration the following criteria:

- Principal molecular structural features,
- Mechanism of action and
- Therapeutic indication.

If significant differences exist within one or more of these criteria, the two products will not be considered as similar. These criteria are explained in the Guideline on aspects of the application of Article 8(1) and 8(3) of Regulation (EC) No 141/2000: Assessing similarity of If significant differences exist within one or more of these criteria, the two products will not be considered as similar.

If your product is considered to be similar to any authorised orphan medicinal product, you will have to provide in Module 1.7.2 justification that one of the following derogations, laid down in Article 8(3) of the Orphan Regulation applies, i.e.:

(a) the holder of the marketing authorisation for the orphan medicinal product has given his consent for submission of your application, in which case a signed letter from the MAH of the orphan medicinal product should be provided confirming the consent for submission of an application for marketing authorisation;

(b) the holder of the marketing authorisation for the orphan medicinal product is unable to supply sufficient quantities of the medicinal product, in which case the applicant should provide a report including details of the supply shortage and justify that patients’ needs in the orphan indication are not being met;
(c) the applicant can establish that their product, although similar to the orphan medicinal product already authorised, is more effective, safer or otherwise clinically superior, in which case a critical report justifying clinical superiority to the authorised product must be provided.

For information on the procedure and timetable for assessment of similarity and, where applicable, derogation report against authorised orphan medicinal products, please refer to question and answer “What is the procedure and timetable for assessment of similarity and, where applicable, derogation report vis-à-vis authorised orphan medicinal products?”.

Please note that if the Agency identifies a possible similarity issue not addressed by the applicant before validation, the applicant will be asked to complete the application with information on similarity and, if applicable, on one of the derogations. Validation of the application will only proceed once the applicant has submitted either a report justifying the lack of similarity or information justifying one of the derogations in Article 8(3).

As considerable time may elapse between validation of an application and adoption of an opinion, if applicants become aware of medicinal products which have been authorised as orphans for a condition related to the therapeutic indication proposed in their application, this information should be communicated promptly to their Product Team Leader at the Agency in order to arrange for the submission of updated application form and modules 1.7.1 and 1.7.2, as applicable.

In any case, the Agency will check at certain milestones of the procedure, i.e. adoption of list of questions, request for supplementary information and prior to adoption of a CHMP opinion whether new orphan medicinal products have been authorised for the same condition.

References

- Regulation (EC) No 141/2000 on orphan medicinal products
- Regulation (EC) No 1234/2008
- Community register of orphan medicinal products
- Guideline on aspects of the application of Article 8(1) and 8(3) of Regulation (EC) No 141/2000: Assessing similarity of medicinal products versus authorised orphan medicinal products benefiting from market exclusivity and applying derogations from that market exclusivity

4.6. Can I group the submission of Extensions with other types of variations?

Marketing authorisation holders may choose to group the submission of one or more extensions together with one or more other variations for the same product into one application, provided that this corresponds to one of the cases listed in Annex III of the Variations Regulation or when this has been agreed upfront with the Agency.

It is possible for a marketing authorisation holder to group extensions with other variation(s) submission (e.g. Type II, Type IB or IA variations), where applicable. Such grouped submissions will follow the review procedure of the highest variation in the group. Please also refer to "What types of variations can be grouped?".

However, no worksharing of extension applications is foreseen in the variations regulation.
References

• Procedural guideline

4.7. How, when and to whom shall I submit my Extension Application? Rev. March 2013

The EMA strongly recommends using the eSubmission Gateway or the eSubmission Web Client as the preferred submission method for all eCTD submissions. More information on how to register and connect to the Gateway / Web Client can be found in the eSubmission website and detailed information on the required naming conventions and file formats can be found in the eSubmission Gateway Q&A document and the Web Client Q&A. Applicants must not send duplicate submissions electronically or via CD-ROM or DVD as this might lead to delays in the handling of applications.

Applications that are sent using the eSubmission Gateway and eSubmission Web Client will receive an automated ‘acknowledgement’, confirming whether the submission has passed the relevant technical validation criteria and whether it has been uploaded to the agency’s review tool. There is no need to send any separate paper cover letters for these submissions, as the cover letter will be in the relevant part of eCTD module 1 in PDF format.

MAHs not yet using the eSubmission Gateway or the Web Client solution should send their Extension applications as CD-ROM or DVD to the attention of the Product and Application Business Support (PA-BUS) at the following address:

Product and Application Business Support (PA-BUS)
European Medicines Agency
Loading Dock
Ontario Way
Canary Wharf
UK - LONDON E14 4HB

Only one CD-ROM or DVD of the complete extension application in eCTD format should be submitted to the Agency, together with one original, signed cover letter when using this format of submission. The Product Team Leader should be indicated in copy ("cc") on the cover letter (no additional copy needed).

Where applicable, revised product information Annexes (including Annex A, if applicable) should be included in electronic (Word and PDF) format (see also Type II variations/ Extensions applications - “When do I have to submit revised product information? In all languages?”) in the same eSubmission Gateway and eSubmission Web Client package in CD-ROM or DVD within a folder called ‘working documents’

One electronic copy of the electronic extension application and supportive documentation should also be submitted to the (Co-)Rapporteur, after the eSubmission Gateway / Web Client confirmation of a technically valid submission. When submitted as CD-ROM or DVD the applicant should dispatch an electronic copy to the (Co-)Rapporteur at the same time as dispatching to the EMA.

Any additional information/documentation requested by the Agency prior to the start of the procedure should be equally provided to (Co-) Rapporteurs.
Upon validation by the Agency, the MAH should forthwith send the extension application to the other Committee members, including any additional data or information supplied during the validation phase (as appropriate).

It is essential that identical eCTD sequences are circulated to Committee Members. Any minor changes that affect the “md5 checksum” will lead to inconsistency and possibly result in future technical invalidity.

Where applications are amended during the agency’s review, such as e.g. responses to a request for supplementary information or a withdrawal, new or consolidated eCTD sequence should be provided in order to maintain the eCTD life-cycle. The same applies in case the outcome of the application review is unfavourable for one or more changes applied for (mixed outcome).

For a full overview of dossier requirements for National Competent Authorities of (Co-)Rapporteur and Committee members, including delivery addresses, please refer to the following document: Dossier requirements for Centrally Authorised Products (CAPs).

The MAH shall submit the Extension application in accordance with the recommended submission dates published on the Agency website (see "submission deadlines and full procedural timetables").

Please note that the EMA only accepts submissions made in a mandatory eCTD format.

For practical aspects of eCTD dossier submission under the Variation Regulation (EC) No 1234/2008, please refer to the ‘Q&A - eCTD Variations’ published on the Agency e-submission website and to the TIGes Harmonised Guidance for eCTD Submissions in the EU.

References

- Commission Regulation (EC) No 1234/2008
- Template for cover letter
- Dossier requirements for Centrally Authorised Products (CAPs)
- TIGes Harmonised Guidance for eCTD Submissions in the EU
- eSubmission website
- eSubmission Gateway Q&A
- eSubmission Gateway Web Client Q&A

4.8. How shall my Extension Application be handled (timetable)? Rev. March 2013

The MAH shall submit the Extension application(s) in accordance with the recommended submission dates published on the Agency’s website.

The submission deadlines and full procedural detailed timetables are published as a generic calendar on the Agency’s website (see: "submission deadlines and full procedural timetables"). The published timetables identify the submission, start and finish dates of the procedures as well as other interim dates/milestones that occur during the procedure.

The Agency shall ensure that the opinion of the CHMP is given within 210 days in accordance with the following standard timetable, which can be shortened in certain circumstances, upon request of the MAH to the CHMP, agreement from the Rapporteur and adoption by CHMP.
<table>
<thead>
<tr>
<th>DAY</th>
<th>ACTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Start of the procedure</td>
</tr>
<tr>
<td>80</td>
<td>CHMP members and Agency receive the Assessment Report from Rapporteur. The Agency sends the Assessment Report to the MAH making it clear that it only sets out the Rapporteur’s preliminary conclusions. The report in no way binds the CHMP and is sent to the MAH for information only.</td>
</tr>
<tr>
<td>100</td>
<td>Rapporteur, other CHMP members and Agency receive comments from Members of the CHMP.</td>
</tr>
<tr>
<td>115</td>
<td>CHMP members and Agency receive a draft list of questions (including draft overall conclusions and draft overview of the scientific data) from Rapporteur.</td>
</tr>
<tr>
<td>120</td>
<td>CHMP adopts the list of questions as well as the overall conclusions and overview of the scientific data to be sent to the MAH by the Agency.</td>
</tr>
<tr>
<td></td>
<td>Clock stop.</td>
</tr>
<tr>
<td>121*</td>
<td>Submission of the responses and restart of the clock.</td>
</tr>
</tbody>
</table>

*Target dates for the submission of the responses are published on the Agency’s Website

After receipt of the responses, the CHMP will adopt a timetable for the evaluation of the responses. In general the following timetable will apply:

<table>
<thead>
<tr>
<th>DAY</th>
<th>ACTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>150</td>
<td>CHMP members and Agency receive the Response Assessment Report from Rapporteur. The Agency sends the Assessment Report to the MAH making it clear that it only sets out the Rapporteur’s preliminary conclusions. The report in no way binds the CHMP and is sent to the MAH for information only.</td>
</tr>
<tr>
<td>170</td>
<td>Comments from CHMP Members to Rapporteur.</td>
</tr>
<tr>
<td>180</td>
<td>CHMP discussion and decision on the need for an oral explanation by the MAH. If oral explanation is needed, the clock is stopped to allow the MAH to prepare the oral explanation.</td>
</tr>
<tr>
<td>181</td>
<td>Restart of the clock and oral explanation.</td>
</tr>
<tr>
<td>185</td>
<td>Final draft of English SmPC, labelling and package leaflet sent by MAH to the Rapporteur, Agency and other CHMP members.</td>
</tr>
<tr>
<td>By 210</td>
<td>Adoption of CHMP Opinion + CHMP Assessment Report.</td>
</tr>
</tbody>
</table>

In cases where the PRAC is involved in the assessment of a type II variation, e.g. when a RMP is submitted within the extension, the following time tables with PRAC mile stones will apply:

<table>
<thead>
<tr>
<th>DAY</th>
<th>ACTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Start of the procedure</td>
</tr>
<tr>
<td>80</td>
<td>CHMP members and Agency receive the Assessment Report from Rapporteur. The Agency sends the Assessment Report to the MAH making it clear that it only sets out the Rapporteur’s preliminary conclusions. The report in no way</td>
</tr>
</tbody>
</table>
Binds the CHMP and is sent to the MAH for information only.

<table>
<thead>
<tr>
<th>DAY</th>
<th>ACTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>87</td>
<td>PRAC Rapporteur circulates the RMP assessment report and proposed RMP LoQ</td>
</tr>
<tr>
<td>100</td>
<td>Rapporteur, other CHMP members and Agency receive comments from Members of the CHMP.</td>
</tr>
<tr>
<td>101-104</td>
<td>PRAC adopts PRAC RMP Assessment Overview and Advice for D120 LoQ</td>
</tr>
<tr>
<td>115</td>
<td>CHMP members and Agency receive a draft list of questions (including draft overall conclusions and draft overview of the scientific data) from Rapporteur.</td>
</tr>
<tr>
<td>120</td>
<td>CHMP adopts the list of questions as well as the overall conclusions and overview of the scientific data to be sent to the MAH by the Agency.</td>
</tr>
<tr>
<td>Clock stop.</td>
<td></td>
</tr>
<tr>
<td>121*</td>
<td>Submission of the responses and restart of the clock.</td>
</tr>
</tbody>
</table>

*Target dates for the submission of the responses are published on the Agency’s Website

After receipt of the responses, the CHMP will adopt a timetable for the evaluation of the responses. In general the following timetable will apply:

<table>
<thead>
<tr>
<th>DAY</th>
<th>ACTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>150</td>
<td>CHMP members and Agency receive the Response Assessment Report from Rapporteur. The Agency sends the Assessment Report to the MAH making it clear that it only sets out the Rapporteur’s preliminary conclusions. The report in no way binds the CHMP and is sent to the MAH for information only.</td>
</tr>
<tr>
<td>167</td>
<td>PRAC adopts PRAC RMP Assessment Overview and Advice for D180 LoOI</td>
</tr>
<tr>
<td>170</td>
<td>Comments from CHMP Members to Rapporteur.</td>
</tr>
<tr>
<td>180</td>
<td>CHMP discussion and decision on the need for an oral explanation by the MAH. If oral explanation is needed, the clock is stopped to allow the MAH to prepare the oral explanation.</td>
</tr>
<tr>
<td>181</td>
<td>Restart of the clock and oral explanation.</td>
</tr>
<tr>
<td>181 to 210</td>
<td>Final draft of English SmPC, labelling and package leaflet sent by MAH to the Rapporteur, Agency and other CHMP members.</td>
</tr>
<tr>
<td>197</td>
<td>PRAC adopts the final PRAC RMP Assessment Overview and Advice</td>
</tr>
<tr>
<td>By 210</td>
<td>Adoption of CHMP Opinion + CHMP Assessment Report.</td>
</tr>
</tbody>
</table>

**Re-examination**

Art. 9(2) of Regulation (EC) No 726/2004, also applies to CHMP Opinions adopted for Extension applications. This means that the MAH may give written notice to the EMA/CHMP that he wishes to request a re-examination within 15 days of receipt of the opinion (after which, if he does not appeal, the opinion shall be considered as final). The grounds for the re-examination request must be forwarded to the Agency within 60 days of receipt of the opinion. The CHMP will appoint different CHMP (Co-) Rapporteurs, to co-ordinate the appeal procedure. In case a PRAC Rapporteur is deemed
necessary, he/she will be appointed. Within 60 days from the receipt of the grounds for appeal, the CHMP will consider whether its opinion is to be revised. If considered necessary, an oral explanation can be held within this 60 day timeframe.

**Decision-Making Process**

Upon receipt of the final CHMP opinion, the commission shall, where necessary, amend the marketing authorisation to reflect the extension within the timeframes set-out in article 9(1) of Regulation (EC) No 726/2004 (i.e. within 67 days after adoption of the CHMP opinion). Detailed practical guidance on the post-opinion phase, including the linguistic checking of the amended product information annexes, is available on the Agency’s website.

The outcome of the evaluation of an extension application in the centralised procedure will result in an extension or a modification of the initial marketing authorisation. Extensions may only be implemented once the Commission has amended the decision granting the marketing authorisation and has notified the holder accordingly.

**References**

- Regulation (EC) No 726/2004

**4.9. What fee do I have to pay for an Extension Application? Rev Feb 2013**

For information on the fee applicable for an extension application for each new strength, new pharmaceutical form or new route of administration, please refer to the explanatory note on fees payable to the European Medicines Agency. Reduced extension fees apply to:

- All quality extensions for which no new clinical data are submitted by the marketing authorisation holder.

If variations are grouped to this extension application, whether consequential or not, they will each attract a separate relevant fee.

The fee will become due on the date of the notification of the administrative validation to the applicant and fees will be payable within 45 calendar days of the date of the said notification. After approximately 15 days an invoice will be sent to the applicants billing address held on the Agency’s file.

The invoice will contain details of the product and type of procedure involved, the fee amount, the customer purchase order number associated with the procedures invoiced and financial information.

Applicants requiring a purchase order number or similar references on the invoice are requested to clearly indicate it on the cover letter or application form accompanying the dossier. The Agency does not accept stand-alone notifications of purchase order numbers that are not associated with a dossier. Applicants not requiring a purchase order number on the invoice should also clearly state this in the cover letter. Applicants are requested to provide this information in the cover letter template.

Guidance on how to pay an invoice can be found on our website.
Where an extension application is considered ‘invalid’ (i.e. an assessment process cannot be started), an administrative fee will be charged by the Agency (see also Explanatory note on fees payable to the EMA).

References
- Fees payable to the European Medicines Agency

4.10. Do I have to submit mock-ups and specimens? Rev Apr 2012

The same mock-up / specimen requirements as for a New Application apply:

At day -10 of the submission of the application:

One English colour full-size mock-up and one multi-lingual colour full-size mock-up (“worst-case”) of the outer and inner packaging for the new pharmaceutical form or strength in each container type in the smallest pack-size must be included in Module 1.3.2 of the application. Mock-ups of the package leaflet may be included (optional).

At submission of the answers to the list of questions (day 121):

Revised mock-ups of labelling and package leaflet need to be provided in case of comments or in case the applicant has changed the overall design.

At the latest 15 working days before launch:

Before the new strength or pharmaceutical form is placed on the market, specimens of the printed outer and immediate packaging and the package leaflet for each new strength and/or new pharmaceutical form in each container type need to be provided to the Agency (using the Specimen Submission Form):

- when first marketed in the EU,
- when first marketed as a multi-lingual pack (if different from the first specimens sent to the Agency),
- when any other multi-lingual pack is marketed with a higher number of languages than the multi-lingual pack(s) previously reviewed.

The above principles also apply to mock-ups for Iceland. The mock-ups should be sent by e-mail to mockups@ima.is. See also http://www.imca.is/IMCA/News/nr/1263

No mock-ups and specimens are required for Norway.

References
- The Revised Checking Process of Mock-Ups and Specimens of outer/immediate labelling and package leaflets of human medicinal products in the Centralised Procedure (EMEA/305821/2006)
4.11. When do I have to submit revised product information? In all languages? Rev Feb 2013

In case the Extension Application requires changes to the product information (e.g. new strength or pharmaceutical form), the same requirements as for a New Application apply:

- At submission and during assessment, only the English language version of the Product Information is submitted and reviewed.

- Translations of the agreed SPC, Annex II, labelling and package leaflet text in all languages are to be provided after adoption of the CHMP opinion. Icelandic and Norwegian language versions of the extension Annexes must be included.

More details on the translation requirements and on the linguistic review process, are available on the Agency’s Website: The new Product Information linguistic review process for new applications in the Centralised Procedure (EMEA/5542/02).

MAHs are reminded that, during assessment, the English product information Annexes should only include those SPC, Labelling and/or PL relevant to the Extension Application concerned.

After adoption of the CHMP Opinion, however, a complete set of Annexes for the medicinal product concerned must be submitted. A ‘complete set of Annexes’ includes Annex, I, II, IIIA and IIIB i.e. all SPC, labelling and PL texts for all strengths and pharmaceutical forms of the product concerned, as well as Annex II.

The complete set of Annexes must be presented sequentially (i.e. Annex I, II, IIIA, IIIB) as one document for each official EU language. Page numbering should start with “1” (bottom, centre) on the title page of Annex I. The electronic copy of all languages should be provided on the Gateway / Web Client package / CD-ROM/DVD as part of the extension application.

The ‘QRD Convention’ published on the Agency’s website should be followed. When submitting the full set of Annexes in PDF format, this should be accompanied by the completed formatting checklist which provides guidance on how to correctly prepare the PDF versions.

The Annexes provided should only reflect the changes introduced by the Extension application concerned. However, in exceptional cases where MAHs take the opportunity to introduce minor linguistic amendments in the texts (e.g. further to a specimen check) this should be clearly mentioned in the cover letter. Alternatively, a listing of proposed changes may be provided as a separate document attached to the cover letter. Any changes not listed, will not be considered as part of the extension application.

In cases where any other ongoing procedures may impact on the product information of the Extension Application, the MAH is advised to contact the Agency in advance of submission or finalisation of the procedure(s) concerned.

For extension applications which affect the Annex A (e.g. introduction of a new strength), the following principles apply:

Upon adoption of the Opinion, the Agency will prepare and send to the MAH the revised English Annex A. After CHMP Opinion (Day 215), the MAH provides the Agency with the electronic versions of the complete set of Annexes in all languages as well as the translations of the revised Annex A as a separate word document.
4.12. **What is the procedure for assignment of new European Union sub-numbers for an extension including additional presentation(s)?** New Nov 2012

At the time of the adoption of a CHMP opinion for an extension application which includes additional presentation(s), the Agency will assign the new EU sub-numbers and include them in the revised Annex A of the medicinal product, which will be transmitted to the Marketing Authorisation Holder together with the CHMP Opinion and respective annexes.

The Marketing Authorisation Holder should include the newly assigned numbers in all language versions of the Annex A and in all applicable sections of the product information, which are submitted following the CHMP opinion for linguistic review.

4.13. **Will there be any publication on the outcome of my Extension application?** Rev Oct 2012

Information on opinions of extension application is not given in the meeting highlights following each CHMP meeting, unless they are grouped with a Type II variation in relation to new indications, changes to an existing indication, addition, change or removal of a contraindication.

References
- CHMP Press Release
- CHMP Monthly Report

4.14. **Do I need to address any paediatric requirements in my extension application?** Rev. Apr 2012

Regulation (EC) No 1901/2006, as amended (the ‘Paediatric Regulation’) lays down obligations, rewards and incentives for the development and placing on the market of medicines for use in children. The Paediatric Regulation places some obligations for the applicant when developing a new medicinal product as well as new uses of an authorised product, in order to ensure that medicines to treat children are subject to ethical research of high quality and are appropriately authorised for use in children, and to improve collection of information on the use of medicines in the various subsets of the paediatric population. The paediatric population is defined as the population between birth and the age of 18 years (meaning up to but not including 18-years).

As set out in Article 8 of the Paediatric Regulation, applications submitted for new indication(s), new pharmaceutical form(s) and/or new route(s) of administration concerning an authorised medicinal product protected either by a supplementary protection certificate or by a patent which qualifies for the granting of such a certificate must include one of the following documents/data in order to be considered ‘valid’:
• The results of all studies performed and details of all information collected in compliance with an agreed Paediatric Investigation Plan (PIP).

  This means that the application will have to include the PIP decision but also the results in accordance with the agreed PIP.

• A decision of the Agency on a PIP including the granting of a deferral

  This means that the application will have to include the PIP decision including the deferral granted and if applicable, any completed studies.

• A decision of the Agency granting a product-specific waiver

• A decision of the Agency granting a class waiver (together with the Agency’s confirmation letter if requested by the MAH)

This requirement applies irrespective of the type of application submitted for such a change(s) i.e. variation or extension (or new marketing authorisation application) and irrespective of whether the change is related to adult or paediatric use.

To define what is a ‘new indication’ for the purpose of the application of Article 8, please refer to the question 17 on the paediatric webpage: ‘What is a new indication in the context of Article 8?’

Where results of PIP studies are submitted and do not support a paediatric indication, applicants are requested to mention in the cover letter the following statement: ‘Submission of paediatric study results performed in compliance with a <completed> paediatric investigation plan which do not support a paediatric indication’.

Applicants should include in the clinical overview a rationale supporting the proposed changes to the Product Information. In particular, if the PIP is completed and the results of all studies are available, the applicant should discuss whether the generated data support or not the intended paediatric indication(s) stated in the PIP.

Inclusion of the results of all studies performed in compliance with an agreed Paediatric Investigation Plan in the Product Information is a prerequisite for benefiting from the paediatric reward (Article 36(1) of Regulation (EC) No 1901/2006).

In addition, in accordance with Article 8, the PIP or Waiver application and the related decision should cover both the new and existing indications, routes of administration and pharmaceutical forms of the authorised medicinal product, taking into account the Global Marketing Authorisation (GMA) concept together with the notion of ‘same marketing authorisation holder’. Further information can be found in the Procedural Advice document on applications for PIPs, Waivers and Modifications which is available on the Agency’s website under ‘Medicines for children’.

Those required data/documents should be included in Module 1.10 of the EU-CTD dossier. As for all applications including results of studies performed in compliance with an agreed PIP, the applicant should also include in Module 1.10 an overview table of the PIP results, indicating in which application(s) they were/are going to be submitted, status of the application(s), as well as their location in the present application.

The following types of application are exempted from the application of Article 8:

• Generics medicinal products (Art 10(1) of Directive 2001/83/EC)

• Hybrid medicinal products (Art 10(3) of Directive 2001/83/EC)

• Similar biological medicinal products (Art 10(4) of Directive 2001/83/EC)
• Medicinal products containing active substance(s) of well-established medicinal use (Art 10a of Directive 2001/83/EC)

Furthermore, when planning submission of their marketing authorisation application, the applicant has to take into account also the need for a "PIP" compliance check to be done.

Such compliance check consists of verifying that the fulfilments of the measures as mentioned in the PIP decision including the timelines for the conduct of the studies or collection of the data are fulfilled. The compliance check procedure is explained in the document “Questions and answers on the procedure of paediatric investigation plan compliance verification at the European Medicines Agency”. Applicants are strongly recommended to apply for the compliance check before submission of the marketing authorisation application to not delay the validation phase.

Further details on the format, timing and content of PIP or waiver applications as well as on the compliance check can be found in the Commission guideline. In addition, deadlines for submission of PIP or Waiver applications, application templates as well as Procedural Advice documents respectively regarding applications for PIPs, Waivers and Modifications and validation of new MAA, Variation/Extension applications and compliance check with an agreed PIP are available on the Agency’s website in section ”Medicines for children”.

References
• Regulation (EC) No 1901/2006
• Commission Guideline on “The format and content of applications for agreement or modification of a paediatric investigation plan and request for waivers or deferrals and concerning the operation of the compliance check and on criteria for assessing significant studies”
• Procedural Advice document related to Paediatric investigation plans (PIPs), waivers and modifications
• Questions and answers on the procedure of paediatric investigation plan compliance verification at the European Medicines Agency
• EMA website, section ”Special Topics - Medicines for children”
5. Grouping of variations


Article 7.2(a) of the Variations Regulation sets out the possibility for a marketing authorisation holder to group several Type IA/IA\textsubscript{IN} variations under a single notification to the same relevant authority:

- **Several** Type IA or IA\textsubscript{IN} affecting **one** medicinal product.
  
  This means for instance that a Type IA variation which is normally not subject to immediate notification can be included in the submission of a Type IA\textsubscript{IN} variation.

- **One** Type IA or IA\textsubscript{IN} affecting **several** medicinal products from the same MAH.

- **Several** Type IA and/or IA\textsubscript{IN} affecting **several** medicinal products from the same MAH, provided that those variations are the same for all medicinal products and are submitted to the same relevant authority.

Applicants belonging to the same mother company or group of companies and applicants having concluded agreements or exercising concerted practices concerning the placing on the market of the medicinal product(s) concerned, have to be taken as “the same marketing authorisation holder”.\(^3\)

All medicinal products concerned should be authorised through the centralised procedure.

Articles 7.2(b) and 7.2(c) of the Variations Regulation set out the possibility for a marketing authorisation holder to group several types of variations affecting one medicinal product, under a single notification/application.

Article 7.2(b) applies for groupings that are listed in Annex III of the Regulation whilst article 7.2(c) applies for groupings of variations which are not listed in Annex III, but which have been agreed with the Agency.

In the case of groupings under Article 7.2(c) it is recommended that the grouping is agreed between the holder and the Agency at least 2 months before submission.

Where the same Type IB or Type II variation, or group of variation(s) affect several medicinal products from the same MAH, the MAH may choose to submit these variations as one application for 'worksharing'. Please also refer to "What is worksharing and what types of variations can be subject to worksharing?"

References

- Procedural Guideline

5.2. What groups of variations would be considered acceptable? Rev. Oct 2012

There are no conditions for the grouping of Type IA/ IA_IN variations concerning one medicinal product. It must be noted however, that when submitting Type IA/ IA_IN variations as part of a group, the legal deadlines for submission of each variation should be respected i.e. a Type IA_IN should always be submitted immediately, whether or not it is grouped with other variations, and any Type IA variation should always be submitted within 12 months following its implementation.

When grouping one or more Type IA/ IA_IN variations affecting several centrally authorised medicinal products from the same MAH, the variation or group of variations must be the same for all medicinal products concerned.
Grouping of other types of variations is only acceptable when they fall within one of the cases listed in Annex III of the Regulation, or, if they do not fall within one of those cases, when the grouping of the variations has been agreed between the Agency and the MAH before submission.

MAHs are advised to inform the Agency at least 2 months in advance of the submission of a group of variations which are not listed in Annex III of the Regulation, together with a justification as to why the holder believes that the proposed group should be acceptable.

When reviewing MAH proposals for grouping of variations, the Agency will consider the following general principles:

- Changes should be consequential and/or related i.e. **meaningful to be reviewed simultaneously**
- Quality, Non-clinical and Clinical changes can normally not be grouped unless justified
- Quality variations to the active substance can normally not be grouped with finished product variations, unless justified
- Grouping should not delay the submission and implementation of updates to the safety information for the medicinal product.

Table 1 presents some examples of acceptable groups of variations listed in Annex III of the Regulation, with further clarification on how such groups will be considered in practice.

Table 2 presents some examples of other groups of variations, which the Agency would or not in principle consider acceptable.

These tables will be reviewed and updated regularly, in view of accumulated experience.

**Table 1. Grouping examples according to Article 7.2(b) of the Variation Regulation (Cases for grouping variations listed in Annex III)**

<table>
<thead>
<tr>
<th></th>
<th>One of the variations in the group is an extension of the marketing authorisation.</th>
<th>Other clinical or non-clinical changes which can be grouped with the Extension application would be expected to be linked to the extension e.g. new indication. Quality changes affecting the drug substance and/or drug product can also be included in the group.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Example: Extension for a new strength/pharmaceutical form + Type II for new indication to be used with this new strength form</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>One of the variations in the group is a major variation of type II; all other variations in the group are variations which are consequential to this major variation of type II.</td>
<td>The current interpretation of ‘consequential’ will apply: “A consequential variation is regarded as a change, which is an unavoidable and direct result of another change (i.e. the ‘main change’) and not simply a change which occurs at the same time.” Example: Type II for new indication + Type IB or IA for addition of a new pack size required for the use in this new indication Grouping of non-consequential quality changes may also be acceptable, under Article 7.2(c) other groups to be agreed with the Agency.</td>
</tr>
</tbody>
</table>
All variations in the group are consequential to a given post-authorisation study conducted under the supervision of the holder. This group will concern all changes necessary to reflect results from post-authorisation measure(s).

“conducted under the supervision of the holder” will be interpreted as any post-authorisation study submitted by the MAH.

The Agency will continue to consider that implementation of a post-authorisation measure is one variation. But, such a single variation should only concern one post-authorisation measure.

### Table 2. Grouping examples according to Article 7.2(c) of the Variation Regulation (Cases for grouping variations agreed by the Agency)

<table>
<thead>
<tr>
<th>Grouping of several drug-drug interaction studies</th>
<th>Grouping acceptable&lt;br&gt;1 Type II per interaction study, but Type IIIs can be grouped in 1 application</th>
</tr>
</thead>
<tbody>
<tr>
<td>e.g. 1 Type II - interaction study with Rifampicin&lt;br&gt;1 Type II - interaction study with oral contraceptive</td>
<td>Grouping acceptable&lt;br&gt;Type IIIs can be grouped in 1 application</td>
</tr>
<tr>
<td><strong>Grouping of variations for change of indication + legal status</strong>&lt;br&gt;e.g. Type II to change the indication&lt;br&gt;Type II to change the legal status (switch to OTC), linked to the new wording of the indication</td>
<td>Grouping acceptable&lt;br&gt;Type IIIs can be grouped in 1 application</td>
</tr>
<tr>
<td><strong>Grouping of Type IB variations and Type IA variations</strong>&lt;br&gt;<strong>Quality</strong>&lt;br&gt;e.g. Type IB – extension of re-test period of the active substance&lt;br&gt;   Type IB – changes in the storage conditions of the active substance&lt;br&gt;e.g. Type IB – changes to a test procedure of the active substance&lt;br&gt;   Type IA – deletion of a non-significant IPC of the finished product&lt;br&gt;<strong>Quality + Administrative</strong>&lt;br&gt;e.g. Type IB Extension of the shelf life of the finished product&lt;br&gt;   Type IA_in Change in the name of a manufacturer responsible for batch release&lt;br&gt;   Type IA Change in ATC Code</td>
<td>Grouping acceptable (both related to active substance)&lt;br&gt;Grouping acceptable (finished product change linked to active substance change)&lt;br&gt;Grouping acceptable (admin change can be combined with quality change as PI Annexes are affected)</td>
</tr>
<tr>
<td><strong>Implementation of agreed wording change(s) requested by the CHMP for which no new additional data are submitted by the MAH</strong></td>
<td>Can be grouped with any upcoming non-quality variation which affects the product information. However, it should not delay the implementation of the requested changes.</td>
</tr>
<tr>
<td><strong>Grouping of variations for extensions of indication</strong>&lt;br&gt;e.g. Data package supportive of 2 different indications e.g. renal cell carcinoma + non-small cell lung cancer</td>
<td>Not acceptable for grouping</td>
</tr>
</tbody>
</table>
**5.3. How shall I present a grouped variations application? Rev Feb 2013**

Grouped variations applications should contain the elements listed in Annex IV of the Variations Regulation and should be presented in accordance with the appropriate headings and numbering of the EU-CTD format.

The submission requirements as set-out in the PAG sections for the different types of variations will also apply to grouped variations, but the application should be provided as one integrated submission package (i.e. one eCTD sequence) covering all changes resulting from the variations.

- One cover letter, clearly indicating that the application concerns a group of variations as well as which type of variation is the highest in the group. Indicate whether the grouping is submitted under Article 7.2(b), i.e. it falls within one of the cases listed in Annex III of the variations regulation or it is submitted under Article 7.2(c), i.e. the grouping has been agreed with the Agency. The cover letter should contain the template table to facilitate submission and registration.

- The completed electronic EU variation application form or the EU variation application form, declaring all variations included in the group in the section ‘type of changes’, as well as a justification for the proposed grouping in the ‘precise scope and background’ section of the application form.

- The present-proposed section of the application form should clearly identify the relevant CTD sections in support of each variation.

- If the group contains an Extension, also the Module 1.2 New Application Form duly completed for the Extension should be provided (see also “How shall I present my extension application?”).

- Supportive documentation for all variations concerned, submitted as one integrated package (i.e. there is no need to submit a separate documentation package for each variation in the group).

- If applicable, one revised summary of product characteristics, labelling and/or package leaflet, including all changes applied for.

- Where the overall design and readability of the outer and immediate packaging and/or package leaflet is affected, the need for the provision of mock-ups or specimens should be discussed with the Medical Information Sector of the Agency on a case-by-case basis.

For a (group of) Type IA/ IAIN variation(s) concerning several marketing authorisations, please refer to “How shall I present and submit my Type IA/IA IN Variation(s)?” and TIGes harmonised Guidance.

**References**

- Procedural guideline
- eCTD Variations Q&A document
- Template for cover letter
5.4. **What procedure number will be given to grouped variation applications?**

- Several Type IA/ IAIN variations affecting **one** medicinal product:

  The usual EMA procedure number for Type IA variations will be given, with the addition of the suffix "/G". The EMA procedure number does not distinguish between Type IA or Type IAIN.

  Example: EMEA/H/C/prod_nb/IA/nn/G

- One or more Type IA/ IAIN variations affecting **several** medicinal products:

  The Agency will allocate a 'high-level' cross-products procedure number, which will be used for the handling of procedures which affect more than one medicinal product. A new procedure code (abbreviation) is used for groups of Type IA/ IAIN variations i.e. “IG”. As the 'high-level' number can not be allocated to one single product, the procedure number will therefore contain “xxxx” as a place-holder for the product number.

  Example: EMEA/H/C/xxxx/IG/002

  This 'high-level' procedure number can be obtained from the Agency shortly before submission by sending your request with a copy of the draft cover letter to: PA-BUS@ema.europa.eu.

  Please note that requesting this high level number in advance is strongly recommended for submissions sent via the eSubmission Gateway or Webclient since this number has to be included in the ‘naming convention of the path name’.

  For each medicinal product concerned by the group of variations, the following grouping number (which includes a reference to the “IG” group to which it belongs) will be given.

  Example: EMEA/H/C/prod_nb/IGxxxx which was submitted as part of a Type IA/ IAIN group affecting several medicinal products “IGxxxx”)

- Several types of variations affecting **one** medicinal product:

  The Agency’s procedure number will reflect the highest type of variation in the group, with the addition of the suffix "/G".

  Example: EMEA/H/C/prod_nb/II/nn/G (grouping of Type II + Type IB variations)

  Example: EMEA/H/C/prod_nb/IB/nn/G (grouping of 3 Type IB variations)

  Example: EMEA/H/C/prod_nb/X/nn/G (grouping of Extension + Type II + Type IB variations)

MAHs are reminded that EMA procedure numbers are allocated by the Agency upon receipt of the application, according to a sequential order for the product concerned which is independent from the type of regulatory procedure submitted. MAHs should therefore carefully consider which will be the next sequential procedure number for the product concerned, taking into account all other regulatory procedures which were submitted previously (or in parallel), and indicate the correct procedure number on the variation application form.
5.5. Can grouped variations be subject to a worksharing procedure? Rev Oct 2010

Grouped variations can be subject to a worksharing procedure, provided that the same group of variations applies to all medicinal products concerned by the worksharing procedure. However, groups including an extension application are excluded from worksharing.

Based on Articles 7 and 20 of the Variations Regulation when the grouping only consists of Type IA/IA\textsubscript{IN} variations affecting several marketing authorisations, this is considered as a “group” of variations and not a “worksharing” procedure. However, it is possible to include a group of Type IA/IA\textsubscript{IN} Variation(s) with a Type IB or Type II variation, which is submitted for a worksharing procedure.

5.6. How will grouped variation applications be handled (timetable)? What will be the outcome of the evaluation of a grouped variation application?

A grouped variation application will be handled and will follow the review procedure of the ‘highest’ variation type in the group.

For example:

- a group of a Type II and 3 Type IB variations will follow the timetable of the Type II variation.
- a group of an Extension and a Type II variation will follow the timetable of the Extension.

In case of grouped Type IA/IA\textsubscript{IN} variations, the Agency will issue a Notification reflecting which variations are accepted or rejected. The MAH shall immediately cease to apply the rejected variation(s) concerned.

For grouping of other types of variations, where not all of the changes applied for can be positively validated, all valid and not valid variations will be clearly listed in the validation letter.

Upon finalisation of the review of the grouped variations, the Agency will issue an Opinion/Notification reflecting the final outcome of the procedure and in accordance with the ‘highest’ remaining approvable variation in the group. Such Opinion/Notification will therefore also list any variations which are not considered approvable, unless these have been withdrawn from the group by the holder during the procedure.

For example:

- Extension + Type II --> Extension evaluation procedure. Extension receives a negative assessment outcome (e.g. quality issues); Type II (e.g. new indication) is however positive.

  MAH withdraws the Extension from the group --> CHMP will adopt a positive opinion on the Type II variation only.

  MAH does not withdraw the Extension from the group --> CHMP will adopt a ‘composite’ opinion reflecting both the negative Extension outcome as well as the positive Type II.

- Type II + Type IB --> Type II evaluation procedure. Type II receives a negative assessment outcome; Type IB is however positive.

  MAH withdraws the Type II from the group --> Agency will issue a positive notification on the Type IB variation.

  MAH does not withdraw the Type II from the group --> CHMP will adopt a ‘composite’ opinion reflecting both the negative Type II outcome as well as the positive Type IB.
In any case, the assessment report will mention the initial and complete scope of the application (listing all variations initially included in the group) and will clarify the procedural timelines and steps taken during assessment.

For CHMP opinions on Extensions and Type II variations, the re-examination procedure set-out in Articles 9(2) and 34 (2) of Regulation (EC) No 726/2004 will apply.

5.7. How and when will the marketing authorisation be updated for grouped variations? Rev. Oct 2012

The post-opinion and decision-making process that will apply to grouped variations, will generally be that of the ‘highest’ type of Opinion/Notification issued at the end of the procedure.

For information on the post-opinion and decision-making process for Type IA, IB and II variations, please refer to the following questions and answers ‘How and when will the updated annexes become part of the marketing authorisation?’ and ‘Which post-opinion steps apply to my type II variation and when can I implement the approved changes?’

The decision granting the marketing authorisation following a grouped application will be amended, where necessary, within a year from the date of notification/CHMP opinion for the variation concerned with the exception of the following grouped variations:

- Groupings including an extension application, which will follow the decision making process applicable to the extension application;
- Groupings including variation(s) listed in Article 23.1a(a);
- Groupings submitted as part of a worksharing application.

Where a group of Type IA/ IAIN variations to the terms of several MAs have been approved, the Commission will update the MA with one decision per product concerned, following the yearly decision-making timeframes for Type IA/ IAIN variations.

5.8. What fee do I have to pay for grouped variations? Rev Feb 2013

Grouped variations, whether consequential or not, will each attract a separate fee corresponding to the fee payable for the individual variation concerned.

Each variation applied for should therefore be declared as a separate variation on the variation application form.

The rules for reduced fees or fee reductions depending on the type of product (e.g. orphans, generics) will apply to grouped variations.

Where a grouping application is considered ‘invalid’ (i.e. an assessment process cannot be started), an administrative fee may be charged by the Agency.

Only one applicant will be invoiced for the grouped procedure. The details of the applicant where the invoice should be sent should be clearly stated in the cover letter.

The fee will become due on the date of the notification of the administrative validation to the applicant and fees will be payable within 45 calendar days of the date of the said notification. After
approximately 15 days an invoice will be sent to the applicants billing address held on the Agency’s file.

The invoice will contain details of the product and type of procedure involved, the fee amount, the customer purchase order number associated with the procedures invoiced and financial information.

Applicants requiring a purchase order number or similar references on the invoice are requested to clearly indicate it on the cover letter or application for accompanying the dossier. The Agency does not accept stand-alone notifications of purchase order numbers that are not associated with a dossier. Applicants not requiring a purchase order number on the invoice should also clearly state this in the cover letter. Applicants are requested to provide this information in the cover letter template.

Guidance on how to pay an invoice can be found on our website.

References

- More information about fees and fee payment in the Centralised Procedure
6. Worksharing of variations

6.1. What is worksharing and what types of variations can be subject to worksharing?

Article 20 of Commission Regulation (EC) N° 1234/2008 (the ‘Variations Regulation’) sets-out the possibility for a MAH to submit the same Type IB or Type II variation, or the same group of variations affecting more than one marketing authorisation from the same MAH in one application.

Applicants belonging to the same mother company or group of companies and applicants having concluded agreements or exercising concerted practices concerning the placing on the market of the medicinal product(s) concerned, have to be taken as “the same marketing authorisation holder”.

Extensions are excluded from worksharing.

Based on Articles 7 and 20 of the Variations Regulation, when a group of variations only consists of Type IA/ IA_in variations affecting several marketing authorisations, this is considered as a “group” of variations and not a “worksharing” procedure. However, it is possible to include a group of Type IA/ IA_in Variation(s) with a Type IB or Type II variation, which is submitted for a worksharing procedure. In such case, the review of the Type IA/ IA_in variation will be performed as part of the worksharing procedure.

In order to avoid duplication of work in the evaluation of such variations, a worksharing procedure has been established under which one authority (the ‘reference authority’), chosen amongst the competent authorities of the Member States and the Agency, will examine the variation on behalf of the other concerned authorities.

Where at least one of the concerned marketing authorisations has been authorised via the centralised procedure, the Agency will be the ‘reference authority’. In all other cases, a national competent authority chosen by the Coordination Group, taking into account the recommendation of the holder, will act as the ‘reference authority’.

Purely national marketing authorisations are excluded from the worksharing procedure.
6.2. **What variation(s) would be considered acceptable for worksharing?**

In order to benefit from a worksharing procedure, it is expected that the same change(s) will apply to the different medicinal products concerned, with either no or limited need for assessment of a potential product-specific impact. Therefore, where the 'same' change(s) to different marketing authorisations require the submission of individual supportive data sets for each medicinal product concerned which each require a separate product-specific assessment, such changes will not benefit from worksharing.

Grouped variations can be subject to a worksharing procedure, provided that the same group of variations applies to all medicinal products concerned by the worksharing procedure.

Examples of changes which would be considered suitable for evaluation under worksharing:

**Clinical/Pharmacovigilance**
- Implementation of class labelling
- Changes to multiple generic MAs containing the same active substance
- Changes to single-substance MA and fixed-combination MA containing the same active substance
- Proposal for combination use, affecting both MAs
- PSUR outcome implementation for MAs with same active substance

**Quality**
- Changes to ASMF
- Update of CEP certificate
- Revision of test method for the active substance

Additional examples will be regularly included in this document, to reflect accumulated experience.
6.3. What pre-submission steps will apply to a worksharing procedure?

Rev Oct 2010

In order to facilitate the planning of a worksharing procedure, MAHs are advised to inform the Agency at least 3 months in advance of the submission of a variation/group of variations to be subject to a worksharing procedure, together with an explanation as to why the holder believes that a worksharing procedure is suitable, by means of a 'letter of intent'.

The 'letter of intent' should provide the following information:

- Type(s) and scope of variation(s)
- Overview of MAs concerned
- Explanation that all MAs belong to the same MAH
- Explanation / justification for suitability of worksharing
- Rapporteurs and Reference Member States (RMS) of the medicinal products concerned, if applicable
- MAH target submission date
- MAH contact person for the worksharing procedure

A template for such a 'letter of intent' is available on the Agency’s website. The letter should be sent to PA-BUS@ema.europa.eu. The Agency will share the letter of intent with the CMD group, in case the proposed worksharing procedure includes nationally authorised medicinal products.

Upon receipt of the letter of intent, the Agency will appoint a coordinating Product Team Leader and will decide whether the proposed worksharing procedure is acceptable. Subsequently, the Agency will initiate the Rapporteur appointment procedure.

Following an ‘Expression of Interest’ and based on a rota system, the CHMP Chairman will appoint a Rapporteur (and Co-Rapporteur when the application includes a new indication) for the procedure. It is expected that the (Co-)Rapporteur will be one of the Rapporteurs of the centrally authorised medicinal products or a CHMP member representing one of the RMSs for the nationally authorised products. The MAH will be informed accordingly.

A shorter pre-submission phase is envisaged, in cases where:

- a proposed worksharing procedure relates to multiple MAs for the same medicinal product authorised via the centralised procedure only;
- the variations subject to the worksharing procedure concern the implementation of urgent safety-related changes;
- the variations subject to the worksharing procedure concern the implementation of changes requested by CHMP (e.g. following PSUR or FUM assessment).

Worksharing procedure for multiple centrally authorised medicinal products ('duplicates')
The submission of a formal letter of intent is not required. Marketing Authorisation Holders are advised to inform by email the PTL for the medicinal products concerned of the intention to submit a worksharing procedure at least one month in advance of the submission of the variation/group of variations.
6.4. **How shall I present a variation application under worksharing?** Rev Oct 2010

The submission requirements as set-out in the PAG sections for the different types of variations will also apply to variations subject to worksharing, but the application should be provided as one integrated submission package (eCTD sequence) per product, covering all variations applied for.

This will include a cover letter and application form, together with separate supportive documentation for each medicinal product concerned and revised product information (if applicable) for each medicinal product concerned.

- One original cover letter addressed to the Agency and National Competent Authorities, in case MRP/DCPs are part of the worksharing procedure, clearly indicating that the application is submitted for a worksharing procedure together with a short overview of all medicinal products concerned, with their respective Rapporteurs and RMSs, as well as an overview of the submission format for the different products, if applicable (e.g. eCTD, NeeS). Please refer to the eCTD Variations Q&A document, for guidance on the submission of variations in eCTD format. In case MRP/DCPs are part of the worksharing procedure, the MAH should also include a confirmation that the worksharing applications have been submitted to all Member States where the products concerned are authorised (= RMSs and CMSs) and that the relevant national fees have been paid. A formal letter with the worksharing applicant and contact person for the worksharing procedure should be provided with the worksharing application. A template cover letter for worksharing procedures including CAPs and MRP only is available on the Agency’s website.

- One completed EU variation application form, listing all medicinal products concerned and declaring all variations included in the group in the section ‘type of changes’, as well as a justification for the proposed worksharing (and grouping if applicable) in the ‘precise scope and background’ section of the application form. The response from the Agency on the acceptability of the worksharing application, further to the submission of the letter of intent should be attached to the application form.

- If MRP/DCPs are part of the worksharing procedure, relevant product and Member State details should be provided as an Annex B to the application form (using the template available on the Agency’s website)

- Supportive documentation for each product (including the revised summary of product characteristics, labelling and/or package leaflet, if applicable). This will allow the Agency and the national competent authorities to update the dossier of each marketing authorisation included in the worksharing procedure with the relevant amended or new information.

- Where the overall design and readability of the outer and immediate packaging and/or package leaflet is affected, the need for the provision of mock-ups or specimens should be discussed with the Medical Information Sector of the Agency on a case-by-case basis.

For queries relating to the presentation of the application, please contact the Agency.

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**References**

- Procedural guideline
- eCTD Variations Q&A document
- Template cover letter for worksharing procedures including CAPs and MRP only
6.5. **How and to whom shall I submit my variation application under worksharing? Rev. March 2013**

The worksharing application must be submitted at the same time to all relevant authorities, i.e. in case the application consists of centrally and nationally authorised medicinal products, to the Agency and all Member States where the products concerned are authorised.

**Submission to the European Medicines Agency**

The EMA strongly recommends using the eSubmission Gateway or the eSubmission Web Client as the preferred submission method for all eCTD submissions. More information on how to register and connect to the Gateway / Web Client can be found in the eSubmission website and detailed information on the required naming conventions and file formats can be found in the eSubmission Gateway Q&A document and specific details how to submit Worksharing applications using the eSubmission Gateway and in the Web Client Q&A. Applicants must not send duplicate submissions electronically or via CD-ROM or DVD as this might lead to delays in the handling of applications.

Applications that are sent using the eSubmission Gateway and eSubmission Web Client will receive an automated 'acknowledgement', confirming whether the submission has passed the relevant technical validation criteria and whether it has been uploaded to the agency’s review tool. There is no need to send any separate paper cover letters for these submissions, as the cover letter will be in the relevant part of eCTD module 1 in PDF format.

MAHs not yet using the eSubmission Gateway or the Web Client solution should send their variation applications for worksharing as CD-ROM or DVD to the attention of the Product and Application Business Support (PA-BUS) at the following address:

Product and Application Business Support (PA-BUS)
European Medicines Agency
Loading Dock
Ontario Way
Canary Wharf
UK - London, E14 4HB

**For Centrally Authorised medicinal products (eCTD mandatory)**

Only one CD-ROM or DVD containing the relevant eCTD sequence for each product, should be submitted to the Agency, together with an original, signed cover letter when using this format of submission. The coordinating Product Team Leader should be indicated in copy ("cc") on the cover letter (no additional copy needed).

**For nationally authorised medicinal products (eCTD not mandatory)**

eSubmission Gateway or Web Client package or alternatively one CD-ROM or DVD of the Variation application form and supportive documentation for each product should be submitted to the Agency. Paper submissions should be avoided.

**Submission to the National Competent Authorities**

Where nationally authorised medicinal products are part of the worksharing, the same application as submitted to the Agency should be submitted to all Member States, even if some products are
not relevant to some MSs. This will allow all the involved Parties (The Agency, MSs and Committee Members) to receive the full data for the worksharing application.

If amendments are requested by the Agency as a result of the validation, updated documentation should also be submitted to the MSs.

For submission addresses for national competent authorities, please refer to the “Transfer of information contained in Notice to Applicants, Volume 2A, Chapter 7”.

**Submission to the Rapporteur and CHMP members**

The dossier requirements for post-authorisation submissions in the centralised procedure should be followed.

For a full overview of dossier requirements for National Competent Authorities of (Co-)Rapporteur and Committee members, including delivery addresses, please refer to the following document: Dossier requirements for Centrally Authorised Products (CAPs).

**References**

- Commission Regulation (EC) No 1234/2008
- Electronic Variation application form / Variation application form, The Rules governing Medicinal Products in the European Union, Notice to Applicants, Volume 2C
- Template for cover letter
- Dossier requirements for Centrally Authorised Products (CAPs)
- Classification Guideline
- Article 5 Recommendation
- TIGes Harmonised Guidance for eCTD Submissions in the EU
- eSubmission website
- eSubmission Gateway Q&A
- eSubmission Gateway Web Client Q&A

**6.6. What procedure number will be given to variation applications under worksharing? Rev Oct 2010**

The Agency will allocate a ‘high-level’ cross-products procedure number, which will be used for the handling of worksharing procedures affecting more than one medicinal product. A new procedure code (abbreviation) is used for worksharing procedures i.e. “WS”. As the ‘high-level’ number can not be allocated to one single product, the procedure number will therefore contain ”xxxx” as a place-holder for the product number.

Example: EMEA/H/xxxx/WS/0003

For each medicinal product concerned by the worksharing procedure, the following worksharing number (which includes a reference to the “WS” procedure to which it belongs) will be allocated:
Example: EMEA/H/C/prod_nb/WS0003 which was submitted as part of the 3rd worksharing procedure received by the Agency "WS/0003"

Worksharing applications for a group of variations will include the suffix "/G" e.g. EMEA/H/xxxx/WS/0004/G and EMEA/H/C/prod_nb/WS/0004/G.

For worksharing procedures, the ‘high-level’ procedure number can be obtained from the Agency shortly before submission by sending your request with a copy of the draft cover letter to: PA-BUS@ema.europa.eu. However, in case of delayed submission, the indicated worksharing number may already have been allocated to another worksharing procedure submitted in the mean time.

6.7. How will variation applications under worksharing be handled (timetable)? What will be the outcome of the evaluation of a variation application under worksharing? Rev Oct 2010

The MAH must submit the variation application for worksharing, at the latest by the recommended submission dates published on the Agency’s website (See also Human Medicines – Procedural Timetables / Submission dates).

In general, variations submitted for worksharing will follow a 60-day evaluation timetable. This period may however be reduced having regard to the urgency of the matter, particularly for safety issues, or may be extended to 90 days for Type II variations concerning changes or additions to the therapeutic indication.

For the detailed evaluation timetable, please refer to the PAG for Type II variations “How shall my Type II application be handled (timetable)?”

Upon finalisation of the review of the variations subject to the worksharing procedure, the Agency will issue an opinion reflecting the final outcome of the procedure. Such opinion will also list any variations (e.g. as part of a group, or for a specific medicinal product) which are not considered approvable, unless they had been withdrawn by the holder during the procedure. The same general principles as for grouped variations apply - see the PAG on grouping "What will be the outcome of the evaluation of a grouped variation application”?

Schematic structure of the CHMP Opinion and Annexes for an application under worksharing, consisting of centrally and nationally authorised medicinal products:

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Note:

The Annex A for each centrally authorised medicinal product included in the worksharing procedure will be annexed to the CHMP opinion.

The Annex B includes information on the nationally authorised medicinal products included in the worksharing application (if applicable). A template for the Annex B is available on the Agency’s website.
6.8. How and when will the marketing authorisations be updated following a worksharing procedure? When can I implement the approved changes? Rev Oct 2010

Upon adoption of the CHMP Opinion on the worksharing procedure, the Agency will inform the MAH, the Commission and Member States concerned (if applicable) as to whether the opinion is favourable or unfavourable (including the grounds for the unfavourable outcome), as well as whether the Commission Decision granting the Community marketing authorisations require any amendments.

Re-examination

Art. 9(2) of Regulation (EC) No 726/2004, also applies to CHMP Opinions adopted for worksharing procedures. This means that the MAH may give written notice to the Agency/CHMP that he wishes to request a re-examination within 15 days of receipt of the opinion (after which, if he does not appeal, the opinion shall be considered as final). The grounds for the re-examination request must be forwarded to the Agency within 60 days of receipt of the opinion. In case the MAH requests that the committee consults a SAG in connection with the re-examination, the applicant should inform the CHMP as soon as possible of this request.

The CHMP will appoint a different (Co-) Rapporteur, to co-ordinate the re-examination procedure. Within 60 days from the receipt of the grounds for re-examination, the CHMP will consider whether its opinion is to be revised. If considered necessary, an oral explanation can be held within this 60 days timeframe.

Decision-Making Process for centrally authorised medicinal products

Upon receipt of the final CHMP opinion, the Commission shall, where necessary, amend the marketing authorisation for each centrally authorised medicinal product to reflect the approved variation(s) within 30 days. A single decision will be issued for each centrally authorised medicinal product.

The Agency will apply the existing post-opinion timeframes, as set-out in the Agency’s Post-Opinion Linguistic Checking Procedure document. The QRD linguistic check will be performed on one set of Annexes of one centrally authorised medicinal product. In case of comments, it will be up to the MAH to correctly implement the same amendments in the other centrally authorised products, as appropriate.

The Agency, in cooperation with the QRD members and the MAH will aim at providing final, checked translations for all centrally authorised products included in the worksharing procedure to the Commission at opinion stage in case of a worksharing procedure for a Type IB variation or by Day +27 in case of a worksharing procedure for a Type II variation. (See also: “When do I have to submit revised product information? In all languages?”).
Upon receipt of the final opinion, the Member States concerned shall approve the final opinion, inform the Agency accordingly and where necessary, amend the national marketing authorisations within 30 days, unless a referral procedure in accordance with Article 31 of Directive 2001/83/EC is initiated within 30 days following receipt of the final opinion.

For practical reasons it has been agreed that if a Member State cannot approve the final opinion of the reference authority, that Member State should initiate an art 31 referral within 10 days after distribution of the final opinion, in order to leave 20 days for the amendment of the marketing authorisations concerned. If a Member State does not initiate an art 31 referral within 10 days after distribution of the final opinion, the final opinion is considered approved by the Member State. For further information, please refer to the CMD(h) Best Practice Guide on Worksharing.

**Implementation**

Type IB variations approved via a worksharing procedure, may be implemented upon receipt of the favourable CHMP opinion.

Type II variations approved via a worksharing procedure, may be implemented 30 days after receipt of the favourable CHMP opinion.

Variations related to safety issues must be implemented within a timeframe agreed between the marketing authorisation holder and the Commission.
6.9. What fee do I have to pay for variation applications under worksharing? Rev Oct 2010

For information on the fees applicable for worksharing applications, please refer to the explanatory note on fees payable to the European Medicines Agency.

Where a worksharing application is considered ‘invalid’ (i.e. an assessment process can not be started), an administrative fee may be charged by the Agency.

Only the worksharing applicant will be invoiced for the worksharing procedure. The details of the applicant where the invoice should be sent to should be clearly stated in the cover letter.

More information about fees and fee payment in the Centralised Procedure

References

- Explanatory note on fees payable to the European Medicines Agency

6.10. When do I have to submit revised product information? In all languages? Rev Oct 2010

In case the Variation(s) subject to worksharing affects SPC, labelling and/or package leaflet, the revised product information Annexes must be submitted as follows:

a. Worksharing procedure for Type II variation(s)

At submission (Day 0)

- English language: complete set of Annexes for all CAPs electronically only in Word format (highlighted)

After CXMP Opinion (Day +5)

- All EU languages (incl. NO+IS): complete set of annexes of one CAP electronically only in Word format (highlighted)

After Linguistic check (Day +25)

- All EU languages (incl. NO+IS): complete set of annexes for all CAPs electronically only in Word format (highlighted) and in PDF (clean)

Only one centrally authorised medicinal product will undergo a linguistic check. In the cases where the changes to the product information may vary between products, the product with the most complex changes will generally be the one subject to linguistic check.
According to Art. 23 of Regulation (EC) No 1234/2008, Commission decisions on worksharing procedures will be adopted without a Standing Committee procedure. Consequently, there will be no further revision of the translations of the Annexes after Day +25.

b. Worksharing procedures for Type IB variations

At submission (Day 0)

- English language: complete set of Annexes for all CAP electronically only in Word format (highlighted)
- All EU languages (incl. NO+IS): complete set of annexes of one CAP electronically only in Word format (highlighted)

Day +25 after start of procedure

- All EU languages (incl. NO+IS): complete set of annexes of all CAPs electronically only in Word format (highlighted) and in PDF (clean)

For such procedures a linguistic review will take place in parallel to the scientific assessment. It is therefore expected that the texts provided at Day +25 after start of procedure will be the final texts.

Overview:

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<th>Type II variation(s)</th>
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* = complete set of Annexes i.e. Annex I, II, IIIA and IIIB submitted as one document per language
The ‘complete set of Annexes’ includes Annex, I, II, IIIA and IIIB i.e. all SPC, labelling and PL texts for all strengths and pharmaceutical forms of the product concerned, as well as Annex II. The complete set of Annexes must be presented sequentially (i.e. Annex I, II, IIIA, IIIB) as one document for each official EU language. Page numbering should start with "1" (bottom, centre) on the title page of Annex I. The ‘QRD Convention’ published on the Agency’s website should be followed. When submitting the full set of Annexes in PDF format, this should be accompanied by the completed formatting checklist which provides guidance on how to correctly prepare the PDF versions.

The electronic copy of all languages should be provided as part of the variation application in the eCTD for the product concerned, on CD-ROM/DVD. Highlighted changes should be indicated via ‘Tools – Track changes’. Clean versions should have all changes ‘accepted’.

Icelandic and Norwegian language versions must always be included.

The Annexes provided should only reflect the changes introduced by the Variation concerned. However, in exceptional cases where MAHs take the opportunity to introduce minor linguistic amendments in the texts (e.g. further to a specimen check) this should be clearly mentioned in the cover letter and in the scope section of the application form. In addition, the section “present/proposed” in the application form should clearly list the minor linguistic amendments introduced for each language. Alternatively, such listing may be provided as a separate document attached to the application form. Any changes not listed, will not be considered as part of the variation application.

In such cases and in cases where any other ongoing procedures may affect the product information Annexes, the MAH is advised to contact the Agency in advance of submission or finalisation of the procedure(s) concerned.

For those variations which affect the Annex A (e.g. introduction of a new presentation), the following principles apply:

Upon adoption of the opinion, the Agency will prepare and send to the MAH the revised English Annex A for each CAP reflecting the new/amended presentation.

After CHMP Opinion (Day +5), the MAH provides the Agency with the electronic versions of the complete set of Annexes in all languages, if applicable, as well as the translations of the revised Annex A for each CAP as a separate word document.

Reference
- The linguistic review process of product information in the centralised procedure – Human
7. Changing the (Invented) Name of a Centrally Authorised Medicinal Product

7.1. Can I change the (Invented) Name of my CAP?

A medicinal product is authorised under the Centralised Procedure with a single name. In accordance with Commission Regulation (EC) No 1234/2008, the (invented) name of a medicinal product may be changed after authorisation through a Type IA\textsubscript{IN} Variation (No A.2).

This can be done either in case of a marketing authorisation being granted under INN (common name) together with a trademark or the name of the MAH or in case the MAH wants to change the initial invented name.

Such a Type IA\textsubscript{IN} variation is possible provided that the check by the Agency on the acceptability of the new name had been finalised and was positive before implementation of the new name. Immediately upon implementation of the change, the MAH must submit a Type IA\textsubscript{IN} variation notification to the Agency for review (see PAG on Type IA variations).

References
- Guideline on the acceptability of invented names for human medicinal products processed through the centralised procedure

7.2. Is the Invented Name (IN) checking procedure mandatory for the new proposed IN?

The checking procedure for the proposed IN is mandatory and is the same as that applied for new medicinal product applications, as described in the Agency pre-submission guidance (see also How will I know if the proposed (trade) name of my medicinal product is acceptable from a public health point of view?).

Therefore, Marketing Authorisation Holders are advised to submit the new proposed IN at the latest 4-6 months prior to their intended implementation of the new name and Type IA\textsubscript{IN} variation application since a final positive outcome of the checking procedure is required before implementation and submission of the Type IA\textsubscript{IN} Variation.

In order to enable applicants to propose names that will be acceptable for centrally approved medicinal products, it is crucial that the “Guideline on the acceptability of invented names for human medicinal products processes through the centralised procedure” (CPMP/328/98), is followed.

References
- Guideline on the acceptability of invented names for human medicinal products processed through the centralised procedure
7.3. How shall I present my IN change application? Rev. March 2013

The application will follow the standard type IA variation dossier requirements as described in this guidance: See "How shall I present my Type IA Variation Notification". The MAH is therefore requested to provide:

**Module 1.0**
- a. Cover letter

**Module 1.2**
- b. Electronic Variation application form or Variation Application form with the following attachments:
  - c. A copy of the relevant page(s) of the Classification Guideline. As requested in the application form, MAHs must tick the boxes in front of each condition and required documentation. It is recommended to add a reference to the location of each required document in the submitted dossier (e.g. 'Appendix 1', 'Appendix 2'…).
  - d. A copy of the Agency’s letter of acceptance of the new name

**Module 1.3**
- e. Product information (Summary of Product Characteristics, Annex II, Labelling and Package Leaflet): see “Type I variations - When do I have to submit revised product information? In all languages?”

The EMA strongly recommends using the eSubmission Gateway or the eSubmission Web Client as the preferred submission methods for all eCTD submissions. More information on how to register and connect to the Gateway / Web Client can be found in the eSubmission website and detailed information on the required naming conventions and file formats can be found in the eSubmission Gateway Q&A document and the Web Client Q&A. Applicants must not send duplicate submissions electronically or via CD-ROM or DVD as this might lead to delays in the handling of applications.

MAHs not yet using the eSubmission Gateway and eSubmission Web Client solutions should send one CD-ROM or DVD of the application in eCTD format = to the attention of the Product and Application Business Support (PA-BUS), as well as to the (Co-)Rapporteur at the time of submission. See also “How shall I present and submit my Type IA/ IAIN Variation(s)?”

The Product Team Leader should be indicated in copy (“cc”) on the cover letter (no additional copy needed).

For a full overview of dossier requirements for National Competent Authorities of CHMP (Co-) Rapporteur and Committee members, including delivery addresses, please refer to the following document: Dossier requirements for Centrally Authorised Products (CAPs).

**References**
- Commission Regulation (EC) No 1234/2008
- Electronic Variation application form / Variation application form, The Rules governing Medicinal Products in the European Union, Notice to Applicants, Volume 2C
- Guideline on the acceptability of invented names for human medicinal products processed through the centralised procedure
- Template for cover letter
7.4. Do I need to submit amended mock-ups/specimens with my variation?

Mock-ups

It is not required to provide mock-ups with the variation application.

Specimens

Where the overall design and readability of the outer and immediate packaging and/or package leaflet is affected, the need for the provision of specimens should be discussed with the Agency Medical Information Sector on a case-by-case basis. For further guidance please refer to “Type I Variations - Do I have to submit mock-ups and specimens?“.

References

- The Revised Checking Process of Mock-Ups and Specimens of outer/immediate labelling and package leaflets of human medicinal products in the Centralised Procedure (EMEA/305821/2006)
8. Annual Re-assessment *Rev. March 2013*

8.1. What is the Annual Re-assessment?

In exceptional circumstances and following consultation with the applicant, an authorisation may be granted subject to certain conditions, so called specific obligations (SOs), in particular relating to the safety of the medicinal product, notification to the national competent authorities of any incident relating to its use, and action to be taken.

Such a marketing authorisation may only be granted when the applicant can show that he is unable to provide comprehensive data on the efficacy and safety of the medicinal product under normal conditions of use and must be based on one of the grounds set out in Annex I of Directive 2001/83/EC (rarity of the condition, state of scientific knowledge, ethical grounds).

Continuation of such a marketing authorisation shall be linked to the annual re-assessment of the conditions mentioned above. The SO(s) may include an identified programme of studies to be conducted within a specified time period and aim at the provision of additional safety and efficacy data, e.g. a registry or an observational cohort study, where data is collected and reported annually based on an agreed protocol.

The outcome of the annual re-assessment will reflect the status of fulfilment of the SO(s) and the impact of the specific obligation data on the benefit / risk profile of the medicinal product and will conclude on whether the marketing authorisation should be maintained, varied or suspended based on the review of these two elements.

References

- Regulation (EC) No 726/2004, Article 14(8)
- Guideline on procedures for the granting of a marketing authorisation under exceptional circumstances

8.2. Are the CHMP Co-Rapporteur and the PRAC involved in the assessment?

The CHMP Co-Rapporteur is normally not involved in the evaluation of the annual re-assessment application. The PRAC will be systematically involved in the assessment and the resulting PRAC advice will focus on the assessment of the SO data and any methodological aspects of the generation of these data in case they are falling within the definition of a non-interventional PASS. With this the PRAC is providing its particular expertise to the CHMP in terms of the SO assessment. It is not required for the PRAC to perform a peer review of the full CHMP assessment report nor is the intention to duplicate the annual-re-assessment.
8.3. How shall I present my annual re-assessment application?

Annual re-assessment applications should be presented as follows, in accordance with the appropriate headings and numbering of the EU-eCTD format:

Module 1: 1.0 Cover letter with the following documents attached:

- A chronological tabulated summary table of the Specific obligations (SOs) stating the following for each: full title, SIAMED reference number, agreed due date indicated in Annex II of the Product Information, date of submission and procedure within which the SO was submitted (if appropriate), and status. The cover letter should also contain the template table to facilitate submission and registration.
- Revised list of pending Specific Obligations (where applicable).

1.3 Product Information

Texts for SmPC, Annex II, Labelling and Package Leaflet, if changes are proposed. See also annual re-assessment - “When do I have to submit (revised) product information? In all languages?”

1.4 Information about the Expert

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

Module 2: 2.5 Clinical Overview

The Expert report addressing the data as well as the status of fulfilment of the SOs and their impact on the overall benefit/risk profile of the medicinal product, in the form of a Clinical Overview update or addendum, will be based on:

- Information already submitted to fulfil SOs
- Information submitted at the anniversary date to address outstanding SOs
- Critical evaluation of status of fulfilment

2.7 Clinical Summaries

Clinical summaries will generally need to be updated, as appropriate, when new clinical study reports are submitted.

Module 5: 5.3.6 Reports of Efficacy and Safety Studies (as appropriate):

5.3.5.1 Study Reports of Controlled Clinical Studies Pertinent to the Claimed Indication
5.3.5.2 Study Reports of Uncontrolled Clinical Studies
5.3.5.3 Reports of Analyses of Data from More Than One Study
5.3.5.4 Other Clinical Study Reports

References

- Regulation (EC) No 726/2004 (EEC), Article 14(8)
8.4. Can I submit PSUR or an RMP with my annual re-assessment application?

A PSUR cannot be submitted as part of an annual re-assessment procedure (see also Q&A 'PSURs').

Updates to the RMP should not be submitted within the annual re-assessment application as a rule. If SO data submitted with the annual re-assessment warrant a RMP update, an updated RMP could exceptionally be submitted. In such a case, it is recommended to liaise with the Agency in advance of the planned submission to agree on the details of such an update.

8.5. When, how and to whom shall I submit my annual re-assessment application?

The annual re-assessment application should in principle be submitted on the anniversary date of the Commission Decision granting the Marketing Authorisation. Flexibility in the submission date could however be envisaged, in order to synchronise the annual re-assessment submission with the submission of data from the SOs. The annual re-assessment application submission could be adjusted within a maximum of +/- 2 months in such cases.

Marketing Authorisation Holders are therefore advised to discuss and agree the annual re-assessment submission date with the Agency and the Rapporteur well in advance of the submission.

The MAH shall submit the annual re-assessment application at the latest by the recommended submission dates published on the EMA website. See also Human Medicines – Procedural Timetables / Submission dates).

The EMA strongly recommends using the eSubmission Gateway or the eSubmission Web Client as the preferred submission methods of all eCTD submissions. More information on how to register and connect to the Gateway / Web Client can be found in the eSubmission website and detailed information on the required naming conventions and file formats can be found in the Gateway Q&A and the Web Client Q&A. Applicants must not send duplicate submissions electronically or via CD-ROM or DVD as this might lead to delays in the handling of applications.

Applications that are sent using the eSubmission Gateway and eSubmission Web Client will receive an automated ‘acknowledgement’, confirming whether the submission has passed the relevant technical validation criteria and weather it has been uploaded to the agency’s review tool. There is no need to send any separate paper cover letters for these submissions, as the cover letter will be in the relevant part of eCTD module 1 in PDF format.

MAHs not yet using the eSubmission Gateway or the Web Client solution should send their annual re-assessment applications as CD-ROM or DVD for the attention of the Product and Application Business Support (PA-BUS) at the following address:

Product and Application Business Support (PA-BUS)
European Medicines Agency
Loading Dock
Ontario Way
Canary Wharf
UK - London, E14 4HB

Only one CD-ROM or DVD (in eCTD format) of the supportive documentation should be submitted to the Agency, together with one original, signed cover letter. The Product Team Leader should be indicated in copy “cc” on the cover letter (no additional copy needed).
Where applicable, revised product information Annexes should be included in electronic (Word and PDF) format (see also Annual Reassessment - 'When do I have to submit (revised) product information? In all languages’) in the same eSubmission Gateway and eSubmission Web Client package or CD-ROM or DVD within a folder called 'working documents'.

One electronic copy of the annual re-assessment application supportive documentation should be submitted to the (Co-)Rapporteurs after the eSubmission Gateway / Web Client confirmation of a technically valid submission. When submitted as CD-ROM or DVD the applicant should dispatch an electronic copy to the (Co-)Rapporteur at the same time as dispatching to the EMA.

The EMA will check whether the application is correct and complete before start of the procedure. Any additional information/documentation requested by the Agency prior to the start of the procedure should be equally provided to (Co-)Rapporteurs.

Upon completion of the Agency check, one electronic copy of the full annual re-assessment application should be provided for each of the other committee members.

It is essential that identical eCTD sequences are circulated to Committee Members. Any minor changes that affect the "md5 checksum" will lead to inconsistency and possibly result in future technical invalidity.

Where applications are amended during the agency’s review, such as e.g. responses to a request for supplementary information, new or consolidated eCTD sequence should be provided in order to maintain the eCTD life-cycle. Please refer to the TIGes Harmonised Guidance and eCTD specific advice.

For a full overview of dossier requirements for National Competent Authorities of (Co-) Rapporteur and Committee members, including delivery addresses, please refer to the following document: Dossier requirements for Centrally Authorised Products (CAPs).

Please note that the EMA only accepts submissions made in a mandatory eCTD format.

Identical annual re-assessment applications for multiple Marketing Authorisations must be submitted separately. Each Marketing Authorisation is considered to be a stand-alone dossier. For this reason no cross-references will be accepted and applications must be submitted for each concerned product as a complete and stand-alone document.

References

- Directive 2001/83/EC
- Regulation (EC) 726/2004
- Template for cover letter
- Dossier requirements for Centrally Authorised Products (CAPs)
- TIGes Harmonised Guidance for eCTD Submissions in the EU
- eSubmission website
- eSubmission Gateway Q&A
- eSubmission Gateway Web Client Q&A
8.6. How shall my annual re-assessment be handled (timetable)?

The EMA will acknowledge receipt of a valid application of an annual re-assessment and shall start the procedure in accordance with the recommended starting dates published on the EMA website.

The submission deadlines and full procedural detailed timetables are published as a generic calendar on the EMA website (see: submission deadlines and full procedural timetables).

The published timetables identify the submission, start and finish dates of the procedures as well as other interim dates/milestones that occur during the procedure.

The following 90-day timetable shall normally apply:

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<th>DAY</th>
<th>ACTION</th>
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<tr>
<td>D 1</td>
<td>Start of procedure</td>
</tr>
<tr>
<td>D 30</td>
<td>CHMP Rap AR circulated to both CHMP/PRAC</td>
</tr>
<tr>
<td>D 35</td>
<td>PRAC Rap (draft) advice circulated to both CHMP/PRAC</td>
</tr>
<tr>
<td>D 46</td>
<td>Adoption of PRAC Advice (with PRAC divergent views appended)</td>
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<tr>
<td>D 60</td>
<td>Comments by CHMP members</td>
</tr>
<tr>
<td>D 80</td>
<td>Updated CHMP Rap AR considering PRAC advice and CHMP comments</td>
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<tr>
<td>D 90</td>
<td>Adoption of CHMP opinion and CHMP AR (or List of Outstanding Issues)</td>
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MAHs are encouraged to contact the Agency in advance of the submission, in case clarification on the timetable for the annual re-assessment application is needed.

The MAH will be informed of the adopted timetable at the start of the procedure.

In case issues are identified which prevent the adoption of an opinion, the CHMP will adopt a List of Outstanding Issues together with a timetable stating the date by when the MAH must submit the requested data. It is expected that no clock-stop will be necessary for submission of responses. For clock-stops longer than 1 month the MAH should send a justified request to the Agency for agreement by the CHMP. The CHMP assessment of the responses will take up to 30 or 60 days depending on the complexity and amount of data provided by the MAH. The MAH will receive the adopted timetable together with the List of Outstanding Issues.

8.7. What could be the outcome of my annual re-assessment?

Depending on the CHMP assessment, one of the following outcomes can be envisaged:

- Maintenance of the MA considering that:
  - SOs remain in place unchanged
  - Data from the SOs does not necessitate changes to the MA (e.g. changes to benefit risk profile of medicinal product and product information)

All SOs will be reviewed again at the time of the next annual re-assessment together with their impact on the benefit/risk profile of the medicinal product.
Variation of the MA considering that:

- SOs need to be modified; and/or
- Data from the SOs necessitates changes to the MA (e.g. changes to benefit risk profile of medicinal product and/or product information)

All SOs will be reviewed again at the time of the next annual re-assessment together with their impact on the benefit/risk profile of the medicinal product.

Suspension/revocation of the MA considering that:

- Data from the SOs affects benefit/risk profile of the medicinal product to the extent it necessitates the suspension/revocation of the MA for the medicinal product

or

- The status of compliance with the SOs is unsatisfactory and therefore the CHMP considers that they, as conditions to the marketing authorisation, have not been fulfilled.

Exceptionally, the CHMP may consider that all specific obligations have been fulfilled and will therefore recommend the lifting of the exceptional circumstances.

The Agency will subsequently forward the opinion to the European Commission, the Member States, Norway and Iceland and the Marketing Authorisation Holder together with the CHMP assessment report. The Decision-Making Process of the European Commission starts once the opinion with annexes in all official EU languages has been received.

When the annexes to the Marketing Authorisation have not been affected by the annual re-assessment, no Commission Decision will be issued.

References

- Directive 2001/83/EC
- Regulation (EC) 726/2004

8.8. Can I submit my annual re-assessment within the renewal?

The annual re-assessment of medicinal products authorised under exceptional circumstances may not be included as part of the 5-year renewal procedure, as their scope is separate.

References

- Guideline on the processing of renewals in the centralised procedure (EMEA/CPMP/2990/00) Rev 4

8.9. Do I have to pay fees for an annual re-assessment?

There is no fee payable for the annual re-assessment.
8.10. **What impact do ongoing Variation(s) (Type IA/IB or Type II) have on the annual re-assessment?**

In case that an ongoing variation (Type IA/IB or Type II) affects the product information and is not yet finalised at the time of the submission of the annual re-assessment application, the last product information adopted/accepted by the EC/CHMP/EMA should be used in the submission of the annual re-assessment application by the MAH.

If the variation procedure is finalised (notification of a Type IA/IB or opinion of the Type II) before or upon finalisation of the annual re-assessment procedure, the accepted/adopted variation changes should be used in the product information of the annual re-assessment.

The Agency advises MAHs to contact the Product Team Leader in advance of the annual re-assessment submission, in order to discuss how to optimally handle the above issue.

8.11. **Do I have to submit mock-ups and specimens?**

No mock-ups or specimens are required for the annual renewal of a conditional marketing authorisation. For details of when to submit mock-ups and specimens in the post-authorisation phase of your medicinal product, please refer to the revised checking process of mock-up and specimens information on the EMA web.

8.12. **When do I have to submit (revised) product information? In all languages?**

Changes to Annexes resulting from the annual re-assessment may be submitted as part of the annual re-assessment procedure. In such cases, revised product information will be considered in the annual re-assessment opinion and implementation of changes will not initiate a separate variation procedure.

In case the annual re-assessment affects the SmPC, Annex II, labelling and/or package leaflet, the revised product information Annexes must be submitted as follows:

<table>
<thead>
<tr>
<th>Day</th>
<th>Language</th>
<th></th>
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</thead>
<tbody>
<tr>
<td>At submission:</td>
<td>EN</td>
<td>- Electronically</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Word format (highlighted)</td>
</tr>
<tr>
<td></td>
<td>Other EEA</td>
<td>- /</td>
</tr>
<tr>
<td>Day 5 after CHMP opinion</td>
<td>All EEA</td>
<td>- Electronically</td>
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<td></td>
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<tr>
<td>Day 25 after CHMP opinion</td>
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<td>- Electronically</td>
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<td>- Word format (highlighted)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- PDF format (clean)</td>
</tr>
</tbody>
</table>
In case the annual re-assessment affects ONLY the Annex II, no or a shorter post-opinion translation timetable may be considered by the EMA on a case-by-case basis.

The ‘complete set of Annexes’ includes Annex, I, II, IIIA and IIIB i.e. all SmPC, labelling and PL texts for all strengths and pharmaceutical forms of the product concerned, as well as Annex II.

The complete set of Annexes must be presented sequentially (i.e. Annex I, II, IIIA, IIIB) as one document for each official EU language. Page numbering should start with “1” (bottom, centre) on the title page of Annex I. The ‘QRD convention’ published on the EMA website should be followed. When submitting the full set of Annexes in PDF format, this should be accompanied by the completed formatting checklist which provides guidance on how to correctly prepare the PDF versions.

The electronic copy of all languages should be provided as part of the annual re-assessment application on CD-ROM/DVD. Highlighted changes should be indicated via ‘Tools – Track changes’. Clean versions should have all changes ‘accepted’.

The Annexes provided should only reflect the changes introduced by the annual re-assessment. However, in exceptional cases where MAHs take the opportunity to introduce minor linguistic amendments in the texts (e.g. further to a specimen check) this should be clearly mentioned in the cover letter or as a separate document attached to the cover letter. Any changes not listed, will not be considered as part of the annual re-assessment.

In such cases and in cases where any other ongoing procedures may affect the product information Annexes, the MAH is advised to contact the Product Team Leader in advance of submission or finalisation of the procedure(s) concerned.

If within 15 days of receipt of the opinion, the MAH does not inform the Agency of any intention to request a re-examination, the Agency will then forward the opinion (and the required annexes), to the Commission, the Member States, Norway and Iceland and the MAH together with the CHMP assessment report.

The Decision-Making Process of the Commission starts once the opinion with Annexes in all official EU languages, as appropriate, has been received. When the Annexes to the Marketing Authorisation have not been affected by the annual re-assessment, no Commission Decision will be issued.

8.13. Will there be any publication on the outcome of my annual re-assessment?

The EPAR (published on the EMA website) will be revised to reflect the CHMP conclusions in relation to the annual re-assessment procedure.

The CHMP meeting highlights published following each CHMP meeting gives information in its Annex on opinions in relation to annual re-assessment applications. This information includes the invented name of the product, its INN, the name of the MAH and the procedure outcome. In addition, it is commented if there are (no) remaining grounds to keep the MA under exceptional circumstances.

References

- CHMP meeting highlights

9.1. How long is my marketing authorisation valid?

In accordance with Article 14 (1-3) of Regulation (EC) No 726/2004, a marketing authorisation is valid for five years from the date of notification of the Commission Decision to the marketing authorisation holder, and is renewable upon application by the Marketing Authorisation Holder. Once renewed, the marketing authorisation will be valid for an unlimited period, unless the competent authority decides, on justified grounds relating to pharmacovigilance, including for example exposure of an insufficient number of patients to the medicinal product concerned, to proceed with one additional five-year renewal.

An exception to the rule mentioned above are those marketing authorisations granted under Art. 14(7) of Regulation (EC) No 726/2004, ‘conditional’ marketing authorisations. They are valid for 1 year and should be renewed annually. For further information on the ‘conditional’ marketing authorisations, see Q&A 50 of the pre-submission procedural guidance ‘Could my application qualify for a conditional marketing authorisation?’.

The renewal decision will usually refer to the expiry date of the preceding marketing authorisation so that the renewed authorisation will be valid from the date of the previous expiry.

Marketing authorisations under exceptional circumstances are also valid for 5 years but are additionally subject to an annual reassessments (See “Annual Re-Assessment”).

References

- Article 14 (1-3) of Regulation (EC) No 726/2004
- Article 24 of Directive 2001/83/EC
- Guideline on the processing of renewals in the centralised procedure (EMEA/CHMP/2990/00 Rev.4)

9.2. When shall I submit my renewal application?

According to the Union legislation, Marketing Authorisation Holders (MAH) must apply for a renewal at least nine months before the expiry date of the Marketing Authorisation (MA).

The MA validity period is expressed in Commission Decisions, as follows:

- Initial MA: by reference to the date of notification of the Commission Decision to the MAH. Such notification dates are published in the Official Journal and can be found in the Commission’s ‘Register’ for each product concerned.
- Renewal: By reference to the previous MA expiry date.

In order for a marketing authorisation to remain valid, a renewal is required five years after the granting of the marketing authorisation, irrespective of whether the marketing authorisation is suspended or not.

In the case a MAH does not submit the renewal application the MA will expire automatically.
In order to ensure that the Commission Decision on the renewal application can be issued before expiry of the MA, MAHs should take into account the following principles when planning for their renewal submission:

- The renewal application must be submitted at least 9 months before the MA expiry date.
- The start of the evaluation process will be the nearest possible starting date, as published by the EMA in the "Human Medicines – Procedural Timetables / Submission dates".
- The CHMP assessment process can take up to 120 days of active time.
- The Decision-Making Process (incl. Standing Committee consultation) for renewal procedures is 67 days.

The MAH should agree in advance the submission date of the renewal application with the EMA who will then liaise with the Rapporteur and Co-Rapporteur, as appropriate, taking into account the recommended starting dates published on the EMA website in order to agree on the time table for the procedure.

In addition, as the quality of the renewal application and of the product information translations will be key to ensure a timely start and finalisation of the renewal procedure, MAHs are strongly advised to contact their PTL for a pre-renewal -submission dialogue at least 1 year in advance of MA expiry.

References

- Guideline on the processing of renewals in the centralised procedure (EMEA/CPMP/2990/00 Rev. 4)
- Community Register of medicinal product : website of the European Commission

9.3. How shall I present my renewal application?

Renewal applications should be submitted in eCTD format and have to contain the documents listed in the Annex 2 of the Guideline on the processing of renewals in the centralised procedure (EMEA/CHMP/2990/00 Rev.4) and which are the following listed below:

Module 1:

1.0 Cover letter. The cover letter should contain the template table to facilitate submission and registration.

1.2 Renewal Application form. The completed electronic EU variation application form (eAF) or the application form, including the details of the marketing authorisation concerned, with the following annexes (the form is available in the Notice To applicants (Volume 2C):

- List of all authorised product presentations for which renewal is sought in tabular format (following the template for Annex A to CHMP Opinion)

Note: The Marketing Authorisation Holder (MAH) 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. In cases where the MAH does not wish to renew certain product presentations (e.g. a certain pharmaceutical form, strength or pack-size), this should be clearly indicated in the cover letter and they should not be included in the appended list.
• 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 submission 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, and PSURs, giving the procedure number (where applicable), date of submission, date of approval (if approved) and brief description of the change
• Chronological list of conditions and Specific Obligations submitted since the granting of marketing authorisation or last renewal indicating scope, status, date of submission and date when issue has been resolved (where applicable)
• Revised list of all remaining conditions and Specific Obligations (where applicable)
• A statement, or when available, a certificate of GMP compliance, not more than three years old, for the manufacturer(s) of the medicinal product listed in the application issued by an EEA competent authority or MRA partner authority. A reference to the Community EudraGMP database, if available will suffice.
• For manufacturing sites of the medicinal product not located in the EEA or in the territory of an MRA partner, a list of the most recent GMP inspections carried out indicating the date, inspection team and outcome
• In accordance with Article 46(f) of Directive 2001/83/EC, manufacturing authorisation holders are required to use as starting materials only active substances which have been manufactured in accordance with the detailed guidelines on good manufacturing practice for starting materials as adopted by the Community. The following declaration are required:
  • A declaration by the Qualified Person (QP) of each of the manufacturing authorisation holders (i.e. located in the EEA) listed in the application form where the active substance is used as a starting material
  • A declaration by the Qualified Person (QP) of the manufacturing authorisation holder(s) listed in the application as responsible for batch release.
  • These declarations should state that all the active substance manufacturer(s) referred to in the application form operate in compliance with the detailed guidelines on good manufacturing practice for starting materials.

1.3.1 Summary of Product Characteristics, Labelling and Package Leaflet
• A relevant example of the proposed texts for SmPC, Annex II, outer and inner labelling and Package Leaflet in English has to be provided. In addition a word version highlighting the changes proposed by the MAH should also be included in the application.
• Note: All other language versions are only to be submitted after adoption of the opinion (See also "When do I have to submit revised product information? In all languages?").

1.3.3 Specimen
Please refer to question 1.9 Do I have to submit mock-ups and specimens?

1.4 Information about the Expert

In cases where MAHs wish to distinguish these declarations from any previous declarations, the EMA Renewal procedure Number may be included on top.

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

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

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

1.8.1 Summary of Pharmacovigilance System (if applicable):

• Proof that the applicant has at his disposal a qualified person responsible for pharmacovigilance,
• Member state in which the QPPV resides and operates his/her tasks
• The contact details of the QPPV
• A statement signed by the marketing authorization holder to the effect that the marketing authorization holder has the necessary means to fulfil the tasks and responsibilities listed in Title IX of Directive 2001/83/EC
• The reference to the location of the pharmacovigilance system master file (country)

The MAH may combine this information in one single statement, signed by the MAH and QPPV. If available, the PSMF number assigned by the extended EudraVigilance Medicinal Product Dictionary (XEVMPD) should be included in the statement.

1.8.2 Risk Management Plan:

The updated RMP and where relevant, the new RMP.

Where there are no new data justifying changes to the latest approved RMP, the MAH should provide in the clinical overview declaration and confirm that the current approved RMP remain unchanged and applicable.

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

Module 2:

2.3 Addendum to Quality Overall Summary

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

The Addendum to the Quality Overall Summary should also include:

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

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

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

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

The Addendum to the Clinical Overview should contain the following information:

Note: Marketing authorisation holders are advised to consider the Good Vigilance Practice Module on PSURs as guidance for the preparation of the sections of the clinical overview described below.

- History of pharmacovigilance system inspections (date, inspecting authority, site inspected, type of inspection and if the inspection is product specific, the list of products concerned) and an analysis of the impact of the findings overall on the benefit/risk balance of the medicinal product.
- Worldwide marketing authorisation status: overview of number of countries where the product has been approved and marketed worldwide.
- Actions taken for safety reasons during the period covered since the initial marketing authorisation or since the last renewal until 90 days prior to renewal submission: description of significant actions related to safety that had a potential influence on the benefit-risk balance of the approved medicinal product (e.g. suspension, withdrawal, temporary halt or premature ending of clinical trial for safety reasons, issue requiring communication to healthcare professionals...).
- Significant changes made to the Reference Information (RI) during the period covered since the initial marketing authorisation or since the last renewal. A track changes version of the document identifying the changes made during the period covered since the initial marketing authorisation or since the last renewal should also be provided until 90 days prior to renewal submission.
- Meaningful differences between the RI and the proposals for the Summary of Product Characteristics. A proposed SmPC, Package leaflet and Labelling should also be provided
- Estimated exposure and used patterns: data on cumulative exposure of subjects in clinical trials as well as of patients from marketing exposure. If the marketing authorisation holder becomes aware of a pattern of use of the medicinal product considered relevant for the implementation of the safety data, a brief description should be provided; such patterns may include in particular off-label use.
- Data in summary tabulations: Summary tabulations of serious adverse events from clinical trials as well as summary tabulations of adverse reactions from post-marketing data sources reported during the period covered since the initial marketing authorisation or since the last renewal until 90 days prior to renewal submission.
- Summaries of significant safety and efficacy findings from clinical trials and non-interventional studies: description of any significant safety findings that had an impact on the conduct of clinical trials or non-interventional studies. It should also address whether milestones from post-authorisation safety studies, post-authorisation efficacy studies, studies from the RMP
pharmacovigilance plan and studies conducted as condition and obligations of the marketing authorisation, have been reached in accordance with agreed timeframes.

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

- Risk evaluation: the MAH should summarise any information related to important safety issues, evaluation and characterisation of risks as well as effectiveness of risk minimisations for the period covered since the initial marketing authorisation or since the last renewal until 90 days prior to renewal submission.

- Benefit evaluation: the MAH should summarise important efficacy and effectiveness information (including information on lack of efficacy) for the period covered since the initial marketing authorisation or since the last renewal until 90 days prior to renewal submission.

- Benefit-risk balance: a discussion on the benefit-risk balance for the approved indication should be presented, based on the above information.

- Late-breaking information: The MAH should summarise the potentially important safety, efficacy and effectiveness findings that arise after the data lock point but during the period of preparation of the addendum to the clinical overview.

The Clinical Expert Statement should:

- Confirm that no new 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.

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

It should be noted that the responsibility for the quality of the submitted documentation lies with the MAH and is crucial to the overall process. For queries relating to the presentation of the application, please contact the EMA.

References

- Guideline on the processing of renewals in the centralised procedure (EMEA/CPMP/2990/00 Rev. 4)

- Electronic Renewal application form / Renewal application form

- Template for cover letter

9.4. How and to whom shall I submit my renewal application?

The EMA strongly recommends using the eSubmission Gateway or the eSubmission Web Client as the preferred submission methods for all eCTD submissions. More information on how to register and
connect to the Gateway / Web Client can be found in the eSubmission website and detailed information on the required naming conventions and file formats can be found in the Gateway Q&A and the Web Client Q&A. Applicants must not send duplicate submissions electronically or via CD-ROM or DVD as this might lead to delays in the handling of applications.

Applications that are sent using the eSubmission Gateway and eSubmission Web Client will receive an automated 'acknowledgement', confirming whether the submission has passed the relevant technical validation criteria and weather it has been uploaded to the agency’s review tool. There is no need to send any separate paper cover letters for these submissions, as the cover letter will be in the relevant part of eCTD module 1 in PDF format.

MAHs not yet using the eSubmission Gateway or the Web Client solution should send their Renewal applications as CD-ROM or DVD for the attention of the Product and Application Business Support (PA-BUS) at the following address:

Product and Application Business Support (PA-BUS)
European Medicines Agency
Loading Dock
Ontario Way
Canary Wharf
UK - London, E14 4HB

Only one CD-ROM or DVD (in eCTD format) of the Renewal application form and supportive documentation should be submitted to the Agency, together with one original, signed cover letter. The Product Team Leader should be indicated in copy “cc” on the cover letter (no additional copy needed).

One electronic copy of the Renewal application form and supportive documentation should be submitted to the (Co)-Rapporteurs, after the eSubmission Gateway / Web Client confirmation of a technically valid submission. When submitted as CD-ROM or DVD the applicant should dispatch an electronic copy to the (Co)-Rapporteur at the same time as dispatching to the EMA.

The EMA will check whether the renewal application is correct and complete ("validation") before start of the procedure. Any additional information/documentation requested by the Agency prior to the start of the procedure should be equally provided to (Co-)Rapporteurs.

Upon validation by the Agency, one electronic copy of the full renewal application should be provided for each of the other committee members, including any additional data or information supplied during the validation phase (as appropriate).

It is essential that identical eCTD sequences are circulated to Committee Members. Any minor changes that affect the "md5 checksum" will lead to inconsistency and possibly result in future technical invalidity.

Where applications are amended during the agency’s review, such as e.g. responses to a request for supplementary information, new or consolidated eCTD sequence should be provided in order to maintain the eCTD life-cycle. Please refer to the TIGes Harmonised Guidance and eCTD specific advice.

For a full overview of dossier requirements for National Competent Authorities of (Co-)Rapporteur and Committee members, including delivery addresses, please refer to the following document: Dossier requirements for Centrally Authorised Products (CAPs).

Please note that the EMA only accepts submissions made in a mandatory eCTD format.

Identical renewal applications for multiple Marketing Authorisations must be submitted separately. Each Marketing Authorisation is considered to be a stand-alone dossier. For this reason no cross-
references will be accepted and Renewal applications must be submitted for each concerned product as a complete and stand-alone document.

References

- Template for cover letter
- Dossier requirements for Centrally Authorised Products (CAPs)
- TIGes Harmonised Guidance for eCTD Submissions in the EU
- eSubmission website
- eSubmission Gateway Q&A
- eSubmission Gateway Web Client Q&A

9.5. How shall my renewal application be handled (timetable)?

The MAH should submit the renewal application by the recommended submission dates published on the EMA website and, in any case, no later than 9 months before the MA ceases to be valid.

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

The timetable for the scientific evaluation by the CHMP will be set in order to allow the Commission Decision to be adopted before the expiry date of the marketing authorisation. Please refer to Annex 1 of the Guideline on the processing of renewals in the centralised procedure.

Full procedural detailed timetables are published as a generic calendar on the EMA website (see: submission deadlines and full procedural timetables).

The published timetables identify the start and finish dates of the procedures as well as other interim dates/milestones that occur during the procedure.

The renewal procedure will involve the CHMP Rapporteur and Co-Rapporteur as well as the PRAC Rapporteur who have been appointed for the medicinal product.

<table>
<thead>
<tr>
<th>Day 1</th>
<th>Start of procedure (see published dates on EMA website)</th>
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<tbody>
<tr>
<td>Day 45</td>
<td>CHMP Rapporteur’s Assessment Report sent to CHMP Co-Rapporteur and PRAC Rapporteur</td>
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<tr>
<td>Day 60</td>
<td>Receipt of Joint CHMP Rapporteur / Co-Rapporteur Assessment report and PRAC Rapporteur Advice including AR on RMP when applicable. Circulate to EMA, CHMP and PRAC members and</td>
</tr>
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</table>
Day 70 | MAH, highlighting major issues if any.

Day 70 | Comments CHMP, PRAC members on the joint Assessment report and PRAC Advice including AR on RMP when applicable.

Day 73-76 | Discussion at PRAC Meeting: Adoption of PRAC Advice including AR on RMP when applicable.

Day 90 | Discussion at CHMP.
- If no outstanding issues: adoption of opinion.
- If outstanding issues: adoption of List of Outstanding Issues + decision on possible oral explanation by MAH

Day 91 | MAH provides answers to list of outstanding issues to CHMP (Co) Rapporteurs/PRAC Rapporteur, CHMP, PRAC members and EMA (without clock stop) or (with clock stop)

Day 106 | Revised AR from CHMP Rapporteur / Co-Rapporteur and PRAC Advice including updated AR on RMP when applicable. Circulated to CHMP and PRAC members and MAH

Day 120 | Adoption of CHMP opinion. Possible Oral explanation by MAH

Re-examination

Art. 9(2) of Regulation (EC) No 726/2004 also applies to CHMP Opinions adopted for renewal applications. This means that the MAH may notify the EMA/CHMP 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 EMA within 60 days of receipt of the opinion. If the MAH wishes to appear before the CHMP for an oral explanation, the request should also be sent at this stage.

The CHMP will appoint a different CHMP Rapporteur and where necessary a different CHMP Co-Rapporteur to co-ordinate the re-examination procedure. In case a PRAC Rapporteur is deemed necessary, he/she will be appointed. 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 days timeframe.

References

- Guideline on the processing of renewals in the centralised procedure (EMEA/CPMP/2990/00 Rev 4)
9.6. **What fee do I have to pay for a renewal?**

For information about fees and fee payment in the Centralised Procedure, please refer to the explanatory note on fees payable to the European Medicines Agency and consult the Fees payable page.

In case an inspection is required, please note that in addition to the renewal fee, an inspection fee will be requested (see also Inspections website).

References

- Fees payable to the European Medicines Agency

9.7. **Can other non-renewal specific changes be included in the renewal application?**

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 as data emerge.

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

Where there are adequate and objective reasons not to renew the marketing authorisation in its existing terms and changes are necessary to the SmPC, labelling and package leaflet 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 SmPC guideline, other relevant guidelines impacting on the product information, or EMA/QRD Product Information Templates should be considered within the renewal procedure.

The section “present/proposed” in the application form should clearly list all changes introduced to the product information (incl. any minor linguistic amendment introduced for each language). Alternatively, such listing may be provided as a separate document attached to the application form. Any changes not listed, will not be considered as part of the renewal application.

References

- Guideline on the processing of renewals in the centralised procedure (EMEA/CPMP/2990/00 Rev. 4)

9.8. **How to handle other ongoing variation applications during the renewal procedure and what impact may ongoing procedures have on the renewal procedure?**

Although MAHs are advised to avoid other procedures at the time of renewal, such situations cannot be excluded.
In case that an ongoing variation (Type IA/IB or Type II) affects the product information and is not yet finalised at the time of the submission of the renewal application, the last product information adopted/accepted by the EC/CHMP/EMA should be used in the submission of the renewal application.

If the variation procedure is finalised before or upon finalisation of the renewal procedure, the accepted/adopted variation changes should be reflected in the renewal product information.

In such cases where any other ongoing procedure may affect the product information, the MAH is advised to contact the Agency in advance of the submission or finalisation of the procedure(s) concerned.

9.9. **Do I have to submit mock-ups and specimens?**

**Mock-ups**

No mock-ups are required at the time of renewal of the marketing authorisation.

**Specimens**

At renewal, the Agency will perform a new check of the specimens across all marketed product presentations. Relevant example specimens (latest versions) should be provided to the EMA, for each strength, pharmaceutical form and container type in the smallest marketed pack-size. Ideally multi-lingual specimens should be provided but, if not available, a single-language specimen may be submitted. As such the Agency will receive and check at least one example specimen of the whole range of marketed product presentations after 5 years, in one submission.

The specimens should be submitted **by post** using the specimen submission form, to the following address:

Mock-ups and specimens  
European Medicines Agency  
7 Westferry Circus  
Canary Wharf  
London E14 4HB  
United Kingdom

The Agency will perform a general check from the viewpoint of readability in parallel to the renewal assessment procedure within 25 working days, and will check if any previous comments on specimens have been duly implemented. The applicant will be informed about the outcome of the check.

In case of comments on the specimens, the MAH should submit responses and/or updated mock-ups, as applicable, to the EMA (murugine@ema.europa.eu) prior to the finalisation of the renewal procedure. EMA will discuss the best and feasible corrective action with the MAH, taking into account the nature and amount of issues identified.

When submitting responses and/or updated mock-ups to the EMA, applicants may use the mock-ups and specimens responses form.

**Note:**

If the MAH plans to change the overall design and readability of the labelling and/or package leaflet around the time of renewal, submission of specimens of the “old” product design will not be necessary. In such a case, the same principles as for Type II Variations will apply (see also Type II Variations – Do I have to submit mock-ups and specimens?). This approach should however be discussed with the
product team leader in advance of the renewal submission (e.g. at the renewal pre-submission meeting).

The above principles also apply to mock-ups for Iceland. The mock-ups should be sent by e-mail to mockups@ima.is. See also http://www.imca.is/IMCA/News/nr/1263.

No mock-ups and specimens are required for Norway.

References

- The checking process of mock-Ups and specimens of outer/immediate labelling and package leaflets of human medicinal products in the Centralised Procedure

9.10. When do I have to submit revised product information? In all languages?

Where the MAH proposes no amendments to the product information, only an electronic copy of the latest approved product information (full set of Annexes) in English must be submitted to the Agency.

In case the renewal application affects SmPC, Annex II, labelling and/or package leaflet, the revised product information Annexes must be submitted as follows:

At submission (Day 0)

- English language version: complete set of Annexes electronically only in Word format (highlighted)

After CXMP Opinion (Day +5)

- All EU languages (incl. EN, NO+IS): complete set of annexes electronically only in Word format (highlighted)

After Linguistic check (Day +25)

- All EU languages (incl. EN, NO+IS): complete set of annexes electronically only in Word format (highlighted) and in PDF (clean)

Translations of the adopted product information in all EU languages (including English, Icelandic and Norwegian) are to be provided electronically (in one Eudralink package) to the Member States Contact Points for Translations by Day +5 and copied to the EMA PTL secretary.

The ‘full set of Annexes’ includes Annex I, II, IIIA, IIB and, if applicable, IV and 127a (i.e. all SmPC, labelling and PL texts for all strengths and pharmaceutical forms of the product concerned, as well as Annex II and , if applicable, Annex IV and 127a as appropriate).

The ‘full set of Annexes’ must be presented sequentially (i.e. Annex I, II, IIIA, IIB, and if applicable, IV) as one word document for each official EU language. Annex 127a (when applicable) must be presented as a separate PDF document with "127a" removed from the title page together with the
word files highlighted with tracked changes. All translations should be numbered as ONE document, starting with “1” (bottom, centre) on the title page of Annex I and Annex (127a) when applicable. The ‘QRD Convention’ published on the EMA website should be followed. When submitting the full set of Annexes in PDF format, this should be accompanied by the completed formatting checklist which provides guidance on how to correctly prepare the PDF versions. Highlighted changes should be indicated via ‘Tools – Track changes’. Clean versions should have all changes ‘accepted’.

The revised Annex A, where applicable, is to be provided as a separate word document per language, to the Agency.

The Annexes provided should only reflect the changes introduced by the renewal application. However, in exceptional cases where MAHs take the opportunity to introduce minor linguistic amendments in the texts (e.g. further to a specimen check) this should be clearly mentioned in the cover letter.

In addition, the section “present/proposed” in the application form should clearly list the minor linguistic amendments introduced for each language.

Alternatively, such listing may be provided as a separate document attached to the application form. Any changes not listed, will not be considered as part of the renewal application.

References

• Guideline on the processing of renewals in the centralised procedure (EMEA/CPMP/2990/00 Rev. 4)
• The new Linguistic Review Process of Product Information in the Centralised Procedure (EMEA/5542/02 Rev. 4.2)

9.11. When will the linguistic checking of the product information take place?

During the scientific renewal assessment, a detailed pre-opinion review of the EN product information will be performed by the Agency (PIQ / Product Information Quality) and QRD (Quality Review Document) members. In parallel to the checking performed by EMA/PIQ and QRD members, Annex IIIB will also be subject to review by experts of Patients’ Organisations (PCWP – Patients’ and Consumers’ Working Party). A compilation of all comments received will be sent to the MAH by day 75. When providing a revised EN version for adoption of the opinion, applicants should inform the Agency if and why certain comments are not taken into account.

Translations of the adopted product information in all other EU languages (Including Icelandic and Norwegian) are to be provided electronically (in one Eudralink package) to the Member States Contact Points for Translations (list of members states contact points for translation) by Day +5 and copied to the PTL secretary.

The following checks post-opinion will apply:

<table>
<thead>
<tr>
<th>Check by</th>
<th>When</th>
<th>Who</th>
<th>Scope</th>
</tr>
</thead>
<tbody>
<tr>
<td>QRD/ ‘Member State’</td>
<td>Day +5 to +19</td>
<td>Member States</td>
<td>Detailed review of (highlighted changes in) all translations</td>
</tr>
</tbody>
</table>
Comments will be sent directly by the Member States to the MAH at the latest by Day +19, with a copy to the PTL secretary.

The MAH will send the final translations with tracked changes, incorporating the Member States’ comments, electronically to the PTL secretary by Day +25.

The Agency will check if all Member States’ comments have been implemented before sending the final translations to the Commission. In order to facilitate and accelerate the check of the implementation of the Member States’ comments, the applicant should indicate in QRD Form 2 for each language if all comments have been implemented or not. In the latter case, a justification should be provided for the appropriate language(s) stating why certain comments are not reflected in the final texts.

In case the Renewal affects only the Annex II, no or a shorter post-opinion translation timetable may be considered by the Agency on a case-by-case basis.

Following receipt of the final translations from the EMA, the Commission will start the 22-day Standing Committee consultation, addressing only legal and public health matters (which means in principle no further linguistic review).

The Commission Decision on the renewal will be issued after consultation of the Standing Committee, by Day +67.

**References**

- The new Linguistic Review Process of Product Information in the Centralised Procedure (EMEA/5542/02 Rev. 4.2)
- SOP/EMEA/0046: PIQ/QRD Pre-opinion Review of Product Information for Renewal Procedures
- Procedure for review of information on medicinal products by Patient’s/Consumers Organisations (PCOs) (EMA/174255/2010 Rev. 2)
- SOP/EMEA/0048: QRD Post-opinion Review of Product Information for Renewal Applications, Annual Reassessments, Type II Variations (60/90 Days) and Referrals

**9.12. What do I need to do if I do not want to renew the Marketing authorisation of certain product presentations or the entire product?**

Marketing Authorisation Holders (MAH) should only complete the renewal application form for those presentations which the MAH would like to renew. In cases where the MAH does not wish to renew certain product presentations (e.g. a certain pharmaceutical form, strength or pack-size) this should be clearly indicated in the cover letter (See also "How shall I present my renewal application").

In case the MAH does not wish to renew the entire Marketing Authorisation (i.e. all presentations) a letter to this effect should be addressed to the Agency and the European Commission, at the latest 9
months prior to the expiry of the concerned Marketing Authorisation, clearly and detailed stating if the marketing authorisation is surrendered for any reasons beyond purely commercial ones.

References
- Article 14(b) of Regulation (EC) No 726/2004
- Directive 2001/83/EC

9.13. **Will there be any publication on the outcome of my renewal application?**

The EPAR (published on the EMA website) will be revised to implement the CHMP conclusions in relation to the renewal procedure.

The CHMP meeting highlights following each CHMP meeting gives information in its Annex on opinions in relation to renewal applications. This information includes the invented name of the product, its INN and the name of the MAH.

In case of an unfavourable opinion, recommending suspension or non-renewal of the MA, a Question and Answer (Q&A) document will be published by the Agency. This will include information and reasons for such an opinion. The information will be provided in lay language, so that it can be understandable for the general public.

References
- CHMP meeting highlights
- EPARs
10. Annual renewal of conditional marketing authorisations –
New March 2013

10.1. How long is my conditional marketing authorisation valid?

In accordance with Article 14 (7) of Regulation (EC) No 726/2004, a conditional marketing authorisation is valid for one year from the date of notification of the Commission Decision to the marketing authorisation holder, and it is renewable upon application by the Marketing Authorisation Holder.

The conditional MA validity period is expressed in Commission Decisions, as follows:

• Initial MA: by reference to the date of notification of the Commission Decision to the MAH. Such notification dates are published in the Official Journal and can be found in the Commission’s ‘Register’ for each product concerned.
• Renewal: By reference to the previous MA expiry date.

In order for a conditional marketing authorisation to remain valid, a renewal application has to be made annually (irrespective of whether the marketing authorisation is suspended).

The renewal decision will usually refer to the expiry date of the preceding marketing authorisation so that the renewed authorisation will be valid from the date of the previous expiry.

For further information on the ‘conditional’ marketing authorisations, see Q&A 50 of the pre-submission procedural guidance ‘Could my application qualify for a conditional marketing authorisation?’.

References

• Article 14 (7) of Regulation (EC) No 726/2004

10.2. When shall I submit my annual renewal application?

According to the legislation, Marketing Authorisation Holders (MAH) must apply for an annual renewal at least six months before the expiry date of the conditional Marketing Authorisation (MA).

In case a MAH does not submit a renewal application, the conditional MA will expire automatically.

Once a renewal application has been submitted within this deadline, the conditional marketing authorisation shall remain valid until a decision is adopted by the Commission in accordance with Article 10 of Regulation (EC) No 726/2004.

In order to ensure that the Commission Decision on the renewal application can be issued ideally before expiry of the conditional MA, MAHs should take into account the following principles when planning for their renewal submission:

• The renewal application must be submitted at least 6 months before the MA expiry date.
• The start of the evaluation process will be the nearest possible starting date, as published by the EMA in the "Human Medicines – Procedural Timetables / Submission dates").
• The CHMP assessment process can take up to 90 days.
• The Decision-Making Process (incl. Standing Committee consultation) for renewal procedures is 67 days.

The MAH should agree in advance the submission date of the renewal application with the EMA who will then liaise with the CHMP and PRAC Rapporteurs, as appropriate, taking into account the recommended starting dates published on the EMA website, in order to agree on the time table for the procedure.

In addition, as the quality of the renewal application will be key to ensure a timely start and finalisation of the renewal procedure, MAHs are strongly advised to contact their PTL for a pre-renewal - submission dialogue.

References
• Community Register of medicinal product : website of the European Commission

10.3. How shall I present my annual renewal application?

In order to allow the CHMP to confirm the benefit-risk balance of the medicinal product and to review the specific obligations and their timeframes for completion, the marketing authorisation holder should provide the following information in their annual renewal application in eCTD format:

Module 1:

1.0 Cover letter. The cover letter should contain the template table to facilitate submission and registration, 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)

Note: In cases where the MAH does not wish to renew certain product presentations (e.g. a certain pharmaceutical form, strength or pack-size), this should be clearly indicated in the cover letter and they should not be included in the appended list.

- Details of contact persons:
  - Qualified person in the EEA for pharmacovigilance
  - Contact person in the EEA with the overall responsibility for product defects and recalls
  - Contact person for scientific service in the EEA in charge of information about the medicinal product

- List of EU Member states/Norway/Iceland where the product is on the market and indicating for each country which presentations are marketed and the launch date

- Chronological list of all post-authorisation submissions since the granting of the Marketing Authorisation or last renewal such as approved or pending Type IA/IB and Type II variations,

4 Please note that there is no application form available for annual renewals and that the application form for standard 5year renewals available on the eSubmission web is not applicable to annual renewals of conditional marketing authorisations and cannot be used
Extensions, Art 61(3) Notifications, other post-authorisation measures (PAMs), USR, and PSURs, giving the procedure number (where applicable), date of submission, date of approval (if approved) and brief description of the change

- Chronological list of conditions and Specific Obligations submitted since the granting of marketing authorisation or last renewal indicating scope, status, date of submission and date when issue has been resolved (where applicable)

- A statement, or when available, a certificate of GMP compliance, not more than three years old, for the manufacturer(s) of the medicinal product listed in the application issued by an EEA competent authority or MRA partner authority. A reference to the Community EudraGMP database, if available, will suffice.

- For manufacturing sites of the medicinal product not located in the EEA or in the territory of an MRA partner, a list of the most recent GMP inspections carried out indicating the date, inspection team and outcome

In accordance with Article 46(f) of Directive 2001/83/EC, manufacturing authorisation holders are required to use as starting materials only active substances which have been manufactured in accordance with the detailed guidelines on good manufacturing practice for starting materials as adopted by the Community. The following declarations are required:

- A declaration by the Qualified Person (QP) of each of the manufacturing authorisation holders (i.e. located in the EEA) listed in the application form where the active substance is used as a starting material

- A declaration by the Qualified Person (QP) of the manufacturing authorisation holder(s) listed in the application as responsible for batch release.

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

1.3.1 Summary of Product Characteristics, Labelling and Package Leaflet

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

- Note: All other language versions are only to be submitted after adoption of the opinion (See also “When do I have to submit revised product information? In all languages?”).

1.4 Information about the Expert

In cases where MAHs wish to distinguish these declarations from any previous declarations, the EMA Renewal procedure Number may be included on top.

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

1.8.1 Summary of Pharmacovigilance System (if applicable):

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

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

- The contact details of the QPPV
• A statement signed by the marketing authorisation holder to the effect that the marketing
authorisation holder has the necessary means to fulfil the tasks and responsibilities listed in Title IX
of Directive 2001/83/EC

• The reference to the location of the pharmacovigilance system master file (country)

The MAH may combine this information in one single statement, signed by the MAH and QPPV. If
available, the PSMF number assigned by the extended EudraVigilance Medicinal Product Dictionary
(XEVMPD) should be included in the statement.

1.8.2 Risk Management Plan:

As a general rule, it is not expected that the data from or the circumstances of the Specific
Obligation(s), which are key to the application, necessitate the submission of an updated RMP or even
a new RMP. Therefore, no updated/new RMP is expected to be submitted.

Where there are no new data from the Specific Obligation(s) justifying changes to the latest approved
RMP, the MAH should provide in the clinical overview a declaration and confirm that the current
approved RMP remains unchanged and applicable. Where there is no RMP for the medicinal product,
this should also be stated in the cover letter.

In case data from the Specific Obligation(s) necessitate an update of the RMP, this should be discussed
with the PTL in advance of the submission, in order that the RMP update timing (with the Renewal or
another temporally adjacent procedure) is agreed.

Module 2:

2.5 Addendum to Clinical Overview

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

The Addendum to the Clinical Overview should contain the following information:

• Discussion of quality, non-clinical, clinical pharmacology, efficacy and safety information as well as
any inspection information accumulated since the latest Renewal (or since the Marketing
Authorisation in case of the first annual Renewal).

• PSUR data, although not primarily assessed within the Renewal procedure should also be described
and discussed and they should include the following elements:
  – History of pharmacovigilance system inspections (date, inspecting authority, site inspected,
type of inspection and if the inspection is product specific, the list of products concerned) and
an analysis of the impact of the findings overall on the benefit/risk balance of the medicinal
product.
  – Worldwide marketing authorisation status: overview of number of countries where the product
has been approved and marketed worldwide.
  – Actions taken for safety reasons during the period covered since the initial marketing
authorisation or since the last renewal until 90 days prior to renewal submission: description of
significant actions related to safety that had a potential influence on the benefit-risk balance of
the approved medicinal product (e.g. suspension, withdrawal, temporary halt or premature
ending of clinical trial for safety reasons, issue requiring communication to healthcare
professionals...).
- Significant changes made to the Reference Information (RI) during the period covered since the initial marketing authorisation or since the last renewal. A track changes version of the document identifying the changes made during the period covered since the initial marketing authorisation or since the last renewal should also be provided until 90 days prior to renewal submission.

- Meaningful differences between the RI and the proposals for the Summary of Product Characteristics. A proposed SmPC, Package leaflet and Labelling should also be provided.

- Estimated exposure and used patterns: data on cumulative exposure of subjects in clinical trials as well as of patients from marketing exposure. If the marketing authorisation holder becomes aware of a pattern of use of the medicinal product considered relevant for the implementation of the safety data, a brief description should be provided; such patterns may include in particular off-label use.

- Data in summary tabulations: Summary tabulations of serious adverse events from clinical trials as well as summary tabulations of adverse reactions from post-marketing data sources reported during the period covered since the initial marketing authorisation or since the last renewal until 90 days prior to renewal submission.

- Summaries of significant safety and efficacy findings from clinical trials and non-interventional studies: description of any significant safety findings that had an impact on the conduct of clinical trials or non-interventional studies. It should also address whether milestones from post-authorisation safety studies, post-authorisation efficacy studies, studies from the RMP pharmacovigilance plan and studies conducted as condition and obligations of the marketing authorisation, have been reached in accordance with agreed timeframes.

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

- Risk evaluation: the MAH should summarise any information related to important safety issues, evaluation and characterisation of risks as well as effectiveness of risk minimisations for the period covered since the initial marketing authorisation or since the last renewal until 90 days prior to renewal submission.

- Benefit evaluation: the MAH should summarise important efficacy and effectiveness information (including information on lack of efficacy) for the period covered since the initial marketing authorisation or since the last renewal until 90 days prior to renewal submission.

- Benefit-risk balance: a discussion on the benefit-risk balance for the approved indication should be presented, based on the above information.

- Late-breaking information: The MAH should summarise the potentially important safety, efficacy and effectiveness findings that arise after the data lock point but during the period of preparation of the addendum to the clinical overview.

Note: Marketing authorisation holders are advised to consider the Good Vigilance Practice Module on PSURs as guidance for the preparation of the sections of relevance described above.

An Interim Report should be included in a separate section in the clinical overview addendum. The interim report on the fulfilment of the specific obligations should include details for each specific obligation. The aim of this report is to inform about the status of the data that is the subject of a specific obligation, to provide interim data as appropriate and agreed, and to inform about the likelihood that the applicant will be able to provide the data. If data from a specific obligation is
available in the form of a clinical study report for submission at the time of an annual renewal application, this should be submitted in Module 5 of such an application.

**Requirements for the interim report on the specific obligations**

One report should be submitted for the product including all remaining specific obligations. The structure and contents of the interim report will vary depending on the type of study and available data. The purpose of the information to be submitted for each study is to allow an assessment of the fulfilment of the specific obligations, and should provide sufficient information to allow an assessment of whether such obligations and their timeframes should be retained or modified. In the typical situation where the specific obligations refer to data collected from clinical trials, the following general structure is suggested for interim reporting:

a) **Title page and synopsis**

For each of the ongoing or new studies that is part of a specific obligation, a short description (limited to one page or less) should be provided. The description should address the expected overall study plan and design.

b) **Introduction**

Describe the status of development of the study, any issues that are still outstanding or that have a significant impact on the feasibility of the study, expected delays, etc.

c) **Accrual**

Describe enrolment, accrual over time, accrual by centre, country, and region, accrual by treatment group, information on data availability and follow-up status, and duration of follow-up. Include analyses of issues such as assumptions about accrual, event rates, implications for study power, evaluation of changes in characteristics of enrolled patients over time; conditional power calculations, implications for timing of final analysis.

d) **Baseline Characteristics**

Display baseline variables by treatment group, eligibility. Describe any issues with screening criteria, impact of exclusion criteria, and issues of generalisability.

e) **Adverse Events**

Describe adverse events by treatment and severity, at the body system level and at the level of preferred term, and describe the occurrence of serious adverse events.

f) **Primary Endpoint Analysis**

Describe the expected timing and, to the extent that this can be published based on the protocol and operating procedures, the outcome, of interim analyses or of final analyses, or other available data, as appropriate.

g) **Study conduct and compliance**

Describe treatment compliance, compliance with efficacy and safety assessments, significant changes in the conduct of the study or planned analyses, important protocol deviations, dropout and missing data, critical quality assurance and quality control findings.

It is understood that, depending on e.g. the design, blinding and progress of trial, one or more of these subheadings may not be applicable. Agreement on the key elements of the interim reports and its optimal format should be sought from the EMA in preparation of the renewal submission.
Final reporting of clinical trials should follow the conventional format of study reports (see ICH Topic E3 Note for guidance on structure and content of clinical study reports, CHMP/ICH/137/95).

10.4. **How and to whom shall I submit my annual renewal application?**

The EMA strongly recommends using the eSubmission Gateway or the eSubmission Web Client as the preferred submission method of all eCTD submissions. More information on how to register and connect to the Gateway / Web Client can be found in the eSubmission website and detailed information on the required naming conventions and file formats can be found in the eSubmission Gateway Q&A document and the Web Client Q&A document. Applicants must not send duplicate submissions electronically or via CD-ROM or DVD as this might lead to delays in the handling of applications.

Applications that are sent using the eSubmission Gateway and eSubmission Web Client will receive an automated ‘acknowledgement’, confirming whether their submission has passed the applicable technical validation criteria and has been uploaded to the agency’s review tool. There is no need to send any separate paper cover letters for these submissions, as the cover letter will be in the relevant part of eCTD module 1 in PDF format.

MAHs not yet using the eSubmission Gateway or the Web Client solution should address and send the Annual renewal applications to the attention of the Product and Application Business Support (PA-BUS) at the following address:

Product and Application Business Support (PA-BUS)  
European Medicines Agency  
Loading Dock  
Ontario Way  
Canary Wharf  
UK - London, E14 4HB

Only one CD-ROM or DVD (in eCTD format ) of the Annual renewal application and supportive documentation should be submitted to the Agency, together with one original, signed cover letter. The Product Team Leader should be indicated in copy “cc” on the cover letter (no additional copy needed).

One electronic copy of the Annual renewal application form and supportive documentation should be submitted to the (Co)-Rapporteurs, after the eSubmission Gateway / Web Client confirmation of a technically valid submission. When submitted as CD-ROM or DVD the applicant should dispatch an electronic copy to the (Co)-Rapporteur at the same time as dispatching to the EMA.

The EMA will check whether the application is correct and complete (”validation”) before start of the procedure. Any additional information/documentation requested by the Agency prior to the start of the procedure should be equally provided to (Co-)Rapporteurs.

Upon validation by the Agency, one electronic copy of the full renewal application should be provided for each of the other committee members, including any additional data or information supplied during the validation phase (as appropriate).

It is essential that identical eCTD sequences are circulated to Committee Members. Any minor changes that affect the “md5 checksum” will lead to inconsistency and possibly result in future technical invalidity. Where applications are amended during the agency’s review, such as e.g. responses to a request for supplementary information , new or consolidated eCTD sequence should be provided in order to maintain the eCTD life-cycle. Please refer to the TIGes Harmonised Guidance and eCTD specific advice.
Identical Annual renewal applications for multiple Marketing Authorisations must be submitted separately. Each Marketing Authorisation is considered to be a stand-alone dossier. For this reason no cross-references will be accepted and Renewal applications must be submitted for each concerned product as a complete and stand-alone document.

For a full overview of dossier requirements for National Competent Authorities of (Co-)Rapporteur and Committee members, including delivery addresses, please refer to the following document: Dossier requirements for Centrally Authorised Products (CAPs).

Please note that the EMA only accepts submissions made in a mandatory eCTD format.

References

- Template for cover letter
- Dossier requirements for Centrally Authorised Products (CAPs)
- TIGes Harmonised Guidance for eCTD Submissions in the EU
- eSubmission website
- eSubmission Gateway Q&A
- eSubmission Gateway Web Client Q&A

10.5. How shall my annual renewal application be handled (timetable)?

The MAH should submit the annual renewal application by the recommended submission dates published on the EMA website and, in any case, no later than 6 months before the MA ceases to be valid.

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

The timetable for the scientific evaluation by the CHMP will be set in order to ideally allow the Commission Decision to be adopted before the expiry date of the marketing authorisation.

Full procedural detailed timetables are published as a generic calendar on the EMA website (see: submission deadlines and full procedural timetables).

The published timetables identify the start and finish dates of the procedures as well as other interim dates/milestones that occur during the procedure.

The renewal procedure will only involve the CHMP Rapporteur as well as the PRAC Rapporteur who have been appointed for the medicinal product.

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<tr>
<th>DAY</th>
<th>ACTION</th>
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<tbody>
<tr>
<td>D 1</td>
<td>Start of procedure</td>
</tr>
<tr>
<td>D 30</td>
<td>CHMP Rapp AR circulated to both CHMP/PRAC</td>
</tr>
<tr>
<td>D 46</td>
<td>Adoption of PRAC Advice (with PRAC divergent views appended)</td>
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<tr>
<td>D 50</td>
<td>CHMP members’ comments</td>
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<tr>
<td>DAY</td>
<td>ACTION</td>
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<td>--------</td>
</tr>
<tr>
<td>D 55</td>
<td>Updated CHMP Rap AR considering PRAC advice and CHMP comments</td>
</tr>
<tr>
<td>D 60</td>
<td>Adoption of CHMP opinion and CHMP AR (or RSI without a clock stop)</td>
</tr>
<tr>
<td>D 66</td>
<td>Responses to RSI</td>
</tr>
<tr>
<td>D 77</td>
<td>CHMP Rapp AR on responses circulated to both CHMP/PRAC</td>
</tr>
<tr>
<td>D 81</td>
<td>Comments by both CHMP and PRAC members</td>
</tr>
<tr>
<td>D 83</td>
<td>Updated CHMP Rap AR considering comments</td>
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<tr>
<td>D 90</td>
<td>Adoption of the CHMP Opinion</td>
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</table>

**Re-examination**

Art. 9(2) of Regulation (EC) No 726/2004 also applies to CHMP Opinions adopted for annual renewal applications. This means that the MAH may notify the EMA/CHMP 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 EMA within 60 days of receipt of the opinion. If the MAH 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 to co-ordinate the re-examination procedure. In case a PRAC Rapporteur is deemed necessary, he/she will be appointed. 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 days timeframe.

**10.6. What fee do I have to pay for a renewal?**

There is no fee payable for the annual renewal of a conditional marketing authorisation.

**References**

- Fees payable to the European Medicines Agency

**10.7. Can other non-renewal specific changes be included in the annual renewal application?**

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 as data emerge.

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

Where there are adequate and objective reasons not to renew the marketing authorisation in its existing terms and changes are necessary to the SmPC, labelling and package leaflet 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 SmPC guideline, other relevant guidelines impacting on the product information, or EMA/QRD Product Information Templates can be considered within the renewal procedure.

10.8. How to handle other ongoing variation applications during the renewal procedure and what impact may ongoing procedures have on the renewal procedure?

Although MAHs are advised to avoid other procedures at the time of renewal, such situations cannot be excluded.

In case that an ongoing variation (Type IA/IB or Type II) affects the product information and is not yet finalised at the time of the submission of the renewal application, the last product information adopted/accepted by the EC/CHMP/EMA should be used in the submission of the renewal application.

If the variation procedure is finalised before or upon finalisation of the renewal procedure, the accepted/adopted variation changes should be reflected in the renewal product information.

In such cases where any other ongoing procedure may affect the product information, the MAH is advised to contact the Agency in advance of the submission or finalisation of the procedure(s) concerned.

10.9. Do I have to submit mock-ups and specimens?

No mock-ups or specimens are required for the annual renewal of a conditional marketing authorisation. For details of when to submit mock-ups and specimens in the post-authorisation phase of your medicinal product, please refer to the revised checking process of mock-up and specimens information on the EMA web.

10.10. When do I have to submit revised product information? In all languages?

Where the MAH proposes no amendments to the product information, only an electronic copy of the latest approved product information (full set of Annexes) in English must be submitted to the Agency.

In case the renewal application affects SmPC, Annex II, labelling and/or package leaflet, the revised product information Annexes must be submitted as follows:

At submission (Day 0)

- English language version: complete set of Annexes electronically only in Word format (highlighted)
After CXMP Opinion (Day +5)

- All EU languages (incl. EN, NO+IS): complete set of annexes electronically only in Word format (highlighted)

After Linguistic check (Day +25)

- All EU languages (incl. EN, NO+IS): complete set of annexes electronically only in Word format (highlighted) and in PDF (clean)

Translations of the adopted product information in all EU languages (including English, Icelandic and Norwegian) are to be provided electronically (in one EudraLink package) to the Member States Contact Points for Translations by Day +5 and copied to the EMA PTL secretary.

The ‘full set of Annexes’ includes Annex I, II, IIIA, IIIB and, if applicable, IV and 127a (i.e. all SmPC, labelling and PL texts for all strengths and pharmaceutical forms of the product concerned, as well as Annex II and, if applicable, Annex IV and 127a as appropriate).

The ‘full set of Annexes’ must be presented sequentially (i.e. Annex I, II, IIIA and IIIB) as one word document for each official EU language. Annex 127a (when applicable) must be presented as a separate PDF document with “127a” removed from the title page together with the word files highlighted with tracked changes. All translations should be numbered as ONE document, starting with "1" (bottom, centre) on the title page of Annex I and Annex (127a) when applicable. The ‘QRD Convention’ published on the EMA website should be followed. When submitting the full set of Annexes in PDF format, this should be accompanied by the completed formatting checklist which provides guidance on how to correctly prepare the PDF versions. Highlighted changes should be indicated via ‘Tools – Track changes’. Clean versions should have all changes ‘accepted’.

The revised Annex A, where applicable, is to be provided as a separate word document per language, to the Agency.

The Annexes provided should only reflect the changes introduced by the renewal application. However, in exceptional cases where MAHs take the opportunity to introduce minor linguistic amendments in the texts (e.g. further to a specimen check) this should be clearly mentioned in the cover letter.

In addition, the section “present/proposed” in the application form should clearly list the minor linguistic amendments introduced for each language.

Alternatively, such listing may be provided as a separate document attached to the application form. Any changes not listed, will not be considered as part of the renewal application.

References

- Guideline on the processing of renewals in the centralised procedure (EMEA/CPMP/2990/00 Rev. 4)
- The new Linguistic Review Process of Product Information in the Centralised Procedure (EMEA/5542/02 Rev. 4.2)
10.11. When will the linguistic checking of the product information take place?

Translations of the adopted product information in all other EU languages (Including Icelandic and Norwegian) are to be provided electronically (in one Eudralink package) to the Member States Contact Points for Translations (list of members states contact points for translation) by Day +5 and copied to the PTL secretary.

The following checks post-opinion will apply:

<table>
<thead>
<tr>
<th>Check by</th>
<th>When</th>
<th>Who</th>
<th>Scope</th>
</tr>
</thead>
<tbody>
<tr>
<td>QRD/ ‘Member State’</td>
<td>Day +5 to +19</td>
<td>Member States</td>
<td>Detailed review of (highlighted changes in) all translations</td>
</tr>
<tr>
<td>PIQ</td>
<td>Day +25 to +27</td>
<td>EMA</td>
<td>Review of implementation of Member States comments</td>
</tr>
</tbody>
</table>

Comments will be sent directly by the Member States to the MAH at the latest by Day +19, with a copy to the PTL secretary.

The MAH will send the final translations with tracked changes, incorporating the Member States’ comments, electronically to the PTL secretary by Day +25.

The Agency will check if all Member States’ comments have been implemented before sending the final translations to the Commission. In order to facilitate and accelerate the check of the implementation of the Member States’ comments, the applicant should indicate in QRD Form 2 for each language if all comments have been implemented or not. In the latter case, a justification should be provided for the appropriate language(s) stating why certain comments are not reflected in the final texts.

In case the Renewal affects only the Annex II, no or a shorter post-opinion translation timetable may be considered by the Agency on a case-by-case basis.

Following receipt of the final translations from the EMA, the Commission will start the 22-day Standing Committee consultation, addressing only legal and public health matters (which means in principle no further linguistic review).

The Commission Decision on the renewal will be issued after consultation of the Standing Committee, by Day +67.

References

- The new Linguistic Review Process of Product Information in the Centralised Procedure (EMEA/5542/02 Rev. 4.2)
- SOP/EMEA/0046: PIQ/QRD Pre-opinion Review of Product Information for Renewal Procedures
- Procedure for review of information on medicinal products by Patient’s/Consumers Organisations (PCOs) (EMA/174255/2010 Rev. 2)
10.12. What do I need to do if I do not want to renew the Marketing authorisation of certain product presentations or the entire product?

In cases where the MAH does not wish to renew certain product presentations (e.g. a certain pharmaceutical form, strength or pack-size) this should be clearly indicated in the cover letter (See also “How shall I present my renewal application”).

In case the MAH does not wish to renew the entire Marketing Authorisation (i.e. all presentations) a letter to this effect should be addressed to the Agency and the European Commission at the latest 6 months prior to the expiry of the concerned Marketing Authorisation, clearly and in detail stating if the marketing authorisation is surrendered for any reasons beyond purely commercial ones.

References
- Article 14(b) of Regulation (EC) No 726/2004
- Directive 2001/83/EC

10.13. What do I need to do if I wish to receive an Opinion of the CHMP that my marketing authorisation is no longer subject to Specific Obligations?

Once the specific obligations have been fulfilled, the Committee may at any time adopt a recommendation for the granting of a marketing authorisation no longer subject to specific obligations. MAHs who consider that all Specific Obligations have been fulfilled should indicate this in the cover letter of the submission, in which the final study report of the last outstanding condition is being submitted. This could be either within an annual renewal application or a variation, whichever is appropriate. Such an Opinion will change the terms to the marketing authorisation, both in relation to the conditions in its Annex II, as well as in its SmPC and Package Leaflet.

References

10.14. Will there be any publication on the outcome of my annual renewal application?

The EPAR (published on the EMA website) will be revised to implement the CHMP conclusions in relation to the renewal procedure.

The CHMP meeting highlights following each CHMP meeting gives information in its Annex on opinions in relation to renewal applications. This information includes the invented name of the product, its INN and the name of the MAH.
In case of an unfavourable opinion, recommending suspension or non-renewal of the MA, a Question and Answer (Q&A) document will be published by the Agency. This will include information and reasons for such an opinion. The information will be provided in lay language, so that it can be understandable for the general public.

References

- CHMP meeting highlights
- EPARs
11. Post Authorisation Safety Study (PASS) New March 2013

11.1. What is a PASS?

A post-authorisation safety study (PASS) is defined in Article 1(15) of Directive 2001/83/EC as any study relating to an authorised medicinal product conducted with the aim of identifying, characterising or quantifying a safety hazard, confirming the safety profile of the medicinal product, or of measuring the effectiveness of risk management measures.

A PASS may be initiated, managed or financed by a MAH voluntarily, or pursuant to an obligation imposed by a competent authority.

For detailed guidance please refer to GVP Module VIII – Post-authorisation safety studies.

11.2. Is a meta-analysis of safety data a non-interventional PASS?

Module VIII of the GVP provides general guidance for the transparency, scientific standards and quality standards of non-interventional PASS conducted by marketing authorisation holders voluntarily or pursuant to an obligation imposed by a competent authority.

Systematic reviews and meta-analyses imposed as an obligation should be considered as non-interventional PASS. In Annex III of the Commission Implementing Regulation (EU) No 512/2012, provisions are made in the format of the study protocol (e.g. Research methods) and the final study report in case the study is a systematic review of a meta-analysis. According to Art 36 of the IR, this means that, de facto, these designs should be considered as non-interventional PASS.

11.3. How will an imposed non-interventional PASS be assessed?

According to Art. 107(n-q) of Directive 2001/83/EC, any non-interventional PASS imposed as a condition to the marketing authorisation will be supervised and assessed by the PRAC. The Committee supervision relates to both the study protocol and the final study report.

Before such a study is conducted, the MAH will have to submit a draft protocol to the PRAC, except for studies to be conducted in only one Member State that requests the study according to Article 22a of Directive 2001/83/EC. For such studies, the MAH shall submit the protocol to the national competent authority of the Member State in which the study is conducted.

For studies with PRAC oversight, the draft study protocol will need endorsement by the PRAC before the study start. The PRAC will issue a letter either endorsing or objecting the proposed protocol or concluding that the proposed study falls within the definition of a clinical trial. In the latter case, the PRAC would no longer be supervising the study, as it would fall under the scope of Directive 2001/20/EC.

Once the PRAC has endorsed the protocol of a non-interventional PASS, any substantial amendments to the protocol will also need to be assessed and agreed by the PRAC.

Finally, the PRAC will assess the final study report and will make recommendations to the CHMP for any regulatory action which is deemed to be necessary based on the study results.
11.4. To whom should the imposed non-interventional PASS protocol and study report be submitted for PRAC assessment?

For non-interventional PASS imposed as a condition to the marketing authorisation, the study protocol should be submitted in 1.8.2 of eCTD. Study results should be submitted in (e)CTD in Module 5. The EMA strongly recommends using the eSubmission Gateway or the eSubmission Web Client as the preferred submission methods for all eCTD submissions. More information on how to register and connect to the Gateway / Web Client can be found in the eSubmission website and detailed information on the required naming conventions and file formats can be found in the Gateway Q&A and the Web Client Q&A. Applicants must not send duplicate submissions electronically or via CD-ROM or DVD as this might lead to delays in the handling of applications.

Applications that are sent using the eSubmission Gateway and eSubmission Web Client will receive an automated ‘acknowledgement’, confirming whether the submission has passed the relevant technical validation criteria and whether it has been uploaded to the agency’s review tool. There is no need to send any separate paper cover letters for these submissions, as the cover letter will be in the relevant part of eCTD module 1 in PDF format.

MAHs not yet using the eSubmission Gateway or the Web Client solution should send their PASS protocols as CD-ROM or DVD for the attention of the Product and Application Business Support (PA-BUS) at the following address:

Product and Application Business Support (PA-BUS)
European Medicines Agency
Loading Dock
Ontario Way
Canary Wharf
UK - London, E14 4HB

Only one CD-ROM or DVD (in eCTD format) of the PASS protocol and supportive documentation should be submitted to the Agency, together with one original, signed cover letter. The Product Team Leader should be indicated in copy “cc” on the cover letter (no additional copy needed).

One electronic copy of the PASS protocol and supportive documentation should be submitted to the (Co)-Rapporteurs after the eSubmission Gateway / web client confirmation of a technically valid submission. Any additional information/documentation requested by the Agency prior to the start of the procedure should be equally provided to (Co-)Rapporteurs.

The EMA will check whether the application is correct and complete before start of the procedure. Any additional information/documentation requested by the Agency prior to the start of the procedure should be equally provided to (Co-)Rapporteurs.

Upon completion of the Agency check, one electronic copy of the full application should be provided for each of the other committee members.

It is essential that identical eCTD sequences are circulated to Committee Members. Any minor changes that affect the "md5 checksum" will lead to inconsistency and possibly result in future technical invalidity.

Where applications are amended during the agency’s review, such as e.g. responses to a request for supplementary information, new or consolidated eCTD sequence should be provided in order to maintain the eCTD life-cycle. Please refer to the TIGes Harmonised Guidance and eCTD for specific advice.
For a full overview of dossier requirements for National Competent Authorities of (Co-)Rapporteur and Committee members, including delivery addresses, please refer to the following document: Dossier requirements for Centrally Authorised Products (CAPs).

Please note that the EMA only accepts submissions made in a mandatory eCTD format.

**References**

- Template for cover letter
- Dossier requirements for Centrally Authorised Products (CAPs)
- TIGes Harmonised Guidance for eCTD Submissions in the EU
- eSubmission website
- eSubmission Gateway Q&A
- eSubmission Gateway Web Client Q&A

**11.5. How is a non-interventional PASS protocol evaluated by the PRAC**

The PRAC evaluation of the PASS protocol is a 60 day procedure, which follows established time tables available from the following webpage.

**11.6. What are the possible outcomes of the PRAC evaluation of a non-interventional PASS protocol?**

The PRAC outcome is a decision which takes the form of a directly legally binding PRAC letter to the MAH with the following options:

- a letter notifying the MAH that the study is a clinical trial falling under the scope of Directive 2001/20/EC;
- a letter of objection specifying the grounds of objection and the timelines for resubmission and reassessment of the protocol;
- a letter of endorsement of the protocol.

The PRAC assessment report is annexed to the letter. In case of a letter of endorsement, the PRAC assessment report may include recommendations for minor amendments to the protocol. These recommendations are for consideration by the MAH and do not require resubmission of the protocol to the PRAC. However, if they result in an amendment to the protocol, these amendments should be listed in section 5 "Amendments and updates" of the protocol.

In the instances when PRAC adopts a letter of objection, submission of an amended protocol may be required within <X month(s)> or within 14 days. In the former case, submission of the amended protocol is requested within 1, 2, 3, ... months depending on the extent of the revisions; the revised protocol will then follow a 30 or 60 day PRAC review procedure. In the case of a re-submission within 14 days, the PRAC will review the amended protocol within 15 days. This 30-day timeframe for the PRAC decision is applied when the PRAC considers that the protocol needs to be resubmitted quickly to allow endorsement at the following PRAC meeting.
**11.7. How strict are the 30 days between PRAC meetings to urgently update a non-interventional PASS protocol?**

The main purpose of the request for a 14-day “urgent” re-submission is to ensure that PRAC can re-evaluate its decision in the following plenary meeting. Timelines may need to be adapted to the PRAC meeting dates, which may result in small variation in the timelines for PRAC assessment.

Urgent re-submission procedures are expected to be used for limited changes to the protocol.

Under circumstances of urgency the protocol submission via Eudralink may be acceptable. However, this must be agreed with EMA PTL and/or PRAC Rapporteurs beforehand. The email address should include the PTL’s email and the product specific mailbox.

**11.8. How is a non-interventional PASS final study report evaluated by the PRAC**

The PRAC evaluation of a PASS final study report is a 60 day procedure. Time tables for this procedure are currently under development and will be shortly available from the EMA web-site.

**11.9. What if non-interventional PASS results lead to the need for a variation?**

If results of the PASS described in a final study report may highlight a safety issue which requires a type II variation. Under these circumstances the MAH should submit the final study report in the context of a Type II variation.

Independently from the MAH evaluation of the need for a safety variation, and following the assessment of the final study report, the PRAC may issue a recommendation to the CHMP for any regulatory action that is deemed to be appropriate.

**References**

- Directive 2001/83/EC
- Regulation (EC) No 726/2004
- Guideline on good pharmacovigilance practices – Module VIII – Post-authorisation Safety Studies
- HMA-EMA Questions and answers on practical transitional measures for the implementation of the pharmacovigilance legislation (EMA/228816/2012 – v.2)
12. Post-Authorisation Measures (PAMs) New June 2013

12.1. What are PAMs?

At the time of finalising an opinion for a procedure, the Agency’s Committee(s) may agree that the applicant/MAH should generate additional data post-authorisation, as it is necessary from a public health perspective to complement the available data with additional data about the safety and, in certain cases, the efficacy of authorised medicinal products. Such post-authorisation measures (PAMs) may be aimed at collecting data to enable the assessment of the safety or efficacy of medicinal products in the post-approval setting.

The existence of such system of post-authorisation measures does not aim at promoting premature approvals of marketing authorisations or post-authorisation procedures. The background and rationale for requesting PAMs will be described in the relevant assessment reports, which will discuss the context and nature of the PAM. Based on the assessment of the Committee(s), PAMs are classified into their appropriate legal framework under which they will be enforced.

The following diagram explains how PAMs are categorised; in addition, each PAM category is explained in the following sections:

Fig.: Schematic overview of decision tree for the classification of PAMs

* plus potentially also additional PhV activity in the RMP [MEA] if linked to a safety concern identified in the RMP
Consequently, PAMs fall within one of the following categories [EMA codes\(^5\)]:

- Specific Obligation [SOB]
- Annex II condition [ANX]
- Additional Pharmacovigilance activity in the RMP [MEA]
- Legally binding measure [LEG]
- Recommendation [REC]

PAMs other than specific obligations can be required for any type of authorisation and will be included in the Opinion of an initial marketing authorisation or further to the Committees’ assessment of additional data/applications submitted post-authorisation.

However, certain medicinal products that are subject to specific obligations need to be distinguished (see also ‘What is a Specific Obligation?’).

The wording of the PAM will describe the issue under investigation that has led to the request together with a clear outline of the study(ies) or activities expected to address it and the deadline for its submission. Compliance with these measures is defined by both the submission of the requested data and adherence to the agreed timeframe.

References

- Directive 2001/83/EC
- Regulation (EC) No 726/2004

12.2. **What is a specific obligation ['SOB']?**

Specific obligations can only be imposed on marketing authorisations granted under exceptional circumstances or on conditional marketing authorisations (see also Q&A 38 ‘Is my medicinal product eligible for approval under exceptional circumstances?’ and Q&A 50 ‘Could my application qualify for a conditional marketing authorisation?’ of the Agency’s pre-submission guidance). These are conditions to the marketing authorisation included in Annex II.E of the Commission Decision and form the basis of the annual re-assessment or the annual renewal. Specific Obligations can only be imposed at the time of the granting of the initial marketing authorisation, i.e. not in the context of post-authorisation procedures such as extension applications or extension of indication variations.

Continuation of a marketing authorisation under exceptional circumstances or the renewal of a conditional marketing authorisation will be determined by the MAH’s compliance with the specific obligations, which are checked annually as part of either the annual reassessment or the annual renewal procedures.

As specific obligations are binding conditions to the marketing authorisation, any modification proposal by the MAH with regards to their description or due date has to be submitted within an appropriate procedure affecting the Annexes, i.e. either within the annual re-assessment, the annual renewal or a variation application.

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\(^5\) These codes relate to the Agency’s product and procedure database called SIAMED and will be used, together with a numbering system, to identify each PAM of a medicinal product both in the database and in any correspondence of the Agency with the MAH.
Where a specific obligation falls within the definition of a non-interventional PASS imposed after 2 July 2012, the MAH will have to follow the procedure for review of PASS protocol and results as described in the Agency’s post-authorisation procedural advice on PASS and in the corresponding Good Vigilance Practice (GVP) Module VII ‘PASS’.

Information not impacting on the description of the condition itself or leading to fulfilment of the condition (e.g. an interim report) can be submitted self-standing as described below (see: How and to whom shall I submit my PAM data?).

References

- Directive 2001/83/EC
- Regulation (EC) No 726/2004
- Commission Regulation (EC) No 507/2006 on conditional marketing authorisation
- EMA post-authorisation procedural advice on PASS
- Guideline on good pharmacovigilance practices (GVP) Module VIII – Post-authorisation safety studies

12.3. What is an Annex II condition [‘ANX’]?

The European Commission can impose on the marketing authorisation holder the obligation to conduct post-authorisation studies on safety and efficacy. These obligations can be imposed at the time of the granting of the marketing authorisation or later, as conditions to the marketing authorisation.

Annex II conditions are post-authorisation measures which, whilst not precluding the approval of a marketing authorisation or other post-authorisation procedure(s), are considered to be key to the benefit / risk balance of the product.

As Annex II obligations are binding conditions to the marketing authorisation, any modification proposal by the MAH with regards to their description or due date has to be submitted within a type II variation application. Information not changing the condition as stated in the Annex II such as an interim report can be submitted self-standing as described below (see: How and to whom shall I submit my PAM data?).

Where an Annex II condition falls within the definition of a non-interventional PASS imposed after 2 July 2012, the MAH will have to follow the procedure for review of PASS protocol and results as described in the Agency’s post-authorisation procedural advice on PASS and in the corresponding Good Vigilance Practice (GVP) Module VII ‘PASS’.

References

- Directive 2001/83/EC
- Regulation (EC) No 726/2004
- EMA post-authorisation procedural advice on PASS
- Guideline on good pharmacovigilance practices (GVP) Module VIII – Post-authorisation safety studies
12.4. What is an additional Pharmacovigilance (PhV) activity in the RMP ['MEA']?

Additional pharmacovigilance activities may be non-clinical studies, clinical trials or non-interventional studies which are required to investigate a safety concern of a medicinal product. These studies are listed in the pharmacovigilance plan of the RMP and are either aimed at identifying and characterising risks, or at assessing the effectiveness of risk minimisation activities.

The conduct of additional pharmacovigilance activities in the RMP may be imposed as either specific obligations [SOB], conditions in Annex II [ANX] or as required post-authorisation activities [MEA] in the RMP (see also GVP Module V – Risk Management systems), all of which are enforceable. All relevant milestones, such as protocol submission and interim reports, together with their due dates should be included in the summary table of additional PhV activities in the RMP. The MAH has the obligation to provide the requested data within the stated timeframes.

Once additional PhV activities have been agreed within the RMP, changes to these measures (e.g. proposals for adjusting due dates of agreed milestones, proposals to change the scope of agreed study or its duration, etc.) have to be either addressed via the appropriate procedures for specific obligations and for Annex II conditions as described above or, in case of required additional PhV activities in the RMP, via a RMP update. Information not impacting on the description of the measure itself, e.g. an interim report, or leading to fulfilment of the measure can be submitted self-standing as described below (see: How and to whom shall I submit my PAM data?).

References

• Directive 2001/83/EC
• Regulation (EC) No 726/2004
• EMA pre-submission procedural advice on RMP
• Guideline on good pharmacovigilance practices (GVP) Module V – Risk management systems

12.5. What is a legally binding measure ['LEG']?

Some post-authorisation measures are already defined as statutory obligations in pharmaceutical legislation. As such, they have to be provided by the MAH upon request of the Agency and its Committees. Examples for such directly binding legal requests are:

• Requests for provision of data in a future PSUR or as a stand-alone cumulative safety review that are not yet linked to a safety concern identified in RMP, therefore not yet identified as a routine/additional PhV activity (Article 23 of Directive 2001/83).
• Updates of the product information or provision of scientific justification subject to assessment where a variation is not required (Article 16 of Regulation 726/2004)
• Obligations to submit any data requested in relation to CAPA (Corrective Action/Preventive Action) in the context of Inspections (Article 111(8) of Directive 2010/84)
These requests are directly addressed to the MAH by the Agency, either within the assessment report of the Committee(s) or within an ‘outcome fax’ informing about Committee’s conclusions, and have to be responded to within the stated time frame.

References
- Directive 2001/83/EC
- Regulation (EC) No 726/2004

12.6. What is a recommendation ['REC']?

During the assessment of an application, the Committee(s) may issue recommendations for further development of the medicinal product, e.g. either in terms of optimising some quality aspects or considerations for extending the patient population. Although these recommendations for further development are not binding to the marketing authorisation, they should be seen as important considerations in view of the potential future use of a medicinal product by the MAH. As such, the Committee(s) will keep an overview of all recommendations made to a marketing authorisation and monitor whether, how and when the MAH has addressed them. Therefore, MAHs are encouraged to use the template for the Cumulative Letter of Recommendations (see link to template) to acknowledge these recommendations.

MAHs should specify the following in their Letter of Recommendations:
- A clear and concise description of each post-approval recommendation.
- The procedure number where the recommendation was given.
- No deadline needs to be mentioned
- When data in relation to a recommendation is provided to the Agency, an updated Letter of Recommendation should be provided, in which the MAH should indicate the date of submission and its format (e.g. as self-standing data, within a variation, within a renewal etc.)

If data obtained in the framework of a recommendation has an impact on the authorised medicinal product and its product information, the MAH has the obligation to submit a variation application as appropriate.

References
- Directive 2001/83/EC
- Regulation (EC) No 726/2004

12.7. Can the classification of my PAM change during its life-cycle?

New data or information regarding the medicinal product becoming available can result in the Committee(s) considering that a PAM should be reclassified. Such reclassification will be performed within the procedure discussing the impact of the new evidence that has become available and will be justified in the assessment report where the measures is, as a consequence, up- or downgraded.
12.8. When shall I submit my PAM?

The MAH should submit the PAM data according to the timeframe agreed with the Agency’s Committee(s) and detailed either in the Annex II, the milestones of the Pharmacovigilance plan in the RMP or the respective Committee assessment report or ‘outcome fax’. MAHs must propose due dates for the submission of the requested post-authorisation data that are realistic and proportionate to the identified potential risk which are then subject to agreement with the Agency’s Committee(s).

If the MAH is unable to provide the required data on time, it must inform the Agency and the Rapporteur in writing as early as possible in advance of the due time of submission. The reason for the delay must be justified and a new submission date proposed and subsequently agreed by the Committee(s). Proposals for changes to specific obligations or conditions must be presented as variation applications, as they impact the benefit-risk balance of the product. Proposals for changes to the additional Pharmacovigilance activities must be presented within an update of the RMP. Proposals for changes to directly legally binding measures have to be notified in writing, together with an appropriate justification, and have to be agreed by the Agency’s Committee(s).

In the case of a non-justifiable delay, the Agency’s Committee will consider taking regulatory action (see also next question).

Data which is presented as a stand-alone PAM (i.e. not within a procedure such as a variation) should be submitted in accordance with the published submission dates for PAMs (see also Human Medicines - Procedural timetables / Submission dates). Assessment of PAM data submitted after the recommended submission date will commence in accordance with the start day of the following month.

References
- Directive 2001/83/EC
- Regulation (EC) No 726/2004

12.9. Should I submit a variation to fulfil a PAM when the need for such variation is anticipated?

Where data generated in answer to a PAM are considered to impact the product information or the marketing authorisation, MAHs should submit a variation application at the time when the PAM is due. The MAH is advised to liaise with the PTL for the product in advance of the submission in case of doubt.

The Agency will start the procedure in accordance with the next upcoming starting date for variations published on the EMA website (see also Human Medicines – Procedural Timetables / Submission dates). In such cases, the MAH should not provide in addition a separate ‘stand-alone’ submission of the PAM data, but clearly indicated in the cover letter of the variation which PAM is being addressed. In addition, the scope section of the variation application form should make reference to the relevant PAM including the EMA reference number and the full description of the relevant PAM. Should such a variation address an additional Pharmacovigilance activity in the RMP, MAHs are reminded to include an appropriate update of the RMP within the variation application.

References
- Directive 2001/83/EC
12.10. How shall I structure my PAM submission dossier?

PAM data as a ‘stand-alone’ submission should include:

A Cover Letter indicating the full description and the reference number of the PAM(s) (The number to be quoted is the number attributed by the Agency at the time of adoption of the PAM). The letter should also indicate whether the PAM relates to Quality, Safety/Efficacy or Pharmacovigilance. Also, the due date should be mentioned, including any agreed extension of it. The cover letter should contain the template table to facilitate submission and registration.

All supportive documentation relevant to the fulfilment of the PAM should be presented in accordance with the appropriate headings and numbering of the EU-eCTD format.

Any Scientific Advice/Protocol Assistance obtained in relation to the fulfilment of PAMs concerned should be included.

In case a variation is submitted to fulfil a PAM, submission of the data should be presented in EU-eCTD format accordingly (see also EMA post-authorisation procedural advice – variations).

References

- Template for cover letter
- EMA post-authorisation procedural advice - variations
- Regulatory and procedural guidance on dossier format

12.11. How and to whom shall I submit my PAM data?

The EMA strongly recommends using the eSubmission Gateway or the eSubmission Web Client as the preferred submission methods for all eCTD submissions. More information on how to register and connect to the Gateway / Web Client can be found in the eSubmission website (http://esubmission.ema.europa.eu/esubmission.html) and detailed information on the required naming conventions and file formats can be found in the Gateway Q&A and the Web Client Q&A. Applicants must not send duplicate submissions electronically or via CD-ROM or DVD as this might lead to delays in the handling of applications.

Applications that are sent using the eSubmission Gateway and eSubmission Web Client will receive an automated ‘acknowledgement’, confirming whether the submission has passed the relevant technical validation criteria and whether it has been uploaded to the agency’s review tool. There is no need to send any separate paper cover letters for these submissions, as the cover letter will be in the relevant part of eCTD module 1 in PDF format.

MAHs not yet using the eSubmission Gateway or the Web Client solution should send their PAM data as CD-ROM or DVD for the attention of the Product and Application Business Support (PA-BUS) at the following address:
Only one CD-ROM or DVD (in eCTD format) of the documentation should be submitted to the Agency, together with one original, signed cover letter. The Product Team Leader should be indicated in copy (“cc”) on the cover letter (no additional copy needed).

One electronic copy should also be sent to the (Co-)Rapporteur and other members at the time of submission. It is essential that identical eCTD sequences are circulated to Committee Members. Any minor changes that affect the “md5 checksum” will lead to inconsistency and possibly result in future technical invalidity. Where applications are amended during the agency’s review, such as e.g. responses to a request for supplementary information, new or consolidated eCTD sequence should be provided in order to maintain the eCTD life-cycle. Please refer to the TIGes Harmonised Guidance and eCTD specific advice.

For a full overview of dossier requirements for National Competent Authorities of (Co-)Rapporteur and Committee members, including delivery addresses, please refer to the following document: Dossier requirements for Centrally Authorised Products (CAPs).

Please note that the EMA only accepts submissions made in a mandatory eCTD format.

References
- Dossier requirements for Centrally Authorised Products (CAPs)
- TIGes Harmonised Guidance for eCTD Submissions in the EU eSubmission webpage
- eSubmission website
- eSubmission Gateway Q&A
- Web Client Q&A

12.12. How shall my submission of PAM be handled (timetable), and what could be the outcome of the evaluation?

A 60-day timetable will normally apply to the assessment of PAM data submitted by the MAH. The submission deadlines and full procedural detailed timetables are published as a standard calendar on the EMA website (see: Human Medicines – Procedural Timetables / Submission dates).

The published timetables identify the submission, start and finish dates of the procedures as well as other interim dates/milestones that occur during the procedure.

The Agency will inform the MAH of the outcome of Committee evaluation in writing. The following may be envisaged depending on Committee’s conclusion:

- PAM is fulfilled and no further action is required.
- PAM is not yet fulfilled, as further clarifications or additional data are required. A list of question(s) to be addressed by the MAH within a given time frame will be issued and a follow-on PAM (such as MEA 003.01) created. The PAM will only be considered as fulfilled, once all requests for
supplementary information have been addressed by the MAH to the Agency’s Committees’ satisfaction.

- PAM is not fulfilled as data provided are considered as not adequate to address the underlying concern. The PAM will be either re-iterated with a clarified scope and adjusted time lines for completion or the Agency’s Committee(s) might initiate Regulatory actions.

References
- Directive 2001/83/EC
- Regulation (EC) No 726/2004

12.13. Do I have to pay fees for the PAM data submission?

There is no fee payable for a PAM stand-alone submission. However, the normal fees are applied to any variations resulting from such PAMs.

12.14. How will the Agency track my post-authorisation measures?

Any post-authorisation measure that is not a recommendation ['REC'] is legally enforceable.

As a consequence, the Agency will keep a record of the request and its due date in its database. Regular database queries will identify any measures that are overdue and the MAH will be reminded of their overdue measures, with a view to provide the data as soon as possible.

Reminders will be sent via e-mail on the 1st month of the overdue submission. MAHs should submit outstanding measures or a justification for non-submission with proposal for change of deadline, if needed, in the form of a variation (e.g. changes to deadline in Annex II), before the next relevant Committee meeting according to the relevant submission dates published on EMA website for the applicable procedure.

Should a MAH submission be overdue by more than 2 months (following 1st reminder) an assessment regarding the impact of the missing data on the safety or efficacy profile of the product will be carried out and the Agency’s Committee will make recommendations regarding the next steps to be taken.

Should a MAH be found to be non-compliant in providing a requested post-authorisation measure within the agreed timeframe or have delays without acceptable justifications, the Agency’s Committee will consider the regulatory action to be taken.

12.15. Regulatory actions

Regulatory actions are to be applied either when the MAH does not react to the reminder to submit outstanding data or when the Agency’s Committee does not agree with a MAH’s request to postpone a deadline, as described above. In such situations, the Rapporteur (or a lead Rapporteur nominated by the Committee in case of more than one affected product) may draft an assessment report on the impact of the lack of data on the benefit/risk balance of the affected product or other analysis to
support a discussion on the next steps by the Agency’s Committee(s). Based on the outcome of such assessment and/or discussion, one or more of the following actions may be taken:

- Letter to the MAH by the Chair of the Committee
- Oral Explanation by MAH to the Committee
- Initiation of a referral procedure with a view to vary/suspend/revoke the MA in light of art. 116 of Directive 2001/83/EC
- Inspection to be performed upon request of the Committee(s)

Such regulatory action in regards to non-compliance of a MAH may be made public by the Agency on the Agency website e.g. in the EPAR(s) of the affected product(s).

Irrespective of the above regulatory actions, the Agency may take at any point in time a decision to take another enforcement action beyond those described here.

**References**

- Directive 2001/83/EC
- Regulation (EC) No 726/2004

**12.16. Will there be any publication on the outcome of my PAM?**

The EPAR (published on the EMA website) will be revised as appropriate to implement the Agency’s Committees’ conclusions in relation to the PAM outcome.

Specific obligations and Annex II conditions are reflected in the Annex II.D and E of the full set of annexes which is published as part of the EPAR. Additional PhV activities in the RMP will be reflected in the public summary of the RMP, which will be made available on the Agency’s EPAR website.

**Reference**

- EPARs
13. **PSURs Rev. March 2013**

### 13.1. What is a Periodic Safety Update Report (PSUR)?

Periodic safety update reports (PSURs) are pharmacovigilance documents intended to provide an evaluation of the risk-benefit balance of a medicinal product. They shall be submitted by marketing authorisation holders at defined time points during the post-authorisation phase.

The legal requirements for submission of PSURs are established in Regulation (EU) No 1235/2010, Directive 2010/84/EU and in the Commission Implementing Regulation (EU) No 520/2012.

The format of PSURs shall follow the structure described in the Commission implementing Regulation (EU) No 520/2012. Please refer to question *In which format should I submit my PSUR?*

Further details and guidance for the submission of PSURs in the EU, including the list of Union references dates and frequency of submission are provided in the following questions and answers.

**References:**
- Regulation (EU) No 1235/2010
- Directive 2010/84/EU
- HMA-EMA Questions and answers on practical transitional measures for the implementation of the pharmacovigilance legislation (EMA/228816/2012 – v.2)
- Guideline on good pharmacovigilance practices (GVP) – Module VII – PSUR

### 13.2. What is the EU single assessment?

The EU single assessment is the assessment of PSURs for medicinal products subject to different marketing authorisations containing the same active substance or the same combination of active substances whether or not held by the same marketing authorisation holder and for which the frequency and dates of submission of PSUR have been harmonised in the list of EU reference dates. This could include a mixture of centrally authorised products, products authorised through the mutual
recognition and decentralised procedures and purely nationally authorised products [DIR Art 107e to 107g] (so-called PSUR “EU single assessment” procedure).

The single assessment procedure including a mixture of centrally authorised products started in July 2012.

The single assessment procedure including a mixture of centrally authorised products and products authorised nationally and through the mutual recognition and decentralised procedures will start for Data Lock Points (DLPs) as of 01 April 2013.

The single assessment procedure involving only nationally authorised medicinal products did not start in 2012 and will not start until further notice which will be communicated on the EMA’s website (www.ema.europa.eu). See question What procedure will be followed for the assessment of my PSUR?

References:

- Guideline on good pharmacovigilance practices (GVP) – Module VII – PSUR

### 13.3. What is the List of European Union reference dates (EURD list) and frequency of submission of PSURs?

The European Union reference date (EURD) corresponds to the date of the first or the earliest known date of the marketing authorisation in the Union of a medicinal product containing the active substance or combination of active substances.

The list of Union reference dates and frequency of submission of PSURs (referred to as the “EU reference dates list” in the GVP Module VII) consists of a list of active substances and combinations of active substances sorted in alphabetical order, for which PSURs shall be submitted in accordance with the EU reference dates and frequencies determined by the Committee for Medicinal Products for Human Use (CHMP) and the Coordination Group for Mutual Recognition and Decentralised Procedures - Human (CMDh) following consultation with the Pharmacovigilance and Risk Assessment Committee (PRAC).

The EU reference dates list has been compiled in order to facilitate the harmonisation of DLPs and frequency of submission of PSURs for medicinal products containing the same active substance or the same combination of active substances subject to different marketing authorisations, authorised in more than one Member State. This will, where appropriate, allow the single assessment of the related PSURs as set out in the new EU pharmacovigilance legislation.

The data lock point is the date designated as the cut-off for data to be included in a PSUR.

The list is a living document, i.e. that it can be amended whenever considered necessary by the PRAC, CHMP or CMDh in response to the emergence of relevant new safety information, newly authorised substances and requests received from the marketing authorisation holders as defined in the legislative provisions 107c(6) of Directive 2010/84/EU.

The principles of the EU reference dates list is included in the GVP Module VII – Periodic safety update report (VII.C.3).

The PSUR frequency as published on the EU reference dates list for a given active substance or combination of active substances overrules the submission schedule described in the legislative provisions 107c(2) of Directive 2010/84/EU and any conditions related to the frequency of submission
of PSURs included in the Marketing Authorisation. This approach is without prejudice to the right of a National Competent Authority (NCA) to request the submission of PSURs at any time.

As a result of the publication of the EU reference dates list, any changes to the PSUR submission frequency and DLP will trigger the obligation of the marketing authorisation holders (MAHs) to submit, where applicable, a variation for the products where contradictory requirements are specified in the Marketing Authorisation. Please refer to Which variation classification should apply to align the PSUR frequency in my marketing authorisation with the EURD list?

For guidance on submission of requests for amendment of the EU reference dates list refer to the question How can I request to amend the list of EU reference dates.

References:

- Guideline on good pharmacovigilance practices – Module VII – PSUR
- List of European Union reference dates and frequency of submission of Periodic Safety Update Reports Introductory cover note (EMA/606369/2012 Rev.3, 21 Dec 12)

13.4. When will the EURD list come into force?

The EURD list will come into force 6 months after its publication as final i.e. after adoption by the CHMP and CMDh following consultation of the PRAC. The list was first published on 1st October 2012 and is binding from DLPs as of 1st April 2013.

13.5. Do I have to submit a PSUR if my medicinal product is not on the EURD list?

If the active substance contained in the medicinal product is not listed on the EURD list, the MAH should continue to submit PSUR according to the condition in the MA if any, otherwise according to the standard submission cycle (i.e. 6-monthly, yearly and thereafter 3-yearly) unless the medicinal product is a generic, well-established authorised under of Directive 2001/83/EC, homeopathic simplified registration and traditional-use registration without conditions in the MA. In addition, PSURs shall also be submitted upon request of national competent authorities or the Commission/EMA.

13.6. How can I request to amend the list of EU reference dates?

Marketing authorisation holders shall be allowed to submit requests to the CHMP or the CMDh, as appropriate, to determine the Union reference dates or to change the frequency of submission of PSUR on one of the following grounds:

- for reasons relating to public health;
- in order to avoid a duplication of the assessment;
- in order to achieve international harmonisation.
The request and its grounds should be considered by the PRAC and the CHMP if it concerns at least one marketing authorisation granted in accordance with the centralised procedure or the CMDh otherwise, which will either approve or deny the request.

The list will then be amended accordingly when appropriate and published on the European medicines web-portal.

For more details on how to submit amendments to the list, please refer to the EURD list cover note (sections 2 and 5).

References:


13.7. **What procedure will be followed for the assessment of my PSUR?**

The procedure involving the PRAC for PSUR assessment for Centrally authorised medicinal products (CAPs) started in July 2012.

However, the single assessment procedure involving only nationally authorised medicinal products did not start in 2012 and will not start until further notice which will be communicated on the EMA’s website (www.ema.europa.eu).

The procedure for the different types of products is summarised below:

- For a single centrally authorised medicinal product (i.e. for a substance or combination of active substances contained in only one medicinal product which is centrally authorised), any PSUR submitted as of 2 July 2012 will follow the new procedure involving the PRAC as detailed in the GVP Module VII.

- For several centrally authorised medicinal products containing the same active substance or combination of active substances and where the submission dates are harmonised, the single assessment procedure involving the PRAC will be followed.

- From 1st April 2013 when the EURD list becomes binding, where centrally and nationally authorised medicinal products contain the same active substance or combination of active substances, the single assessment procedure involving the PRAC will be followed for the PSURs submitted according to the DLPs stated in the EURD list. For more details please refer to the EURD list.

- Where nationally authorised medicinal products containing the same active substance or combination of active substances are authorised in more than one Member State and follow already the current worksharing scheme (WS), please refer to HMA website where arrangements for the assessment of these PSURs is provided until the single assessment procedure involving the PRAC is implemented.

- For nationally authorised medicinal products containing the same active substance or combination of active substances and which are authorised in more than one Member State but which are not covered by the current WS scheme, the assessment of the PSUR remains at an individual national level until the single assessment procedure involving the PRAC is implemented.
Please note that for purely nationally authorised medicinal products identified by the MAH as not authorised in more than one Member State, the assessment of the PSUR will remain at an individual national level as it is outside the scope of the single assessment procedure defined in the legislation.

13.8. **In which format should I submit my PSUR?**

As set out in the Commission Implementing Regulation, the new format and content of PSUR shall apply from 10 January 2013. The format and content of the PSUR is outlined in the Guideline on good pharmacovigilance practices (GVP) Module VII – Periodic safety update report.

PSURs that are submitted to the EMA, in relation to Centrally Authorised products have to follow the mandatory eCTD format. Submissions of Nationally Authorised Products that are sent to the EMA as part of a ‘single assessment’ procedure (mixture of centrally and nationally authorised medicinal products), should be sent electronically only. Preferably in eCTD format but NeeS format is also accepted as a temporary measure. Please see *How and to whom should I submit my PSUR?*

**References:**


13.9. **Do I need to include line listings in my PSUR?**

PSURs prepared under the new format and content will not contain line listings. However the MAH may have to provide them upon request of the EMA or the national competent authorities.

13.10. **What are the timelines for the submission of PSURs?**

Marketing authorisation holders should submit to the Agency PSURs within 70 or 90 days from the data lock point as established in GVP Module VII which is as follows:

- within 70 calendar days of the data lock point (day 0) for PSURs covering intervals up to 12 months (including intervals of exactly 12 months); and

- within 90 calendar days of the data lock point (day 0) for PSURs covering intervals in excess of 12 months;

- the timeline for the submission of ad hoc PSURs requested by competent authorities will be normally specified in the request, otherwise the ad hoc PSURs should be submitted within 90 days of the data lock point.
The timetables for the PSUR single assessment procedure involving CAPs and mixture of CAPs and NAPs are published at the EMA website. The column submission date referred to in the timetable corresponds to the deadline date for the submission of PSURs i.e. Day 70 or Day 90 following the DLP as published in the EURD list.

References


13.11. How and to whom should I submit my PSUR?

Until the EMA delivers the new PSUR repository, the following should be considered with regards to the PSUR submission involving Centrally Authorised medicinal Products (CAPs) and Nationally Authorised medicinal Products (NAPs):

PSURs for CAPs:

Submission to the European Medicines Agency:

The EMA strongly recommends using the eSubmission Gateway or the eSubmission Web Client as the preferred submission method for all eCTD submissions. More information on how to register and connect to the Gateway / Web Client can be found in the eSubmission website and detailed information on the required naming conventions and file formats can be found in the eSubmission Gateway Q&A document and in the Web Client Q&A. Applicants must not send duplicate submissions electronically or via CD-ROM or DVD as this might lead to delays in the handling of applications.

MAHs not yet using the eSubmission Gateway or the Web Client solution should send their PSURs as CD-ROM or DVD to the attention of the Product and Application Business Support (PA-BUS) at the following address:

Product and Application Business Support (PA-BUS)
European Medicines Agency
Loading Dock
Ontario Way
Canary Wharf
UK - London, E14 4HB

Only one CD-ROM or DVD (in eCTD format) containing the relevant eCTD sequence for each product, should be submitted to the Agency, together with an original, signed cover letter when using this format of submission. The coordinating Product Team Leader should be indicated in copy (“cc”) on the cover letter (no additional copy needed).

One electronic copy of the PSUR (in eCTD format) should be submitted to the (Co)-Rapporteurs, after the eSubmission Gateway / Web Client confirmation of a technically valid submission. When submitted as CD-ROM or DVD the applicant should dispatch an electronic copy to the (Co)-Rapporteur at the same time as dispatching to the EMA.

The EMA will check (only eCTD technical validation) whether the application is correct and complete before start of the procedure. Any additional information/documentation requested by the Agency prior to the start of the procedure should be equally provided to (Co)Rapporteurs.
Upon completion of the Agency check (only eCTD technical validation), one electronic copy of the PSUR should be provided for each of the other committee members.

It is essential that identical eCTD sequences are circulated to Committee Members. Any minor changes that affect the "md5 checksum" will lead to inconsistency and possibly result in future technical invalidity.

Where applications are amended during the agency’s review, such as e.g. responses to a request for supplementary information or comments sent by the MAH during the procedure, new or consolidated eCTD sequence should be provided in order to maintain the eCTD life-cycle.

For a full overview of dossier requirements for National Competent Authorities of (Co-) Rapporteur and Committee members, including delivery addresses, please refer to the following document published on the EMA website: Dossier requirements for Centrally Authorised Products (CAPs).

Please note that the EMA only accepts submissions made in a mandatory eCTD format.

**PSURs for single assessment procedure involving CAPs and NAPs:**

Article 2 of Directive 2001/83/EC lays down transitional provisions regarding PSUR submission requirements. Until the EMA can ensure the functionalities agreed for the PSUR repository, MAHs shall submit PSURs to all Member States in which the medicinal product has been authorised.

The centralised submission of PSURs is a key element for the optimisation of the functioning of the EU PSUR single assessment procedure for substances contained in both CAPs and NAPs. As a consequence, MAHs concerned are requested to submit their PSURs to all the PRAC and CHMP members representing the National Competent Authorities (NCAs) of the countries where the medicinal products have been authorised, to the PRAC Independent Scientific experts and CHMP Co-Opted Members, to the PRAC rapporteur of the procedure and to the EMA. For more details please refer to the EURD list.

**13.12. Do I have to submit a PSUR for my generic medicinal product?**

For medicinal products referred to in Article 107 b (3) of the Directive 2001/83/EC, the requirement to submit PSUR is waived, unless otherwise specified in the marketing authorisation or required through the EURD list (see dedicated column "Are PSURs required for products referred to in Articles 10(1), 10a, 14, 16a of Directive 2001/83/EC as amended? Yes/No" of the EURD list). National Competent Authorities can also request PSUR for generic medicinal products at any time on the grounds detailed in Article 107c (2) of the Directive.

Therefore, if the substance contained in the medicinal product is not included in the EURD list and no specific condition providing for the submission of PSUR is included in the marketing authorisation of the product concerned, no PSUR is required. However please note that for substances contained in NAPs (including generics) with a DLPs up to 31/08/2014, should be submitted as requested by the EU Regulatory Network in line with “List of substances under PSUR Work Sharing scheme and other substances contained in Nationally Authorised Products with DLP synchronised”, until the single assessment of these substances starts. For more details, please refer to HMA website.
13.13. Do I have to submit a PSUR for my hybrid medicinal product?

Medicinal products authorised in accordance with Article 10(3) of Directive 2001/83/EC (hybrid application) irrespective of the change applied for (e.g. new strength, new route of administration, etc) are not exempted from the obligation to submit PSUR therefore PSUR submissions are required for hybrid medicinal products.

13.14. For my product authorised as a generic/hybrid, whom should I contact to establish the corresponding PSUR requirements?

For centrally authorised medicinal products, please liaise with the Agency through the PTL of your product to clarify.

13.15. Do I have to submit a PSUR for my medicinal product containing a well-established substance?

For medicinal product containing a well-established substance, the requirement to submit a PSUR is only waived for those authorised in accordance with Article 10a of Directive 2001/83/EC. Medicinal products containing a known substance authorised through another legal basis are required to submit PSURs.

13.16. Is the PSUR worksharing still applicable?

Until the single assessment starts for nationally authorised medicinal products, the current PSUR worksharing scheme will continue. (See HMA website where current arrangements can be found and an update of the process will be published).

13.17. If the PSUR cycle of my medicinal product is changed as per the EURD list, can I submit my PSUR according to the new Data Lock Point (DLP) without submitting a variation?

MAHs should follow the new PSUR cycle as defined in the EURD list, independently of a higher or lower frequency than the current one. However, in case the PSUR cycle is stated in the marketing authorisation of a medicinal product, a variation will have to be submitted to align the MA in line with EURD list. For centrally authorised products, please refer to the Implementation plan for the update to Annex II of the QRD template. For nationally authorised products please refer to the NCAs websites.

13.18. Which variation classification should apply to align the PSUR frequency in my marketing authorisation with the EURD list?

As set out in the legislation the MAH will have to vary their marketing authorisation where the PSUR cycle is specified in the MA and will need to be brought in line with the EURD list. Instead of specifying the PSUR frequency, PSUR statements cross-referring to the EURD list will be mentioned (in the Annex II for CAP) in order to avoid the need to submit variation when there will be changes to the EURD list. For centrally authorised products, please refer the QRD templates.

In order to facilitate the implementation pending the publication of the final revised variation classification guideline, the CMDh issued in accordance with Article 5 of Regulation (EC) No 1234/2008, a recommendation on classification of an unforeseen variation for change in the PSUR frequency or date of submission, which can be found on the CMDh website. It is classified as a type IAIN variation.
For centrally authorised products, an implementation plan has been published on the EMA website providing further details.

13.19. **How will my PSUR submission be handled?**

In accordance with the new legislative framework, the procedure for the PSUR assessment for a single PSUR or several PSURs for the same active substance involves the PRAC and if applicable either the CHMP or the CMDh.

The timelines for assessment are for up to 134 days followed by 67 days of Commission decision making process (if applicable).

The submission deadlines and full procedural detailed timetables are now published as a generic calendar on the EMA website.

Upon technical validation by the EMA of the submitted PSUR, the following timetable shall apply to the PSUR evaluation:

<table>
<thead>
<tr>
<th>Day</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 0</td>
<td>Start of the procedure according to the published timetable</td>
</tr>
<tr>
<td>Day 60</td>
<td>PRAC Rapporteur’s preliminary assessment report</td>
</tr>
<tr>
<td>Day 90</td>
<td>MAH and PRAC members’ comments</td>
</tr>
<tr>
<td>Day 105</td>
<td>PRAC Rapporteur’s updated assessment report (if necessary)</td>
</tr>
<tr>
<td>Day 120</td>
<td>PRAC recommendation adoption with the final PRAC assessment report</td>
</tr>
<tr>
<td>Day 134</td>
<td>CHMP opinion / CMDh position</td>
</tr>
</tbody>
</table>

In case the PRAC adopts a recommendation on the maintenance of the marketing authorisation, there is no requirement to transmit such recommendation to the CHMP or CMDh and the procedure ends with the adoption of the PRAC recommendation.

In case of the PRAC recommends any regulatory action i.e. variation, suspension or revocation of the marketing authorisation, the PRAC recommendation adopted in accordance with the new procedure for a single CAP or the single PSUR assessment procedure will be transmitted to the CHMP if it includes at least one CAP or to the CMDh if it includes only NAPs. At its next meeting following the PRAC recommendation, the CHMP or the CMDh, as applicable, will adopt an opinion or a position, respectively. Subsequently, competent authorities in Member States, or the European Commission for centrally authorised products, shall take the necessary measures to vary, suspend or revoke the marketing authorisation(s), in accordance with the outcome of the assessment.

The outcome of the PSUR assessment results in a legally binding decision or position in case of any action to vary, suspend, revoke the marketing authorisations of the medicinal products containing the concerned active substance or combination of active substances, on the basis of the position of the CMDh or the opinion of the CHMP following the recommendations from the PRAC. Furthermore,
marketing authorisation holders are reminded of their obligation to keep their marketing authorisation up to date in accordance with the current legislative framework [REG Art 16(3)] and [DIR Art 23(3)]. The recommendations are therefore implemented in a harmonised and timely manner for all products within the scope of the procedure across the EU.

Amendments to the SmPC, package leaflet and labelling as a result of the PSUR assessment should be implemented without subsequent variation submission for centrally authorised products and through the appropriate variation for nationally authorised products, including those authorised through the mutual recognition and decentralised procedures.

Reference:

13.20. Does every PSUR assessed by PRAC need to go to CHMP or CMDh?

In case of any regulatory action i.e. variation, suspension or revocation of the marketing authorisation, the PRAC recommendation adopted in accordance with the new procedure for a single CAP or the single PSUR assessment procedure will be transmitted to the CHMP if it includes at least one CAP or to the CMDh if it includes only NAPs.

In case the PRAC adopts a recommendation on the maintenance of the marketing authorisation, there is no requirement to transmit such recommendation to the CHMP or CMDh and the procedure ends with the adoption of the PRAC recommendation.

13.21. In the PSUR work sharing scheme, should I still submit a Core Safety Profile (CSP) at the time of the PSUR submission?

For new format PSURs, CSPs are no longer required; please see GVP Module VII.B.4 for the reference documentation to include under the new format.

13.22. Will existing CSPs be updated?

As the new format for PSUR benefit-risk evaluation is introduced, existing CSPs will not be updated.

13.23. Why are some DLPs included in the EURD list so far in the future?

The PSUR frequencies and DLPs included in the EURD list have been defined by the NCAs following a risk based approach. These have subsequently been adopted by the CHMP and CMDh following consultation of the PRAC.

It should be noted that DLPs put in the long-term future are likely to be amended on a monthly basis to take into account any need to re-evaluate the risk-benefit profile of a substance/product earlier or, in particular, in case of emergence of any pharmacovigilance concerns.
Products containing the same active substance may currently follow different DLPs and PSUR frequencies. Therefore the "reporting period" for the related PSURs submitted according to the 1st DLP in the EURD list will vary. The frequency in the EURD list corresponds to estimation on when the subsequent (i.e. 2nd) PSUR will have to be submitted according to the EURD list.

**13.24. Do I have to submit a PSUR if my combination product is not on the EURD list but one or more standalone components are listed?**

If the specific fixed combination medicinal product is not listed on the EURD list and if the medicinal product does not fall within the categories of medicinal products exempted by the legislation of the obligation to submit PSUR, the MAH should continue to submit PSURs according to the condition in the MA if any, otherwise according to the standard submission cycle (i.e. 6-monthly, yearly and thereafter 3-yearly). Stakeholders can request the inclusion of the fixed combination in the EURD list for reasons related to public health, in order to avoid duplication of assessment or in order to achieve international harmonisation. Instructions on how to submit comments and requests to amend the EURD list can be found on the EURD list webpage.

**13.25. As a MAH of products referred to in Articles 10(1), 10a, 14 and 16a of Directive 2001/83/EC, how should I communicate any safety information to National Competent Authorities and the Agency?**

Products referred to in Articles 10(1), 10a, 14 and 16a of Directive 2001/83/EC are exempted from routine submission of PSURs. Therefore, alternative mechanisms such as signal management and emerging safety issues channels should be used to communicate relevant new safety information to regulatory authorities (see GVP Module VI and Module IX). Additionally, product information should be kept up-to-date in line with Article 16(3) of Regulation (EC) No 726/2004 / Article 23(3) of Directive 2001/83/EC by submitting the appropriate variations taking account of the current scientific knowledge, which includes the conclusions of the assessment and recommendations made public by means of the EMA and National Competent Authority websites and, when available, the European medicines web-portal.

**13.26. Do I have to submit a PSUR for my medicinal product authorised under the older Directive?**

Medicinal products which have been authorised through the equivalent legal basis as the current Articles 10(1) and 10a legal basis before the re-codification of the Directive 2001/83/EC i.e. respectively Article 4.8 a(iii), first paragraph (essential similarity) of Directive 65/65/EEC / 10 a(iii), first paragraph of Directive 2001/83/EC and Art 4.8 a(ii) (well established use) of Directive 65/65/EEC / 10.1 a(ii) of Directive 2001/83/EC are, by analogy, not required to submit PSUR unless there is a specific condition in the authorisation or there is an indication in the EURD list that PSUR submission is required, or in response to a specific request.
13.27. If the medicinal product is not marketed, is the MAH required to submit a PSUR?

The MAH is required to submit PSURs once a medicinal product is authorised in the EU, even if it is not marketed.

Reference:

13.28. In the view of the upcoming renewal application, how shall I manage my PSUR submission?

PSUR, PSUR addendum, Summary Bridging Report and line listing should no longer be submitted as part of the renewal application. The clinical overview submitted in the renewal application should include relevant information to support the benefit-risk re-evaluation of the medicinal product. Please refer to the Guideline on the processing of renewals in the centralised procedure (EMEA/CPMP/2990/00 rev.4, 22 June 2012).

Reference
- Guideline on the processing of renewals in the centralised procedure (EMEA/CPMP/2990/00 Rev.4, 22 June 2012)
14. Article 46 paediatric study submission

14.1. What is the "Article 46 paediatric study submission"?

Article 46 of Regulation (EC) No 1901/2006 (The Paediatric Regulation) sets out the obligation for the MAH to submit to the EMA any MAH-sponsored studies involving the use in the paediatric population of a centrally authorised medicinal product, whether or not they are part of a PIP.

This covers:

- Clinical studies and trials (phase I to IV)
- Completed or discontinued clinical studies;
- Published or not clinical studies;

Studies should be submitted regardless of the region where they were performed, the aim, outcome, population studied and indication.

Reference

- Article 46 (1-5) of Regulation (EC) No 1901/2006, as amended

14.2. When shall I submit my article 46 paediatric study application?

The MAH should submit the paediatric study(ies) within 6 months of its completion and irrespective whether or not it is part of a PIP (completed/or not yet completed) or whether or not it is intended for submission later on as part of a variation, extension or new stand alone Marketing Authorisation Application.

Completion of a study is defined in the Commission guideline on PIP/Waiver/Deferral/Modification as the last visit of the last patient, as foreseen in the latest version of the protocol (as submitted to competent authorities).

Reference

- ICH Topic E3, Note for Guidance on Structure and Content of Clinical Study Reports, CPMP/ICH/137/95
- Commission Communication, Guideline on the format and content of applications for agreement or modification of a paediatric investigation plan and requests for waivers or deferrals and concerning the operation of the compliance check and on criteria for assessing significant studies, 2008/C243/01, Official Journal of the European Union, 24 September 2008
14.3. How shall I present my article 46 paediatric study application at submission?

The submission of the paediatric study(ies) should include the following documents, preferably presented in accordance with appropriate headings and numbering of the EU_CTD format:

- Cover Letter (see template) including information on the context in which the article 46 paediatric study submission is made (e.g. submission as part of FUM/SO, stand alone studies or studies included in a development program) and statement that there are no regulatory consequences identified by the MAH.
- A short critical expert overview clarifying the context of the data, including information on the pharmaceutical formulation used in the study, the existence of a suitable paediatric formulation and if relevant, conditions for an extemporaneous formulation
- Final clinical study report
- For a paediatric study that is part of a development program, a line listing (see template) of all the concerned studies

In case amendments to be introduced to SPC, labelling and/or PL are identified by the MAH, a variation should be submitted directly containing the article 46 paediatric study(ies). The application should be presented in EU-CTD format accordingly to the guidance for variation (see also in this guidance: Type II variation).

References

- ICH Topic E3, Note for Guidance on Structure and Content of Clinical Study Reports, CPMP/ICH/137/95

14.4. How and to whom shall I submit my article 46 paediatric study application? Rev. March 2013

The EMA strongly recommends using the eSubmission Gateway or the eSubmission Web Client as the preferred submission method for all eCTD submissions. More information on how to register and connect to the Gateway / Web Client can be found in the eSubmission website and detailed information on the required naming conventions and file formats can be found in the eSubmission Gateway Q&A document and the Web Client Q&A. Applicants must not send duplicate submissions electronically or via CD-ROM or DVD as this might lead to delays in the handling of applications.

Applications that are sent using the eSubmission Gateway and eSubmission Web Client will receive an automated ‘acknowledgement’, confirming whether the submission has passed the relevant technical validation criteria and whether it has been uploaded to the agency’s review tool. There is no need to send any separate paper cover letters for these submissions, as the cover letter will be in the relevant part of eCTD module 1 in PDF format.

MAHs not yet using the eSubmission Gateway or the Web Client solution should send their applications as CD-ROM or DVD to the attention of the Product and Application Business Support (PA-BUS) at the following address:
Only one CD-ROM or DVD (in eCTD format) of the application should be submitted to the Agency, together with one original, signed paper cover letter when using this format of submission. The Product Team Leader should be indicated in copy “cc” on the cover letter (no additional copy needed).

One electronic copy should also be sent to the CHMP (Co-) Rapporteur and other CHMP members at the time of submission.

In case the article 46 paediatric study(ies) needs to be submitted as a variation, MAHs should refer to requirements for Type II variation procedure in this guidance document.

It is essential that identical eCTD sequences are circulated to Committee Members. Any minor changes that affect the "md5 checksum" will lead to inconsistency and possibly result in future technical invalidity. Where applications are amended during the agency’s review, such as e.g. responses to a request for supplementary information, new or consolidated eCTD sequence should be provided in order to maintain the eCTD life-cycle. Please refer to the TIGes Harmonised Guidance and eCTD specific advice.

For a full overview of dossier requirements for National Competent Authorities of (Co-) Rapporteur and Committee members, including delivery addresses, please refer to the following document: Dossier requirements for Centrally Authorised Products (CAPs).

Please note that the EMA only accepts submissions made in a mandatory eCTD format.

References

- Template for cover letter
- Dossier requirements for Centrally Authorised Products (CAPs)
- TIGes Harmonised Guidance for eCTD Submissions in the EU
- eSubmission website
- eSubmission Gateway Q&A
- Web Client Q&A
### 14.5. How shall the evaluation of my article 46 paediatric study application be handled (timetable), and what could be the outcome of the evaluation?

The following **60-day timetable** shall apply to the **assessment of the paediatric study** submitted by the MAH:

<table>
<thead>
<tr>
<th>Day</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 1</td>
<td>Start of the procedure as per published timetable (see below)</td>
</tr>
<tr>
<td>Day 30</td>
<td>Receipt of Rapporteur’s Assessment Report</td>
</tr>
<tr>
<td>Day 45</td>
<td>CHMP Members’ comments</td>
</tr>
<tr>
<td>Day 50</td>
<td>Receipt of Rapporteur’s updated Assessment Report (if necessary)</td>
</tr>
<tr>
<td>Day 60 (CHMP meeting)</td>
<td>CHMP adoption of conclusion or Request for Clarifications</td>
</tr>
<tr>
<td>(up to Day 90 if a Request for Clarification is needed)</td>
<td></td>
</tr>
</tbody>
</table>

The submission deadlines and full procedural detailed timetables are published as a generic calendar on the EMA website (see: submission deadlines and full procedural timetables).

The published timetables identify the submission, start and finish dates of the procedures as well as other interim dates/milestones that occur during the procedure.

The EMA will inform the MAH of the outcome of CHMP evaluation. The following may be envisaged depending on CHMP’s conclusion:

- The article 46 paediatric study submission is fulfilled and no further action is required.

- The article 46 paediatric study submission is fulfilled, however, additional data (not directly linked to the paediatric study submitted) are required. These further data can be classified as a new follow-up-measure (FUM) in agreement with the Rapporteur/EMA and treated accordingly. A Letter of Undertaking is required and a Siamed number will be issued by the EMA (see also FUM/SO data in this guidance).

- The article 46 paediatric study submission is fulfilled, however, a variation is needed to amend the product information in accordance with the CHMP conclusion. The variation submission is normally requested within 60 days after adoption of the CHMP conclusion. If the MAH is unable to submit the variation within this timeframe, he must justify the delay and inform the EMA/Rapporteur and propose a new submission date. A 30-day variation timetable will normally apply to implement the agreed amendments to SPC, labelling and/or PL as requested by the CHMP following the assessment of the paediatric studies and for which no new or additional data are submitted by the MAH (see also Type II Variation procedure in this guidance).

- The article 46 paediatric study submission is fulfilled however, further data are expected in the context of a variation/line extension application, prior any final conclusion is made. In agreement with the Rapporteur/EMA, a Letter of Undertaking is required and Siamed number(s) will be issued by the EMA (see also FUM/SO data in this guidance).
The article 46 paediatric study submission is not fulfilled and further clarifications are required. The CHMP will request additional clarifications (directly linked to the paediatric study submitted) and a 30 days extension of the timeframe will normally apply.

As the timetable will be maximum 90 days (including one single request for clarification only), it should be noted that the responsibility for the quality of the submitted documentation lies with the MAH and is crucial to the overall process.

14.6. Do I have to pay fees for the article 46 paediatric study submission?

There is no fee payable for article 46 paediatric studies. However, the normal fees are applied to any variations containing Article 46 paediatric data or variations resulting from the assessment of such article 46 paediatric study submission.

14.7. Will there be any publication on the outcome of my article 46 paediatric study?

The EPAR (published on the EMA website) will be revised as appropriate to implement the CHMP conclusions in relation to the article 46 paediatric study outcome.

Note: The policy on transparency for post-authorisation procedures is currently being revised and will be reflected in this document at a later stage.

References

- EPARs
15. Transfer of Marketing Authorisation

15.1. What is a Transfer of Marketing Authorisation? Rev. Sep 2011

A Transfer of Marketing Authorisation (MA) is the procedure by which the MA is transferred from the currently approved Marketing Authorisation Holder (MAH) to a new MAH which is a different person/legal entity.

Such a Transfer is needed for example, in the event of a merger/acquisition where the MAH is taken over by another company and ceases to exist as a separate legal entity.

In case the same Transfer is sought for several medicinal products, an application must be submitted for each MA (i.e. 1 application per main EU authorisation number).

It is recommended to liaise with the Product Team Leader (PTL) at least 1 month before submission of the application, in order to ensure correctness of the documents to be provided for the Transfer application, especially in view of the short timeframe (30 days) of the procedure (See also "How shall my Transfer of Marketing Authorisation application be handled (timetable)?").

A change of name and/or address of the MAH is not a Transfer if the holder remains the same person/legal entity. Such change should be notified through a Type IA_{IN}, A1.variation application.

A Transfer of MA does not include a Transfer of Orphan designation since this is subject to a different procedure. (See also "Do I also have to transfer the Orphan designation when my medicinal product has been granted such a designation?")

A Transfer of a MA can only be initiated once a MA has been granted. However, in case there is a need to change the proposed MAH during the initial Marketing Authorisation Application procedure, the applicant who initially applied for the MA is advised to contact the Agency.

From this point onward:

- The MAH of the MA to be transferred is termed the Transferor.
- The person/company to whom the Transfer is to be granted is termed the Transferee.

References

- Commission Regulation (EC) No 2141/96 of 7 November 1996 concerning the examination of an application for the Transfer of a marketing authorisation for a medicinal product falling within the scope of Council Regulation (EC) No 2309/93
- Commission Regulation (EC) No 1085/2003 of 3 June 2003 concerning the examination of variations to the terms of a marketing authorisation falling within the scope of Council Regulation (EC) No 2309/93

15.2. How shall I present my application for the Transfer of Marketing Authorisation? Rev. Sep 2011

Transfer applications should be presented as follows, in accordance with the appropriate headings and numbering of the EU-CTD format.
Module 1: 1.0 Cover letter (signed by the Transferor) with the following documents attached:

All documents to be submitted from the Transferee or Transferor, as appropriate, using preferably headed paper. A template for each document is attached as a model to provide guidance on the information that should be included in each document.

1) The name of the medicinal product concerned, the authorisation number(s) and the date(s) on which the authorisation(s) was (were) granted. (Attachment 1)

2) The identification (name, address, contact person at address, telephone number and email) of the Transferor and the Transferee. (Attachment 2)

3) A document certifying that the complete and up-to-date file concerning the medicinal product or a copy of this file including any data/documents related to the paediatric obligations has been made available to or has been transferred to the Transferee. (Attachment 3)

4) A document stating the date on which the Transferor and the Transferee finalise the transitional organisational arrangements and the Transferee takes over all responsibilities. This is referred to as the implementation date. The transitional period between the notification of the Commission decision on the transfer of a marketing authorisation and the implementation date should be proportionate to the organisational activities that need to be performed by the Transferor and Transferee. (See also Transfer of Marketing Authorisation - “How to choose the implementation date?”) (Attachment 4)

If applicable, this document should include a “Statement of activities performed by the Transferor during the transitional period”. This statement should briefly provide the Agency with an overview of the organisational activities which will be performed by the Transferor - as agreed with the Transferee - during the transitional period. The transitional period is the period between the date of notification of the Commission Decision on the Transfer and the implementation date.

5) Proof of establishment of the Transferee within the EEA. (Attachment 5)

6) Documents showing the capacity of Transferee to perform all the responsibilities required of a MAH under Community Pharmaceutical legislation:

   • 6.1) A document identifying the qualified person responsible for Pharmacovigilance (QPPV) within the meaning of Article 23 of Regulation (EC) No 726/2004, together with his/her Curriculum Vitae stating home address, email address, telephone and fax number. The qualified person responsible for Pharmacovigilance must be permanently and continuously at the disposal of the Transferee and must be established (reside) within the European Economic Area. (Attachment 6.1)

   • 6.11) In case a Detailed Description of the Pharmacovigilance System (DDPS – Module 1.8.1) is authorised as part of the Marketing Authorisation, and the transfer has resulted in a change of the QPPV, a signed statement from the Transferee and new QPPV must be included, confirming that the Transferee has the services of the new QPPV and has the necessary means for the collection and notification of any adverse reaction occurring either in the Community or in a third country. (Attachment 6.11)

   • 6.2) A document identifying the scientific service in charge of information about the medicinal product within the meaning of Article 98 of Directive 2001/83/EC, as amended, including the address, email address, telephone and fax number. (Attachment 6.2)

   • 6.3) A document identifying the person/company authorised for communication between the Transferee and the Agency after authorisation on the Transfer of MA. (Attachment 6.3)
• 6.4) A document identifying the contact details of the person responsible for quality defects and batch recall within the meaning of Article 79 of Directive 2001/83/EC, as amended, including the Name, address, telephone, fax and email address. (Attachment 6.4)

7) If the medicinal product concerned has not yet been marketed in the EU in any of its presentations, this should be specified in a signed statement. Attachment 7)

8) A Letter of Undertaking signed by the Transferee listing any remaining Follow-up Measures or Specific Obligations. Where no Follow-up Measures or Specific Obligations remain a letter stating this must be submitted as well. (Attachment 8)

9) A signed statement that no other changes have been made to the product information other than those to the details of the MAH and, if appropriate, the details of the local representatives. (Attachment 9)

10) Confirmation from the NRG on the acceptability of the proposed name, if applicable. (See also "How can I change the name of a product composed of INN + company name, as a result of the Transfer?")

Documents 1, 2, 3, 4 and 9 must be signed by both the Transferor and the Transferee.

Document 7 must be signed by the Transferor.

Documents 6 and 8 must be signed by the Transferee.

1.3 Product Information

1.3.1 SPC, Annex II, Labelling and Package Leaflet

The revised product information (SPC, Annex II, labelling, and package leaflet) in all languages (EU languages, Iceland and Norway):

• All EU languages (incl. NO+IS): complete set of annexes
  electronically only
  in Word format (highlighted)
  in PDF format (clean)

(See also "How to present my Product Information?")

1.3.2 Mock-up

English and multi-lingual ('worst-case') colour mock-up of outer and immediate packaging for each pharmaceutical form in each container type (e.g. blister and bottle, vial and pen) in the smallest pack-size (see also Transfer of Marketing Authorisation – Do I have to submit mock-ups and specimens?).

It is recommended to liaise with the Product Team Leader at least 1 month before submission of the application if there are any questions on the documents to be provided in order to ensure the completeness of the Transfer application, especially in view of the short timeframe, 30 days, of the procedure (see "How shall my Transfer of Marketing Authorisation application be handled (timetable)?").

Reference
15.3. How and to whom shall I submit my Transfer of Marketing Authorisation application? Rev. March 2013

The EMA strongly recommends using the eSubmission Gateway or the eSubmission Web Client as the preferred submission method for all eCTD submissions. More information on how to register and connect to the Gateway / Web Client can be found in the eSubmission website and detailed information on the required naming conventions and file formats can be found in the eSubmission Gateway Q&A document and the Web Client Q&A. Applicants must not send duplicate submissions electronically or via CD-ROM or DVD as this might lead to delays in the handling of applications.

Applications that are sent using the eSubmission Gateway and eSubmission Web Client will receive an automated ‘acknowledgement’, confirming whether the submission has passed the relevant technical validation criteria and whether it has been uploaded to the agency’s review tool. There is no need to send any separate paper cover letters for these submissions, as the cover letter will be in the relevant part of eCTD module 1 in PDF format.

MAHs not yet using the eSubmission Gateway or the Web Client solution should send their Transfer applications as CD-ROM or DVD to the attention of the Product and Application Business Support (PA-BUS) at the following address:

Product and Application Business Support (PA-BUS)
European Medicines Agency
Loading Dock
Ontario Way
Canary Wharf
UK - LONDON E14 4HB

Only one CD-ROM or DVD (in eCTD format) of the Transfer should be submitted to the Agency, together with one original, signed paper cover letter when using this format of submission. The Product Team Leader should be indicated in copy ("cc") on the cover letter (no additional copy needed).

Revised Annexes in all languages should be included in electronic (Word and PDF) format in the same eSubmission Gateway and eSubmission Web Client package or CD-ROM or DVD within a folder called ‘working documents’. Changes in Word documents should be indicated via ‘Tools – Track changes’. Clean PDF versions should have all changes ‘accepted’.

One electronic copy should also be sent to the CHMP (Co-)Rapporteur and other CHMP committee members, to maintain their eCTD life cycle of the dossier.

For a full overview of dossier requirements for National Competent Authorities of (Co-)Rapporteur and Committee members, including delivery addresses, please refer to the following document: Dossier requirements for Centrally Authorised Products (CAPs).
Please note that the EMA only accepts submissions made in a mandatory eCTD format.

**References**
- Template for cover letter
- Dossier requirements for Centrally Authorised Products (CAPs)
- TIGes Harmonised Guidance for eCTD Submissions in the EU
- eSubmission website
- eSubmission Gateway Q&A
- eSubmission Gateway Web Client Q&A

**15.4. How shall my Transfer of Marketing Authorisation application be handled (timetable)? Rev. Sep 2011**

MAHs should notify the EMA of their intention to transfer a MA prior to the planned submission date. A Transfer application follows a 30-day procedure following receipt of the application. There are no set of submission dates. However, in order to choose the best submission date especially in case of any other pending/expected procedures, the transferor should contact the Product Team Leader at least 1 month before submission of the application.

When changes to a manufacturer are envisaged, please (See also “Can I include changes to manufacturing sites in my Transfer of marketing authorisation application?”). If necessary, a pre-submission meeting can be organised by the EMA upon request of the MAH.

Within approximately 10 days upon receipt of the Transfer application, the EMA will check whether the Transfer application is correct and complete.

In case of an incorrect or incomplete Transfer application the applicant will be notified, requesting the amended and/or additional documentation. This document should be provided via eCTD submission within 10 calendar days from the date of the EMA notification in order to allow time for checking the amended/new documentation and for finalisation of the opinion within 30 days (as required by Art. 4 of Regulation (EC) No 2141/96). The EMA will not be able to issue a favourable opinion on the Transfer in case the documentation is incomplete.

Within 30 days of the receipt of an application, the Transfer opinion will be sent to the Transferor, Transferee, European Commission and the competent authorities of Iceland and Norway.

Subsequently, the European Commission will issue a decision on the Transfer of the MA. The transfer of the marketing authorisation shall be authorised from the date of the notification of the Commission decision on the Transfer.

However, the Agency by mutual agreement with the Transferor and the Transferee can set an implementation date for the Transfer. This implementation date should be understood as the date on which the Transferee takes over all responsibilities. This date is stated on the opinion adopted by the Agency and also on the European Commission decision. (See also “How to choose the implementation date?”).
15.5. How to choose the implementation date? Rev. Sep 2011

The implementation date is the date on which the Transferee takes over ALL responsibilities as the Holder of the MA.

Such a date will be proposed by the Transferor and Transferee in the Transfer application and will subsequently be agreed with the EMA. The implementation date will be stated in the opinion of the Transfer.

For the Transfer of a Marketing Authorisation covering medicinal products already marketed by the Transferor, the proposed date should be set taking into account the following timelines (see also "How shall my Transfer of Marketing Authorisation application be handled (timetable)?"):

- The EMA timeframe for finalisation of the opinion is 30 days from the receipt of an application (Day A).
- The Commission will subsequently issue a Commission Decision on the Transfer of the marketing authorisation. As of the date of notification of the Commission Decision on the Transfer of the marketing authorisation (Day B), the Transfer is effective and the Transferee becomes the new MAH of the medicinal product.
- Between Day B and Day C (implementation day) there is a transitional period during which the previous MAH and the new MAH have to finalise their organisational arrangements, as defined in the Transfer application (e.g. contractual agreements as regards batch release). The Transfer application should include information as to the date on which the Transferor will release the last produced batch in the distribution chain, duly justifying why that particular date has been chosen. The transitional period between the notification of the Commission decision on the transfer of a marketing authorisation (Day B) and the implementation date (Day C) should be proportionate to the organisational activities that need to be performed by the Transferor and Transferee. Nevertheless, it should be noted that as of Day B, the Transferee becomes the new MAH of the medicinal product and the EMA will only deal with the new MAH for any further regulatory activity (e.g. variations applications).
- Before Day B the Transferor is responsible for released batches. As of Day B, the new MAH can start releasing batches. The batches released by the new MAH should be in accordance with the Annexes of the Commission Decision on the Transfer and therefore, these batches should have the name of the new MAH in the Product Information. During this transitional period and on the basis of the arrangements agreed between Transferor and Transferee, batches bearing the name of the previous MAH can be released as well. Nevertheless, it should be noted that as of Day B, the responsibility on all released batches rely on the new MAH.
- After Day C only the new MAH (Transferee) can release batches on the market. The batches that have been released before Day C and that bear the name of the previous MAH can remain on the market.

Reference

- Commission Regulation (EC) No 2141/96 of 7 November 1996 concerning the examination of an application for the Transfer of a marketing authorisation for a medicinal product falling within the scope of Council Regulation (EC) No 2309/93
For the Transfer of a Marketing Authorisation covering medicinal products not yet marketed by the Transferor, the proposed date should refer to the day on which the Commission Decision on the Transfer will be issued.

15.6. What fee do I have to pay for my Transfer of Marketing Authorisation application?

For information on the fee applicable for Transfer applications, please refer to the explanatory note on fees payable to the European Medicines Agency. Such fee covers all authorised presentations of a given medicinal product.

The Agency will issue an invoice upon receipt of the Transfer application to the MAH. Fees will be payable within 45 calendar days of the date of receipt of the invoice. The invoice will be sent to the billing address indicated by the MAH and will contain clear details of the products and procedures involved, the type of fee, the amount of the fee, the bank account to where the fee should be paid and the due date for payment. Where more than one procedure is processed in a given month a summary invoice or statement will be issued at the end of each month for payment within 30 days of the end of the month.

To facilitate this operation, a marketing authorisation holder who is demanding a Purchase Order Number on the Agency invoice must quote this Number clearly on the cover letter of the given application. The Agency will no longer accept separate notifications of Purchase Order Numbers not associated with the dossier. A marketing authorisation holder must state the following sentence on the cover letter of each application:

Please quote Purchase Number .......... on the invoice.

If the marketing authorisation holder does not require a Purchase Order Number on the Agency invoice, this must also be clearly stated in the cover letter.

For more information about fees and fee payment in the Centralised Procedure, please consult the Agency’s fees page.

In case of an unfavourable EMA opinion on the transfer of the Marketing Authorisation, the Transfer fees will be charged by the Agency.

References

- Council Regulation (EC) No 297/95 on fees payable to the European Agency for the Evaluation of Medicinal Products, as amended
- Explanatory note on fees payable to the EMA

15.7. How to handle planned/ongoing variations procedures during the Transfer of Marketing Authorisation?

MAHs should avoid submitting variation procedures in parallel to a Transfer of MA application.

MAHs are strongly advised to contact the EMA Product Team Leader in advance of the submission of the Transfer of application, in order to discuss how to handle any planned/ongoing procedures.
15.8. How to handle remaining Follow-up Measures (FUMs) / Specific Obligations (SOs) when transferring a Marketing Authorisation?

Post-authorisation commitments such as FUMs or SOs, may have been agreed for the medicinal product to be transferred at the time the CHMP opinion was recommended or at subsequent opinions. If FUMs/SOs are still remaining for the medicinal product concerned, it is the responsibility of the Transferee to fulfil those FUMs/SOs within the timeframe previously agreed with the CHMP. Therefore, a Letter of Undertaking signed by the Transferee must be submitted including all FUMs or SOs still remaining to be addressed as per the undertaking letter signed by the Transferor on the day of the adoption of the initial CHMP opinion or subsequent opinions.

In case no FUMs or SOs remain a letter stating this must be submitted. See also “How shall I present my application for the Transfer of my marketing authorisation?”

Detailed information on FUMs/SOs fulfilment as well as the Letter of Undertaking template can be found in the Follow-up measures/Specific Obligations section of this guidance.

Reference

- Commission Regulation (EC) No 2141/96 of 7 November 1996 concerning the examination of an application for the Transfer of a marketing authorisation for a medicinal product falling within the scope of Council Regulation (EC) No 2309/93

15.9. Do I have to submit mock-ups and specimens? Rev Apr 2012

Mock-ups

According to point 6 in the Annex to Regulation (EC) No 2141/96 on transfers of centrally authorised medicinal products, mock-ups are to be included in the transfer application. At submission, applicants must therefore provide an English and multi-lingual ('worst-case') colour mock-up of outer and immediate packaging for each pharmaceutical form in each container type (e.g. blister and bottle, vial and pen) in the smallest pack-size. The mock-ups will be reviewed by the EMA (Medical Information Sector) in parallel to the handling of the transfer procedure, and any mock-up comments will be sent to the MAH within 15 working days from the start of the procedure.

Specimens

Relevant revised example specimens should be provided to the EMA by the new MAH, in line with the requirements for New Applications and Extensions at the latest 15 working days before launch. If the transfer only affects the MAH details on the packaging and package leaflet without any impact on overall design, one relevant example (multi-lingual if possible) of the revised outer and immediate packaging and package leaflet of one presentation is sufficient. A declaration from the new MAH stating that only the details of the MAH have been modified, and that such changes will be introduced in all product presentations should be included in the 'Specimen Submission Form'. The EMA will perform a general check from the viewpoint of readability within 15 working days, and will check if any previous
comments on specimens have been duly implemented. The applicant will be informed about the outcome of the check.

The above principles also apply to mock-ups for Iceland. The mock-ups should be sent by e-mail to mockups@ima.is. See also http://www.imca.is/IMCA/News/nr/1263

No mock-ups and specimens are required for Norway.

References

- The Revised Checking Process of Mock-Ups and Specimens of outer/immediate labelling and package leaflets of human medicinal products in the Centralised Procedure (EMEA/305821/2006)

15.10. Do I also have to transfer the Orphan designation when my medicinal product has been granted such a designation?

When transferring the MA of a designated Orphan medicinal product, the MAH must also transfer the Orphan designation of the product concerned in accordance with Article 5(11) of Regulation (EC) No 141/2000 in order to maintain the orphan status.

Transfers of Orphan designation and Transfer of MA are two different procedures and must be handled as such. The applications for Transfer of the Orphan designation and Transfer of the MA should preferably be submitted to the EMA at the same time. The cover letter accompanying each of the applications should make reference to the two applications, as the two procedures will be handled in parallel by the EMA.

Fee waivers can only apply to the transferred medicinal product once the Transfer of the Orphan designation is completed.

In preparing an application to transfer an Orphan designation, sponsors should follow the guidance given in the European Commission’s “Guideline on Format and Content of Applications for Designation as Orphan Medicinal Products and on the Transfer of designation from one sponsor to another (ENTR/6283/00) and in the “Checklist for sponsors applying for the transfer of orphan medicinal product (OMP) designation” (EMEA/41277/07) which are published on the EMA website.

References

- Guideline on the format and content of applications for designation as orphan medicinal products and on the Transfer of designation from one sponsor to another, (ENTR/6283/00)
- Checklist for sponsors applying for the transfer of orphan medicinal product (OMP) designation” (EMEA/41277/07)

15.11. Can I include changes to manufacturing sites in my Transfer of Marketing Authorisation application?

Changes to a manufacturer(s) resulting from the Transfer of the MA are not considered part of the Transfer procedure. Therefore, the appropriate variations should be submitted separately. These
variations will be handled separately from the Transfer procedure. In such case, the MAH is advised to contact the EMA prior to submitting a Transfer application in order to discuss the appropriate timeframe of such variation(s).

In addition, when the need for GMP inspections is anticipated by the MAH, it is advisable to contact the EMA in advance of the variation and Transfer submission.

15.12. Can I change the Qualified Person for Pharmacovigilance information as part of my Transfer of Marketing Authorisation application?

Rev. March 2013

A change to the Qualified Person for Pharmacovigilance (QPPV) resulting from the transfer of the marketing authorisation can be notified as part of the transfer application without the need for a separate variation (see also “How shall I present my application for the Transfer of Marketing Authorisation”).

This applies to all MAs with or without a DDPS as well as to MAs that have introduced the Summary of the Pharmacovigilance System in their marketing authorisation dossier.

Other changes to the DDPS, a switch from a DDPS to a Summary of the Pharmacovigilance System or the first introduction of a Summary of the Pharmacovigilance System cannot be included as part of the transfer application. The appropriate variation application for changes to the DDPS or introduction of a Summary of the Pharmacovigilance System should be submitted separately from the transfer application.

References

- Guidelines on Good Pharmacovigilance Practices : Module I – Pharmacovigilance systems and their quality systems and Module II – Pharmacovigilance system master file
- Commission Regulation (EC) No 1234/2008 of 24 November 2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products
- Guideline on the details of the various categories of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products (2010/C 17/01)

15.13. How can I change the name of a product composed of INN + company name, as a result of the Transfer? New Sep 2011

In the case the Transfer procedure concerns a product whose name is constructed as (INN + company name of the Transferor), the MAH identification is an integral part of the name and therefore, the change of the name can be considered as an element intrinsically linked to the Transfer procedure. As a result, the new name for the product, constructed as (INN + company name of the Transferee) can be notified as part of the Transfer application without the need for a separate variation. Before the Transfer application is submitted, the MAH should have the confirmation of the NRG that the proposed new name is acceptable. (See also “How will I know if the proposed (invented) name of my medicinal product is acceptable from a public health point of view?”).
Please note that this is not applicable for products with invented names. In this case, in order to change the name of the product, the corresponding variation is required and it should be submitted separately to the Transfer procedure.

15.14. **Will there be any publication on the Transfer of Marketing Authorisation?**

The EPAR (published on the EMA website) will be revised to implement the change in Marketing Authorisation Holder.

**Reference**

- EPARs
16. Transparency *Rev. March 2013*

Since the establishment of the EMA, transparency has been an important feature of the Agency’s operation. This resulted in the introduction of the European Public Assessment Reports (EPARs) in line with the requirements of the Community legislation, but also led to various initiatives (going beyond legislative requirements) adopted by the EMA Management Board in the form of transparency measures (EMEA/MB/52/03/Rev.1/final).

In addition, the new EU Pharmacovigilance legislation [Regulation (EU) No 1235/2010 and Directive 2010/84/EU] increases further the level of transparency of safety information and outlines in several legislative provisions that the EMA’s website will serve as the European medicines web portal for the dissemination of information for medicinal products authorised in the European Union and shall make public all relevant information in accordance with the provisions of the new legislation.

The new EU Pharmacovigilance legislation introduces a new scientific Committee at the EMA, the Pharmacovigilance Risk assessment committee (PRAC) which will advise the Committee on Medicinal Products for Human Use (CHMP) and the Coordination Group for Mutual Recognition and Decentralised Procedures (CMDh) on safety issues in relation to medicines in the EU.

Below are outlined the current high level transparency measures with regards to the outputs of the EMA’s scientific Committees PRAC and CHMP with regards (mainly) to post-authorisation procedures of centrally authorised human medicinal products.

Other type of applications or parts of dossiers such as orphan designations and paediatric investigation plans are outside the scope of this Question and Answer document. Relevant information on this type of applications along with an overview of the EMA transparency measures can be found on the EMA’s website (www.ema.europa.eu) under Special topics-Transparency.

16.1. Which transparency measures apply with regards to the PRAC meeting?

- **PRAC agendas**

  The PRAC has been publishing agendas of its meetings since its formation in July 2012. PRAC Agendas are published on the EMA website on a monthly basis around the time of the PRAC meeting but always prior to the start of the meeting.

  The agendas are published in full with the exception of few elements that are redacted to take into account the confidential nature of some issue and principles for personal data protection. Details on how these principles are applied are outlined in the "Countdown to July 2012: the establishment and functioning of the PRAC” published on the EMA website.

  The published PRAC agendas can be found on the EMA’s website (www.ema.europa.eu) under About us-Committees-PRAC.

- **PRAC meeting highlights**

  The PRAC has been publishing meeting highlights since its September 2012 meeting. PRAC meeting highlights are published on the EMA website on a monthly basis, normally the day after each PRAC meeting.

  This document makes publicly available a selection of information from the PRAC meeting including topics with major public health interest (e.g. start and finalisation of safety review referrals). This
transparency/communication tool may be complemented with a dedicated Press Release and/or a Question and Answer document on each topic in some cases. The published PRAC meeting highlights can be found on the EMA’s website (www.ema.europa.eu) under About us-Committees-PRAC.

- **PRAC minutes**

  The PRAC has been publishing minutes of its meetings since its formation in July 2012. PRAC minutes are published in full (with the exceptions listed above) on the EMA website after their adoption at the end of the following scientific meeting. The publication of the PRAC minutes takes place on a monthly basis, and once the minutes have been adopted at the next PRAC meeting. The classification of PRAC outputs with regards to the relevant regulatory procedure, as reported in the minutes, is outlined in the "Countdown to July 2012: the establishment and functioning of the PRAC” published on the EMA. The published PRAC minutes can be found on the EMA’s website (www.ema.europa.eu) under About us-Committees-PRAC.

**16.2. Which transparency measures apply with regards to the CHMP meeting?**

- **CHMP agendas and minutes**

  The EMA does not currently CHMP agendas and minutes but aims to start publishing them by the end of 2013. Please see the EMA press release “European Medicines Agency announces plan to publish committee agendas and minutes-Latest initiative on enhancing transparency”.

- **CHMP meeting highlights**

  CHMP meeting highlights are published on the EMA website on a monthly basis usually on the day after each CHMP meeting. The published CHMP meeting highlights can be found on the EMA’s website under About us/Committees/CHMP/Committee meeting reports (www.ema.europa.eu).

- **CHMP summaries of opinions or Refusal question-and-answer**

  CHMP summaries of positive opinions or Refusal question-and-answer document are product specific and published on the EMA’s website (www.ema.europa.eu).

- **Major changes made to the authorisation of medicines, which have been recommended by the CHMP to improve safety for patients can be found on the EMA’s website (www.ema.europa.eu) under Find medicine-Human medicines-Patient Safety.**

  A full list of all changes made to a centrally authorised medicine are outlined in the European Public Assessment Report. Please refer to question/answer Which transparency measure applies for the publication of assessment reports?

- **Referrals**

  More information on referrals such as start of the procedure, referrals under evaluation, recommendations provided by PRAC, opinions provided by CHMP, positions provided by CMDh and European Commission final decisions, can be found on the EMA’s website (www.ema.europa.eu) under Find medicine-Human medicines-referrals.

  Information on referral procedures can be found on the EMA’s website (www.ema.europa.eu) under Regulatory- Human medicines-Referral procedures.
16.3. Which EMA transparency measures apply for on-going procedures?

- **Publication of information on on-going medicine evaluations**
  - The EMA publishes since the 01st of March 2012 information on on-going medicine evaluations. This applies to all new medicines for human use under evaluation by the CHMP. Information published relates to the INNs and therapeutic areas for all new innovative medicines under evaluation, along with information on the type of salt, ester or derivative of the active substance. For generic and biosimilar medicines, it includes the INN and therapeutic area. Publication of this information can be found on the EMA website (www.ema.europa.eu) under Find Medicine-Medicines under evaluation.
  - The EMA publishes since the 7th of November 2012 information on on-going applications for extensions of indication of human medicines. This information is published in the minutes of the PRAC. The new level of transparency involves the publication of information on applications for changes to the authorised use of medicines where a change to the risk-management plan (RMP) is needed.

16.4. Which transparency measure applies for the publication of assessment reports?

- **European Public Assessment Reports (EPARs)**
  
The EMA publishes an EPAR for every centrally authorised medicinal product evaluated by the CHMP and received a Marketing Authorisation (MA) by the European Commission.

  EPARs contain a number of separate documents published on the EMA website, including:
  - a Question and Answer document summarising the view of the Committee in public-friendly language;
  - the approved product information (SmPC, labelling and Package Leaflet) available in all official EU languages updated throughout the life-cycle of the products;
  - the assessment report of the initial application and of major post-authorisation applications (e.g. new indication).
  - Divergent positions, if any, are appended to the assessment report;
  - a tabulated list of steps taken after the granting of Marketing Authorisation of the medicinal products. When a product is withdrawn or suspended, documents are updated accordingly.

  In addition, refusal EPAR is published following the refusal of a MA application and a withdrawal EPAR is published following the withdrawal of a MA application.

  The published EPARs can be found on the EMA’s website (www.ema.europa.eu) under Find medicine-Human medicines-EPARs. This webpage includes information on authorised medicines, withdrawn post-approval, refused.

  Information on withdrawn applications (both Initial authorisation application and Post-authorisation application) can be found on the EMA’s website (www.ema.europa.eu) under Find medicine-Human medicines-Withdrawn applications.

- **Pending a decision by the European Commission**
  
  Information on opinions with positive/negative outcome for Initial and Post-authorisation can be found on the EMA’s website (www.ema.europa.eu) under Find medicine-Human medicines-Pending EC decisions.

  These opinions are replaced by a full EPAR once the European Commission has decided - taking the European Medicines Agency’s opinion into consideration - to grant or refuse a marketing authorisation.
16.5. Which specialised databases are publicly available?

- Side effects of medicines
  
  Information on suspected side effect reports are available in the European database of suspected adverse drug reaction reports (www.adrreports.eu). Certain defined data fields are publicly available since June 2012. This website allows users to view the total number of individual suspected side effect reports submitted to the EudraVigilance database for each centrally authorised medicine. They can sort these reports by age group, sex, type of suspected side effect and outcome.

- Clinical trials
  
  Information on clinical trials is available in a public register called EU Clinical Trials Register (www.clinicaltrialsregister.eu). This gives access to information on interventional clinical trials for medicines authorised in the EU, as well as Iceland, Liechtenstein and Norway, and trials authorised to be carried out outside the EU as part of a paediatric investigation plan:
  
  The Agency also maintains a public database of studies conducted in children that were completed by the date of entry into force of the Paediatric Regulation on 26 January 2007: Article 45 paediatric studies database (art45-paediatric-studies.ema.europa.eu).

- Manufacturing inspections
  
  Information on inspections of the manufacturing sites for medicines performed by regulatory authorities in the EU, Iceland, Liechtenstein and Norway are available in a public database called EudraGMP.

- ENCePP database
  
  The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) is a collaborative scientific network coordinated by the EMA and developed in collaboration with European experts in the fields of pharmacoepidemiology and pharmacovigilance. Its goal is to further strengthen the postauthorisation monitoring of medicinal products in Europe by facilitating the conduct of multi-centre, independent, post-authorisation studies focusing on safety and on benefit:risk, using available expertise and research experience across Europe. This network comprises relevant research centres, medical-care centres, healthcare databases, electronic registries and existing European networks covering certain rare diseases, therapeutic fields and adverse drug events of interest. More information is provided at www.encepp.eu.

16.6. Does the EMA provide monthly figures on centralised procedures for human medicines?

- Statistics
  
  Monthly Statistics reports on medicinal products for human use (cumulative figures for the year to date) are published on the EMA website. This document provides current information related to the volume and evaluation of marketing authorisation and post-authorisation applications received by the EMA. The purpose is only to provide on-going factual information. Commentaries and analysis are provided in the EMA’s annual reports.
  
  The published Monthly Statistics reports can be found on the EMA’s website (www.ema.europa.eu) under News and events-Statistics.

  More information on the work of the EMA along with overview of the EMA transparency measures can be found on the EMA’s website (www.ema.europa.eu) under Special topics-Transparency.
References

- Regulation 726/2004 (EC), as amended by Regulation (EU) No 1235/2010

- Information on the 2010 pharmacovigilance legislation can be found on the EMA website under Special topics-Safety of medicines and under Regulatory-Human medicines-Pharmacovigilance

- Countdown to July 2012: the establishment and functioning of the PRAC” (EMA/315258/2012)

- New EU pharmacovigilance legislation – Key concepts (EMA/186974/2012)

- Policy on agendas and minutes
  The Agency is adopting a phased approach to the publication of minutes and agendas of its remaining four committees. It will systematically publish all of its committees’ agendas and minutes before the end of 2013 (EMA press release, EMA/480386/2012, 18 July 2012)

- EMA Access to documents Policy
  - European Medicines Agency policy on access to documents (related to medicinal products for human and veterinary use) (EMA/110196/2006 30, November 2010)
  - Output of the European Medicines Agency policy on access to documents related to medicinal products for human and veterinary use (EMA/127362/2006, 30 November 2010)

- Heads of Medicines Agencies/European Medicines Agency guidance document on the identification of commercially confidential information and personal data within the structure of the marketing authorisation application – release of information after the granting of a marketing authorisation (published at the EMA and HMA website on 27 March 2012)
  - Principles to be applied for the implementation of the Heads of Medicines Agencies/European Medicines Agency guidance on the identification of commercially confidential information and protected personal data in marketing authorisation applications (published at the EMA website on 27 March 2012)
  - Overview of comments received on 'Heads of Medicines Agencies / European Medicines Agency guidance document on the identification of commercially confidential information and protection of personal data within the structure of the marketing-authorisation dossier – release of information after granting of a marketing authorisation' (published at the EMA website on 15 June 2012)

- European database of adverse drug reaction reports website
  http://www.adrreports.eu/
  - See also Question and answer document on the European database of adverse drug reaction reports website (EMA/259836/2012, 31 May 2012)

- European Network of Paediatric Research at the European Medicines Agency (Enpr-EMA)

- Draft EMA Transparency Policy
  This draft policy and related links can be found on the EMA website (www.ema.europa.eu) under Special topics-Transparency.

- EMA Work programmes can be found on the EMA website (www.ema.europa.eu) under About us-How we work

- EMA Road Map to 2015 can be found on the EMA website (www.ema.europa.eu) under About us-How we work
• EMA conflicts of interest Policy
  This policy and related links can be found on the EMA website (www.ema.europa.eu) under About us-How we work

• New EMA Transparency policy measures (EMEA/MB/52/03)

• Public consultation on EMA transparency initiatives (EMEA/D/21621/03/Consultation)

• Outcome of public consultation on new EMA transparency initiatives (EMEA/D/16906/00)

• Current status of public consultation on new transparency initiatives (EMEA/D/10983/00)

• Public consultation on new EMA transparency initiatives (EMEA/D/6135/00)

• Points to Consider for an EMA Communication Policy (EMEA/MB/011/98)
17. Pharmacovigilance system summary New March 2013

17.1. Requirements regarding the summary of the pharmacovigilance system

Companies are requested to provide a summary of their pharmacovigilance system, which the marketing authorisation holder (MAH) will introduce, in accordance with Article 8(3)(ia) of Directive 2001/83/EC.

The requirement for the summary of the pharmacovigilance system was introduced by the new pharmacovigilance legislation (Directive 2010/84/EU amending Directive 2001/83/EC) and replaces the previous requirement for the detailed description of pharmacovigilance system in the dossier.

The summary of the pharmacovigilance system should be provided in Module 1.8.1 of the application and includes the following elements:

- proof that the applicant has at his disposal a qualified person responsible for pharmacovigilance,
- the Member States in which the qualified person resides and carries out his/her tasks,
- the contact details of the qualified person,
- a statement signed by the applicant to the effect that the applicant has the necessary means to fulfil the tasks and responsibilities listed in Title IX of Directive 2001/83/EC,
- a reference to the location where the pharmacovigilance system master file (PSMF) for the medicinal product is kept.

The MAH may combine this information in one single statement using the required statement as per Article 8(3)(ia) “the applicant/MAH has the necessary means to fulfil the tasks and responsibilities listed in Title IX of Directive 2001/83/EC”, signed by the MAH and qualified person for pharmacovigilance (QPPV).

The requirement for the summary of the pharmacovigilance system is the same for any marketing authorisation application, independent of the legal basis for the application.

The obligation to maintain a PSMF and to submit a summary of pharmacovigilance system applies to all existing marketing authorisations irrespective of whether they contain a DDPS or not.

17.2. Requirements regarding the pharmacovigilance system and pharmacovigilance system master file

The MAH has to operate a pharmacovigilance system for the fulfilment of his pharmacovigilance tasks.

The pharmacovigilance system master file (PSMF) is a detailed description of the pharmacovigilance system used by the MAH with respect to one or more authorised medicinal products.

The PSMF is not part of the marketing authorisation (MA) dossier and is maintained independently from the MA. It should be permanently available for inspection and should be provided within 7 days to the Competent Authorities if requested. The PSMF must be located either at the site in the Union where the main pharmacovigilance activities of the marketing authorisation holder are performed or at the site in the Union where the QPPV operates. The QPPV has to both reside and operate in the Union.

Applicants are required, at the time of initial marketing authorisation application, to have in place a description of the pharmacovigilance system that records the system that will be in place and
functioning at the time of granting of the marketing authorisation and placing of the product on the market. During the evaluation of a marketing authorisation application the applicant may be requested to provide a copy of the pharmacovigilance system master file for review.

The pharmacovigilance system master file has to describe the pharmacovigilance system in place at the current time. Information about elements of the system to be implemented in future may be included, but these should be clearly described as planned rather than established or current.

The pharmacovigilance system will have to be in place and functioning at the time of granting of the marketing authorisation and placing of the product on the market.

17.3. **Subcontracting pharmacovigilance activities**

The MAH may subcontract certain activities of the pharmacovigilance system to third parties. He will nevertheless retain full responsibility for the completeness and accuracy of the pharmacovigilance system master file.

The MAH will have to draw up a list of its existing subcontracts between himself and the third parties, specifying the product(s) and territory(ies) concerned.

When delegating any activities concerning the pharmacovigilance system and its master file, the MAH retains ultimate responsibility for the pharmacovigilance system, submission of information about the pharmacovigilance system master file location, maintenance of the pharmacovigilance system master file and its provision to competent authorities upon request. Detailed written agreements describing the roles and responsibilities for pharmacovigilance system master file content, submissions and management, as well as to govern the conduct of pharmacovigilance in accordance with the legal requirements, should be in place.

For more guidance on the requirements for pharmacovigilance system and PSMF, please refer to the relevant Good Vigilance Modules.

17.4. **When to submit a summary of the pharmacovigilance system?**

For marketing authorisations granted before 2 July 2012 and for marketing authorisation application that were ongoing at the time of entry into force of the legislation (2 July 2012) which were not updated with the summary of the pharmacovigilance system during evaluation, MAHs are required to include a summary of the MAH’s pharmacovigilance system at the following times whichever is the earlier:

- At the time of submission of the renewal application,
- At time of submission of the annual renewal application for a conditional marketing authorisation,
- By 2 July 2015 at the latest.

Until the summary of the pharmacovigilance system is introduced in the dossier as per transitional measures described above, the relevant variations to update the DDPS, when necessary, will have to be submitted by the MAH for the DDPS.

17.5. **Which variation to introduce or change the summary of the pharmacovigilance system?**

Pending the publication of the final revised variation classification guideline, the CMDh issued a recommendation on classification of two unforeseen variations in accordance with Article 5 of Regulation (EC) No 1234/2008, one for the introduction of the pharmacovigilance system summary
and the other for changes to the QPPV names and/or contact details and/or to the PSMF location which can be found on the CMDh website.

The introduction of the summary of pharmacovigilance system requires a type IA\textsuperscript{IN} variation (the ‘implementation’ is when the Company introduces the PSMF, i.e. when it internally approves the use of the PSMF). Changes to the QPPV information can be introduced as part of the first introduction of the pharmacovigilance system summary in one single variation type IA\textsuperscript{IN}, as the QPPV information is part of the required information in the summary. If the QPPV information is changed as part of the introduction of the summary of the pharmacovigilance system, the MAH should clearly indicate the change in the application form (i.e. in the present/proposed table of the application form).

The transition period to introduce the summary of the pharmacovigilance system described in Question 3 applies per marketing authorisation, therefore it is the MAH decision to introduce the summary of pharmacovigilance system for each product at different times or to introduce the summary for several products at the same time. However, once a product is included in a PSMF, the relevant type IA\textsuperscript{IN} should be submitted to update the MA for this product and reflect the use of the PSMF accordingly.

One grouped type IA\textsuperscript{IN} variation may be used by the same MAH to introduce the pharmacovigilance system summary at the same time for all the relevant CAPs. Please see EMA post-authorisation procedural advice – Grouping of variations.

The same grouped variation may be used to introduce a summary of the pharmacovigilance system for several medicinal products with or without a DDPS. In that case, the information on which product has a DDPS and which product does not should appear clearly in the application form (i.e. in the present/proposed table of the application form).

Once the summary of pharmacovigilance system is introduced, changes to the QPPV names and/or contact details and/or to the PSMF location are managed via a type IA\textsuperscript{IN} variation (the ‘implementation’ is when the Company makes the change in the PSMF, i.e. when it internally approves the change in the PSMF). For more information on the conditions and documentation for this type IA\textsuperscript{IN} variation, please see the CMDh website on Article 5 recommendation.

### 17.6. Pharmacovigilance system master file number

Marketing authorisation holders are encouraged to request a PSMF number (MFL EVCODE) for their PSMF in advance of the relevant application introducing the PSMF (renewal or variation applications) in order to include the PSMF number in their application.

If available, the PSMF number (MFL EVCODE) assigned by the extended EudraVigilance Medicinal Product Dictionary (XEVMPD) should be included in the statement in Module 1.8.1. However this information is not part of the compulsory elements as per Article 8(3)(ia) of Directive 2001/83/EC.

For more information on how to obtain a PSMF number, please refer to the Detailed Guidance on electronic submission of information on medicines (When to submit a summary of the pharmacovigilance system?).

### References

- Directive 2001/83/EC
- Directive 2010/84/EU


• HMA-EMA Questions and answers on practical transitional measures for the implementation of the pharmacovigilance legislation (EMA/228816/2012 – v.2)

• Guideline on good pharmacovigilance practices - Module I – Pharmacovigilance systems and their quality systems (EMA/541760/2011)

• Guideline on good pharmacovigilance practices - Module II – Pharmacovigilance system master file (EMA/816573/2011)

• Commission regulation (EC) No 1234/2008 of 24 November 2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products

• Volume 2C of the Rules Governing Medicinal Products in the European Union - Regulatory Guidelines : Guideline on the details of the various categories of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products

• Article 5 CMDh Website

• EMA post-authorisation procedural advice – Grouping of variations

• Detailed Guidance on electronic submission of information on medicines.
18. Article 61(3) Notifications


Article 61(3) refers to Directive 2001/83/EC in which a so-called “61(3) Notification” is defined as a change to an aspect of the Labelling and/or Package Leaflet (PL) text not connected with the Summary of Product Characteristics (SmPC). In order for a 61(3) Notification to be valid, the change must affect the English labelling and/or PL text, with consequential amendments to all other language versions. Such change could for instance be a change in the local representatives listed at the end of the PL, inclusion of Braille on the packaging, minor changes to the labelling, clarifications in the PL, etc. Changes to the SmPC and/or Annex II are not acceptable within a 61(3) Notification.

Therefore, if a marketing authorisation holder (MAH) wishes to either introduce any labelling/PL text additional to that in Commission Decision Annexes (IIIA, IIIB) or to change the labelling/PL text, not connected to the SmPC, outside any other regulatory procedure (e.g. Type II variation, renewal .....). he must first notify this change to the EMA as per Article 61(3) of the Directive, the EMA shall inform the marketing authorisation holder within 90 days whether the proposed change is accepted or not. The EMA shall also inform the Commission, who shall amend the Marketing Authorisation Annexes in the context of the next regulatory procedure (see: How and when will the updated Annexes become part of the Marketing Authorisation?).

The 61(3) Notification procedure should also be followed in case amendments to the package leaflet are required following ‘User Testing’, when the User Testing report and amended leaflet can not be included in an upcoming regulatory procedure which affects the Annexes (e.g. Type II variation).

However, where a change to the labelling/PL impacts only on the overall lay-out, design, readability, etc. and not on the actual labelling/PL text in Annex IIIA or IIIB, such changes are not considered to fall under the scope of a 61(3) Notification. In such case, the need for an EMA review of the proposed changes by means of the provision of specimens, should be discussed with the EMA Medical Information Sector (muspecimens@ema.europa.eu), as outlined in “The Revised Checking Process of Mock-Ups and Specimens of outer/immediate labelling and package leaflets of human medicinal products in the Centralised Procedure” on the EMA website.

References

- Directive 2001/83/EC
- The Revised Checking Process of Mock-Ups and Specimens of outer/immediate labelling and package leaflets of human medicinal products in the Centralised Procedure (EMEA/305821/2006)

18.2. Is the Rapporteur involved in 61(3) Notifications?

The Rapporteur is normally not involved in the review of a 61(3) Notification. However, the Rapporteur may be involved on a case-by-case basis depending on the changes requested (e.g. extensive PL revision following User Testing).
18.3. When can I submit my 61(3) Notification? Rev. Apr 2012

There are no recommended submission dates for 61(3) Notifications. The Marketing Authorisation Holder should, however, consider whether the changes applied for in the 61(3) Notification could reasonably be included in an upcoming regulatory procedure (e.g. Type II or Type IB procedure affecting the product information).

Applicants are recommended to liaise with the Product Team Leader/Administrative Assistant before submission of the application if there are any questions on the documents to be provided in order to ensure the completeness of the application for the 61(3) Notification (see: How shall I present my 61(3) Notification? and How shall my 61(3) Notification be handled (timetable), and what could be the outcome?)


The submission of a 61(3) Notification should include:

- Cover Letter indicating the product name, listing all changes applied for together with a list of ongoing/upcoming regulatory procedures affecting the Annexes and including a confirmation that the proposed changes only affect Annex III). The attachments: "Formatting checklist" and "Present and Proposed” table should be provided, if applicable. The cover letter should include identical information to the "eCTD envelope” and to the information printed on the CD/DVD. It is recommended to include the history of the lifecycle sequences of the product up to the enclosed submission as an annex to the cover letter.

- If applicable, any supportive relevant documentation (e.g. User Testing reports) to the 61(3) Notification, presented under the appropriate headings and numbering of the EU-CTD format.

- The revised product information Annexes (see also: When do I have to submit revised product information?).

18.5. How and to whom shall I submit my 61(3) Notification? Rev. March 2013

The EMA strongly recommends using the eSubmission Gateway or the eSubmission Web Client as the preferred submission method for all eCTD submissions. More information on how to register and connect to the Gateway / Web Client can be found in the eSubmission website and detailed information on the required naming conventions and file formats can be found in the eSubmission Gateway Q&A document and the Web Client Q&A. Applicants must not send duplicate submissions electronically or via CD-ROM or DVD as this might lead to delays in the handling of applications.

Applications that are sent using the eSubmission Gateway and eSubmission Web Client will receive an automated ‘acknowledgement’, confirming whether the submission has passed the relevant technical validation criteria and whether it has been uploaded to the agency’s review tool. There is no need to send any separate paper cover letters for these submissions, as the cover letter will be in the relevant part of eCTD module 1 in PDF format.

MAHs not yet using the eSubmission Gateway or the Web Client solution should send their 61(3) notifications as CD-ROM or DVD to the attention of the Product and Application Business Support (PA-BUS) at the following address:
Only one CD-ROM or DVD (in eCTD format) of the 61(3) Notification should be submitted to the Agency, together with one original, signed paper cover letter when using this format of submission. The Product Team Leader should be indicated in copy “cc” on the cover letter (no additional copy needed).

Revised product information Annexes should be included in electronic (Word and PDF) format in the same eSubmission Gateway and eSubmission Web Client package or CD-ROM or DVD within a folder called 'working documents'.

One electronic copy should also be sent to the CHMP (Co-) Rapporteur and other CHMP members to maintain their eCTD life cycle of the dossier.

For a full overview of dossier requirements for National Competent Authorities of (Co-) Rapporteur and Committee members, including delivery addresses, please refer to the following document: Dossier requirements for Centrally Authorised Products (CAPs).

Please note that the EMA only accepts submissions made in a mandatory eCTD format.

References

- Template for cover letter
- Dossier requirements for Centrally Authorised Products (CAPs)
- TIGes Harmonised Guidance for eCTD Submissions in the EU
- eSubmission website
- eSubmission Gateway Q&A
- eSubmission Gateway Web Client Q&A

18.6. How shall my 61(3) Notification be handled (timetable), and what could be the outcome? Rev. Apr 2012

The following 90-day timetable shall apply to 61(3) Notifications:

<table>
<thead>
<tr>
<th>Day</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 1 (Day following receipt of the 61(3) Notification) e-CTD submission)</td>
<td>Start of the procedure</td>
</tr>
<tr>
<td>By Day 10</td>
<td>Initial check to determine if the MAH’s proposed changes are within the scope of Article 61(3) of</td>
</tr>
</tbody>
</table>
The following outcomes may be envisaged:

- The proposed change does not fall under the scope of an Article 61(3) of Directive 2001/83/EC. In that case, the Marketing Authorisation Holder will be informed accordingly within 10 days following the day of receipt of the 61(3) Notification, and the procedure will be stopped or updated documentation will be requested.

- Changes are acceptable and an EMA Notification is issued within 90 days.

- Changes are not acceptable (even after receipt of additional/revised information if required), and an EMA refusal letter will be issued within 90 days.

In all cases, the EMA will inform the MAH of the outcome of the Notification check within 90 days.

### 18.7. What fee do I have to pay for a 61(3) Notification?

There is no fee payable for 61(3) Notifications.

### 18.8. Do I have to submit mock-ups and specimens? Rev. Apr 2012

**Mock-ups**

No mock-ups are required to be provided with the 61(3) Notification.

**Specimens**

Where the overall design and readability of the outer and immediate packaging and/or package leaflet is affected as part of the Notification, the need for the provision of specimens should be discussed with the EMA Medical Information Sector on a case-by-case basis (e.g. specimens would be required when proposing major changes in lay-out, use of different colours as part of the 61(3) Notification, but not e.g. when only limited text is added/revised in a PL section).

In case specimens are required, in principle only one relevant example (multi-lingual if possible) would need to be sent to the EMA at the latest 15 working days before marketing. However, depending on the nature and extent of the change(s) concerned, additional specimens may be required by the EMA. The EMA will perform a general check from the viewpoint of readability within 15 working days, and will check if any previous comments on specimens have been duly implemented. The MAH will be informed about the outcome of the check.

**Note:**
In case the MAH wishes to receive EMA feedback on their proposed new packaging in advance of the specimen review, the EMA could agree with the MAH on a case-by-case basis, to review draft mock-ups before specimen submission.

The above principles also apply to mock-ups for Iceland. The mock-ups should be sent by e-mail to mockups@ima.is. See also http://www.imca.is/IMCA/News/nr/1263

No mock-ups and specimens are required for Norway.

References

- The Revised Checking Process of Mock-Ups and Specimens of outer/immediate labelling and package leaflets of human medicinal products in the Centralised Procedure (EMEA/305821/2006)

18.9. How and when do I have to submit revised product information? In all languages? Rev. Apr 2012

The electronic copy of all languages should be provided on CD-ROM/DVD as part of the Notification application, highlighted changes should be indicated via ‘Tools – Track changes’. Clean versions should have all changes ‘accepted’.

- All EU language (incl. NO+IS): complete set of Annexes
electronically only
in Word format (highlighted)
in PDF (clean)

The ‘complete set of Annexes’ includes Annex I, II, IIIA and IIIB i.e. all SmPC, labelling and PL texts for all strengths and pharmaceutical forms of the product concerned, as well as Annex II.

The complete set of Annexes must be presented sequentially (i.e. Annex I, II, IIIA, IIIB) as one document for each official EU language. Page numbering should start with "1" (bottom, centre) on the title page of Annex I. The Annexes should be presented in strict compliance with the QRD Convention published on the EMA website. When submitting the full set of Annexes in PDF format, this should be accompanied by the completed formatting checklist guidance on how to correctly prepare the PDF versions.

The Annexes provided should only reflect the changes introduced by the 61(3) Notification. However, in exceptional cases where MAHs take the opportunity to introduce minor linguistic amendments in the texts (e.g. further to a specimen check) this should be clearly mentioned in the cover letter. Alternatively, such changes may be provided as a separate document attached to the cover letter. Any changes not listed in the Notification cover letter, will not be considered as part of the 61(3) Notification.
18.10. **How and when will the updated Annexes become part of the Marketing Authorisation?** *Rev. Apr 2012*

Upon finalisation of a 61(3) Notification, the changes to the product information Annexes will be reflected in the framework of the next regulatory procedure for which a Commission Decision will be issued. For example, the changes could be included with the Commission Decision of a subsequent Type II variation affecting the product information Annexes or with the six-monthly Commission Decision following a Type I Variation (as outlined in Type I variations *How and when will the updated Annexes become part of the Marketing Authorisation?*).

However, the agreed changes can be implemented upon receipt of the EMA Notification without awaiting the update of the Marketing Authorisation through a Commission Decision, and the agreed changes should be included in the Annexes of any regulatory procedure subsequent to the 61(3) Notification.

18.11. **Will there be any publication on the outcome of my 61(3) Notification?** *Rev. Apr 2012*

The EPAR (published on the EMA website) will be revised to implement the outcome of the 61(3) Notification, after issuance of the EMA Notification.

**References**

- EPARs
19. Marketing and cessation notification

The following guidance only focuses on marketing and cessation information but does not address the requirements to provide in the context of pharmacovigilance, the volume of sales and volume of prescriptions (see Questions and answers on notification to the EMA of actual marketing and cessation of placing on the market for centrally authorised products (EMEA/180078/2005) and Questions and answers on the application of the so-called ‘sunset clause’ to centrally authorised medicinal products (EMEA/180079/2005)).

19.1. What is the meaning of “actual marketing” / “placing on the market”?

The definition hereafter is based on the general principles outlined in the Chapter 1 of volume 2A of the Notice to Applicants.

In this context, the terms “actual marketing” and “placing on the market” should be defined as when the medicinal product is “released into the distribution chain” i.e. out of the direct control of the Marketing Authorisation Holder.

References

- Article 13(4) (first paragraph) of Regulation (EC) No 726/2004
- Article 23a (first paragraph) of Directive 2001/83/EC, as amended
- Chapter 1 (section 2.4.2), The Rules governing Medicinal Products in the European Union, Notice to Applicants, Volume 2A

19.2. What is the meaning of “cessation of placing on the market”?

The definition hereafter is based on the general principles outlined in the Chapter 1 of volume 2A of the Notice to Applicants.

The “cessation of placing on the market” shall be defined by analogy to the placing on the market, as the “cessation of release into the distribution chain” with the consequence that the concerned product is no longer available for the supply to the patients.

It means that the date of cessation shall be the date of the last release into the distribution chain.

References

- Article 13(4) (first paragraph) of Regulation (EC) No 726/2004
- Article 23a (first paragraph) of Directive 2001/83/EC, as amended
- Chapter 1 (section 2.4.2), The Rules governing Medicinal Products in the European Union, Notice to Applicants, Volume 2A
**19.3. What information should be reported to the Agency on the medicinal product marketing status?**

The actual marketing of a medicinal product shall be reported to the Agency per presentation and per Member State. For centrally authorised medicinal products, presentation corresponds to pack-size.

The MAH shall also notify the Agency of a cessation (temporary/permanent) in marketing their medicinal product.

However, temporary cessation should only be reported when it may cause a public health concern. The MAH has to exercise his best judgement to determine when it is appropriate to report such a cessation but can always seek advice from the EMA, when required.

MAHs are advised that where cessation is due to efficacy, safety and/or quality related issues for which already particular procedures are established, reporting of such cessation is without prejudice to applying the other specific related procedures (e.g. quality defect, pharmacovigilance issues, etc.), as appropriate.

A date is to be reported for actual marketing which shall be defined as Day/Month/Year. By analogy, a cessation in placing on the market should also be defined as an exact date. If MAHs experience difficulties in identifying the exact date, the cessation date should still be defined as D/M/Y, mentioning the last day of the nearest week or month for the purpose of the sunset clause monitoring.

**References**

- Article 13(4) (first paragraph) of Regulation (EC) No 726/2004
- Chapter 1 (section 2.4.2), The Rules governing Medicinal Products in the European Union, Notice to Applicants, Volume 2A

**19.4. When and how to notify the Agency with the marketing status overview?**

The so-called marketing status overview refers to the picture of the marketing situation of a specific product, at one time point of the product life-cycle, per presentation and per Member State.

MAHs should inform the EMA of the marketing status of their medicinal product(s) reflecting on the different situations previously detailed, according to the timelines given hereafter and using the electronic tabular format that is provided.

The MAH should notify the Agency within 30 days of the initial placing on the market of the product within the Community. Thereafter, any subsequent placing on the market or change in the marketing status should be reported through updates provided following the PSUR-cycle timelines and after renewal, annually in accordance with anniversary of the Commission Decision date. The reporting table should be attached to the cover letter. (See also What is the reporting format to the Agency?)

An updated report should be provided on a regular basis according to the above mentioned timelines, even if there are no changes in the marketing status of the medicinal product over that period of time.

Furthermore, in addition to these regular updates when there is a cessation which may cause a public health concern, the MAH should notify the Agency (see When and how to report cessation to the Agency?).
When addressing such a notification cessation, the MAH should provide in addition a full updated table of the product marketing status.

19.5. **When and how to report cessation to the Agency?**

Permanent and temporary cessations where the MAH identifies that there may be a public health concern should be notified to the Agency at least 2 months in advance of the cessation, unless exceptional circumstances apply. However, the MAH is advised to inform the Agency at the earliest possible opportunity i.e. as soon as the interruption is foreseen. If the MAH was thinking of ceasing to market a product several months beforehand, but did not have an exact date defined, the MAH could give the EMA a provisional date and then subsequently update it with more precise information.

It is anticipated that the MAH provides detailed information to the Agency to consider impact of such cessation. This should include e.g. grounds, length of cessation period, Members State(s) concerned, company’s intention to provide information to prescribers and patients, etc. The Rapporteur and CHMP will be involved as appropriate.

MAHs are advised that reporting is without prejudice to other procedures. Where cessation is due to efficacy, safety and/or quality related issues for which particular procedures are established, the specific related procedure should be followed in addition (e.g. quality defect, pharmacovigilance issues, etc.). (See also What is the reporting format to the Agency?)

The 2-month notice period for notifying to the Agency a cessation in placing on the market which might be of public health concern may not be met in exceptional circumstances.

It is recognised that there are some cases where the MAH cannot anticipate the interruption of the placing on the market of the medicinal product within the required timeframe as reasons for the interruption are outside of their control. Cases should be considered on a case-by-case basis.

This includes cases of “force majeure” (e.g. burning down of manufacturing site, natural disaster, major manufacturing difficulties, out of stock of active substance or any ingredient of the medicinal product including packaging material, urgent safety and quality concerns...), as well as the cases concerning urgent provisional measures and suspension.

However, when the 2-month notice period cannot be respected, the MAH shall inform the Agency as soon as the interruption is considered likely or known.

Permanent cessations in placing on the market of any presentation in any Member State where no potential public health concern is identified by the MAH should be reported at the time of the reporting of the marketing status overview.

**References**

- Article 13(4) (first paragraph) of Regulation (EC) No 726/2004
- Article 20 of the Regulation (EC) No 726/2004
- Articles 107(2), 116 and 117 of the Directive 2001/83/EC, as amended
19.6. What is the reporting format to the Agency and to whom to report?

MAHs should inform the EMA of the marketing status of their medicinal product(s) using the electronic template which is provided in Q&A “When and how to notify the Agency with the marketing status overview?”

All marketing status reports either relating to the first marketing, updates or cessation of marketing should be sent by the MAH to the mailbox address (marketingstatus@ema.europa.eu) and should be copied to the PTL for the first marketing and a specific cessation of marketing of the medicinal product as described in previous question (see When and how to notify the Agency with the marketing overview? and When and how to report a cessation to the Agency?). Hence,

- First marketing reports should be sent within 30 days of the initial placing on the market of the product within the Community;
- Updated reports (whether there are changes or not) should be sent at time of PSUR submission and after renewal, annually in accordance with anniversary of the Commission Decision date;
- Cessation reports as well as detailed information on the cessation should be sent 2-month before the interruption, otherwise as soon as the interruption is considered likely or known.

19.7. Do requirements for notification of marketing and cessation apply to existing medicinal products?

This provision applies to all centrally medicinal products whether authorised before or after the date of entry into force of the Regulation i.e. 20 November 2005. However, for medicinal products authorised before this date, MAHs have to notify the EMA only of the actual marketing and cessation regarding all the various presentations of their medicinal product per Member State as of 20 November 2005.

19.8. What is the intended use of the marketing status reporting for the purpose of the sunset clause monitoring?

The marketing status overview/reporting provides data that are the basis for the monitoring of the sunset clause (See also Sunset clause monitoring).

References

- Article 13(4) (first paragraph) of Regulation (EC) No 726/2004
- Chapter 1 (section 2.4.2), The Rules governing Medicinal Products in the European Union, Notice to Applicants, Volume 2A

19.9. Is there a database to notify and collect the marketing status information?

To make the reporting for the MAH easier and to facilitate the tracking of this information by the EMA for the purpose of the sunset clause monitoring, the Agency intends to collect data electronically through the EudraVigilance Medicinal Product Dictionary (EVMPD). EVMPD extension will allow a direct
and up-to-date reporting by the MAH to the Agency with the view to track a three-year period without marketing so-called “sunset period” and to make the marketing status information public (See also Sunset clause monitoring). This particular functionality within EVMPD is not available yet. The EMA will make a public announcement prior to the entry into force of this extension of the database.

19.10. Does the EMA intend to publish information about marketing status of the medicinal products?

MAHs should be aware that when the particular reporting functionality within EVMPD will be set up, the information on availability of the medicinal product and its various presentations per Member State will be made public by the EMA as “marketed”/ “not marketed” based on the data entered in EVMPD by the MAH.
20. Sunset clause monitoring

20.1. What is the sunset clause?

The so-called “sunset clause” is a provision leading to the cessation of the validity of the marketing authorisation if:

• the medicinal product is not placed on the market within three years of the authorisation being granted or,
• where a medicinal product previously placed on the market is no longer actually present on the market for three consecutive years.

The European Commission may grant exemptions on public health grounds and in exceptional circumstances if duly justified.

References

• Article 14(4-6) of Regulation (EC) No 726/2004
• Article 24(4-6) of Directive 2001/83/EC, as amended
• Chapter 1 (section 2.4.2), The Rules governing Medicinal Products in the European Union, Notice to Applicants, Volume 2A

20.2. Does the sunset clause apply to existing medicinal products?

This new provision applies prospectively to all centrally authorised medicinal products from the date of entry into force of the Regulation i.e. 20 November 2005.

Therefore, for medicinal products for which a MA has been granted before 20 November 2005 and for which no presentation are marketed in the Community at this date, the three-year period which leads to cessation of the MA will start as of 20 November 2005.

References

• Chapter 1 (section 2.4.2), The Rules governing Medicinal Products in the European Union, Notice to Applicants, Volume 2A

20.3. What are the requirements to maintain a marketing authorisation for a centrally authorised medicinal product?

The marketing authorisation of a medicinal product will remain valid if at least one presentation/pack-size of the existing product presentations is placed on the market in the Community (in at least one Member State) including Iceland, Norway and Liechtenstein.
The marketing authorisation of a centrally authorised medicinal product includes the initial marketing authorisation and all variations (e.g. additional presentations,...) and extensions (e.g. new strengths, new pharmaceutical forms,...) authorised for this specific medicinal product. This notion has been applied since the beginning of the centralised procedure and is reflected in the way the EU numbers are allocated to a specific centrally authorised medicinal product and all its presentations.

References
- Chapter 1 (section 2.4.2), The Rules governing Medicinal Products in the European Union, Notice to Applicants, Volume 2A

20.4. What are the principles for the monitoring of the sunset clause?

A three-year period without marketing of a medicinal product in the EEA can be encountered further to the granting of the marketing authorisation: when a medicinal product has never been marketed or, after marketing of a medicinal product has been completely stopped.

The term “no longer actually present on the market” should be understood in the same way as “ceases to be placed on the market”. Therefore, the sunset clause period in case of a complete marketing cessation of the product shall start from the last date of release into the distribution chain of the medicinal product. For definition and modalities of reporting of cessation, details are given in Marketing and cessation notification.

The EMA has set up a system to monitor the marketing status of centrally authorised medicinal product. This is done in view to notify the Commission when a three consecutive year period without marketing has elapsed and that the sunset clause provision should take effect.

The MAH should be aware of the overall timing with regard to the sunset clause period for their product and for taking any actions, should they wish to retain the marketing authorisation.

References
- Article 13(4) and Article 14(4-6) of Regulation (EC) No 726/2004

20.5. In case of a protection period to be respected before placing the medicinal product on the market, when will the sunset clause period start?

The determination of the start of the 3-year period from granting of the marketing authorisation should be the date when the medicinal product can be marketed by the marketing authorisation holder, taking into account, e.g. the market exclusivity and other protection rules which have to be respected.

For a medicinal product for which a MA will be granted after 20 November 2005, The Commission Decision will, in most cases, trigger the 3-year period.

However, following new data protection rules in the revised legislation, the 3-year period for generic and similar biological medicinal products will start as of the end of the 10 or 11-year protection period of the reference medicinal product.
Furthermore, other protection rules might need to be respected. Such information is not known by the Agency. MAHs are therefore advised to inform the EMA of the existence and if known, the expiry date of the other protection period(s) to be respected as appropriate. This should be notified within 60 days from the date of the granting of the MA.

References:

- Chapter 1 (section 2.4.2), The Rules governing Medicinal Products in the European Union, Notice to Applicants, Volume 2A
- Summary record of the 58th meeting of the Pharmaceutical Committee (1st June 2005) – published on the Commission website on 10 October 2005,
- Article 14(11) of Regulation (EC) No 726/2004
- Article 10(1) of Directive 2001/83/EC, as amended

20.6. When is the sunset timer ON/OFF?

The following situations can lead to the start of the sunset clause period (“ON”):

- Granting of the Marketing authorisation

At the time of the granting of the marketing authorisation, the medicinal product may not be immediately placed on the Community market. As a consequence, the sunset timer will start running from the granting of the marketing authorisation by the Commission or when the MAH can legally place the medicinal product on the market. (See also In case of a protection period to be respected before placing the medicinal product on the market, when will the sunset clause period start counting?)

- A temporary or permanent cessation of placing on the market the medicinal product

The MAH is obliged to inform the Agency of any product cessation (see Marketing and cessation notification). When there is no longer any presentation of the medicinal product placed on the Community market, the sunset timer will start running from the last date of release into the distribution chain of the medicinal product.

The following situations lead to the stop of the sunset clause period (“OFF”):

- Initial placing on the Community market

The sunset timer will stop running at the time of the first placing on the market of one presentation in one Member State.

- At the re-placing on the market after a temporary cessation of the whole medicinal product

As soon as a medicinal product is again placed on the Community market after a temporary cessation, the sunset timer will stop running at this date.

- Exemption

As soon as an exemption is granted by the Commission for a medicinal product, the sunset timer will be stopped.
20.7. **What about exemptions?**

The Commission may grant exemptions from the application of the sunset clause on public health grounds and in exceptional circumstances.

Exemptions can apply at any time of the marketing authorisation life cycle (i.e. at the time of the marketing authorisation, during the marketing authorisation life, or approaching the expiry of the sunset clause period) depending on the type of exemptions.

At submission stage the following exemptions might be applicable:

- Medicinal products to be used in emergency situations, in response to public health threats duly recognised either by the WHO or by the Community (Decision No 2119/98/EC).

- Antimicrobial medicinal products such as antibiotics, antivirals and immunologicals (for active and passive immunisation) aimed at the prevention and/or treatment of disease caused by bio-terror agents in response to an emergency public health need.

It will be up to the MAH to justify why an exemption should apply based on public health grounds and in exceptional circumstances. A request for an exemption including a justification should be notified to the Commission and each justification will be considered on a case-by-case basis. A copy of such request should also be addressed to the EMA.

**References**

- Article 14(6) of Regulation (EC) No 726/2004
21. Other

21.1. Which EMA inspection-related activities may occur during the post-authorisation phase?

The Agency’s Inspections Sector activities that may occur during the post-authorisation phase include the following: verification of compliance with the principles of Good Manufacturing Practice (GMP), Good Clinical Practice (GCP), Good Laboratory Practice (GLP), verification of compliance with pharmacovigilance obligations and inspections of blood establishments under the Plasma Master File (PMF) certification system.

The Sector is responsible for co-ordinating any GMP, GCP, GLP, pharmacovigilance and blood establishment inspections requested by the CHMP in connection with the assessment of marketing authorisation applications, post-authorisation applications, PMF certificate applications and/or the assessment of matters referred to these committees in accordance with Community legislation. These inspections may be necessary to verify specific aspects of the clinical or laboratory testing or manufacture and control of the product and/or to ensure compliance with GMP, GCP, GLP, pharmacovigilance obligations and quality assurance systems.

When the MAH anticipates the need for EMA inspections in the context of post-authorisation activities (e.g. addition of manufacturing site, submission of pivotal clinical data supporting new indications...), it is advised to contact the EMA in advance of submission in order to clarify the requirements and the timeframe applying to such inspections.

MAH is liable to pay a fee for each inspection specifically requested by CHMP or CVMP in the framework of post-authorisation activities. The basis for charging fees for inspections is provided by Council Regulation (EC) No 297/95, as amended, Article 3(4) refers in broad terms to the fee that may be charged for “any inspection”.

In addition as part of the Agency’s responsibility for the coordination of the supervision of authorised medicinal products under practical conditions of use, the Inspections Sector, in cooperation with the EDQM, operates a Sampling and Testing Programme.

Communication and action by Member States in response to suspected product defects relating to centrally authorised medicines are also coordinated by the Sector.

Apart from inspection and supervision related activities, the Agency has been given responsibility for issuing certificates of medicinal products in accordance with WHO requirements which confirm the status of centrally authorised medicinal products and GMP compliance of the sites manufacturing the pharmaceutical forms.

The Sector also coordinates activities in connection with the GMP annexes of the various Mutual Recognition Agreements (MRA) that have been negotiated between the European Community and non-European countries.

References

- Relevant references are available on the EMA inspection website
21.2. Can I request Scientific advice / Protocol assistance during the post-authorisation phase?

Scientific advice or Protocol assistance can be requested during the initial development of the medicinal product (i.e. before submission of the Marketing Authorisation Application), and also during the post-authorisation phase.

Scientific advice or Protocol assistance requested during the post-authorisation phase are generally related but not restricted to the following cases:

- The MAH may seek Scientific advice/Protocol assistance from the Scientific Advice Working Party (SAWP) in the framework of:
  - a new formulation or dosage form
  - an extension of indication
  - a paediatric development plan
  - a new or a change of manufacturing process

- The CHMP may request a “Protocol consultation” from the SAWP in the framework of specific obligations/ follow-up measures in case of any outstanding issues identified by the (Co-) Rapporteurs after assessment of protocols proposed by the MAH for the fulfilment of such post approval commitments. However, this procedure does not prevent the MAH to request, on its own initiative, Scientific advice or Protocol assistance in the framework of specific obligations/ follow-up measures when the company wishes to get feedback from the CHMP on particular issues. In this case, the MAH should follow the usual procedure as described earlier on.

For any Scientific advice or Protocol assistance application, applicants should refer to the EMA guidance for companies requesting scientific advice or protocol assistance which gives an overview of the procedure to obtain Scientific advice or Protocol assistance together with guidance to companies when preparing their application.

References

- EMA Guidance for Companies Requesting Scientific Advice (SA) and Protocol Assistance (PA) (EMEA/H/4260/01)


Centrally authorised medicinal products placed on the market of one Member State can be marketed in any other part of the European Community by a distributor (“Parallel distributor”) independent of the Marketing Authorisation Holder.

The EMA has been given the responsibility by the European Commission to check compliance of a parallel distributed product with the conditions laid down in Community legislation on medicinal products and with the marketing authorisations. This includes the checking of mock-ups of outer/inner labelling, package leaflets, coloured copy of the repackaged presentations, and of wholesale distribution and manufacturing authorisations.
Therefore, prior to initiating parallel distribution of a specific product, parallel distributors must notify the EMA in accordance with the FAQ (frequently asked questions) on Parallel Distribution.

The EMA will check the conformity of the proposed labelling and package leaflet with the text of the latest annexes to the Community Marketing Authorisation for the product concerned within 30 working days following validation of the notification and will notify the parallel distributor of any objections or comments. Where there are no objections or when objections have been completely addressed by the parallel distributor, the EMA issues a Notice and sends it to the parallel distributor, the National Competent Authority of the Member State of destination, the National Competent Authority of the Member State where the parallel distributor is located (if different from the Member State of destination) and the Marketing Authorisation Holder (MAH) of the medicinal product, informing that the regulatory check has been completed and indicating that the product proposed for parallel distribution complies with the terms of the Community Marketing Authorisation of the concerned Centrally Authorised Medicinal Product.

More details on parallel distribution are available in the FAQ (frequently asked questions) on Parallel Distribution, which parallel distributors, Marketing Authorisation Holders and National CompetentAuthorities may have on the parallel distribution notification procedure.

Reference

- Title IV of Regulation 726/2004 (EC)
- FAQ (frequently asked questions) on Parallel Distribution

21.4. **How do I notify the European Medicines Agency of changes to my Contact Persons specified in the application form? Rev May 2012**

Applicants/Marketing Authorisation Holders are required to notify the European Medicines Agency of any upcoming changes to the following contact persons as specified in the application form for initial marketing authorisation (sections 2.4.1-2.4.5 and 2.5.1.1), so that the EMA SIAMED Database can be updated accordingly:

- Contact person at MAH address (referred to in section 2.4.1 of the application form). As this contact person is used by the European Commission for notification of Commission Decisions to the MAH, this information should be maintained up to date and any changes (occurring also in the post-authorisation phase) notified promptly to the European Medicines Agency.

- Person/Company authorised for communication between the marketing authorisation holder and the competent authorities (referred to in sections 2.4.2 and 2.4.3 of the application form). Section 2.4.2 refers to changes to the contact person during the initial application for marketing authorisation. After authorisation of the medicinal product, change(s) to the person/company authorised for communication with the Agency (referred to in section 2.4.3 of the application form) should be notified promptly to the European Medicines Agency.

- Qualified person in the EEA for Pharmacovigilance (referred to in section 2.4.4 of the application form).

With regard to the qualified person in the EEA for pharmacovigilance (QPPV) the notification to the Agency should be handled as follows:
1. If a Detailed Description of Pharmacovigilance System (DDPS – Module 1.8.1) is authorised as part of the Marketing Authorisation (MA), a change in QPPV should be submitted via a Type IAIN variation application, provided that the pharmacovigilance system itself remains unchanged.

2. In all other cases, the change in QPPV should be promptly notified to the EMA

   • Scientific service of the MAH in the EEA as referred to in Article 98 of Directive 2001/83/EC (referred to in section 2.4.5 of the application form)
   • Contact person in the EEA for product defects and recalls, as defined in Article 79 of Directive 2001/83/EC (referred to in section 2.5.1.1 of the application form)

Any of the above changes should be notified exclusively in writing on company headed paper by fax or letter (which can also be sent electronically) and should be addressed to Product and Application Business Support (PA-BUS) only.

Applicants/Marketing Authorisation Holders are advised to use this template for such notifications.

Reference

• EU-CTD Module 1.2 Application Form
• Guidelines on Pharmacovigilance for Medicinal Products for Human Use, Volume 9A of the Rules governing Medicinal Products in the European Union


From 1 January 2010, eCTD is the only acceptable electronic format for all applications and all submission types in the context of the centralised procedure.

This applies to all applications (new and existing) and all types of submissions to the European Medicines Agency in the context of the centralised procedure (e.g. new applications, supplementary information, variations, renewals, Follow Up Measures (FUMs), Periodic Safety Update Reports (PSURs), Notifications etc).

The mandatory format is applicable also for procedures started and submitted before 01/01/2010 (e.g. responses to list of questions).

When submitting an application in eCTD, any Word documents required for Module 1 (e.g. product information Annexes) and Module 2 should be located in a separate folder to the eCTD and should not be included in the XML backbone, but made available on the same hard media.

There is no obligation to submit a full, reformatted eCTD for already authorised products. However, if Marketing Authorisation Holders wish, they may provide the European Medicines Agency with information reformatted as eCTD for their already authorised products. In particular, the European Medicines Agency would encourage the submission of reformatted quality information in eCTD, in order to facilitate the handling of variations and line extensions.

One electronic copy in eCTD format (CD-ROM or DVD) of the documentation should be submitted to the European Medicines Agency, together with one original, signed cover letter. The Product Team Leader should be indicated in copy “cc” on the cover letter (no additional copy needed). Additional
cover letters arriving together or separately from the submission of media will create delays in processing, therefore we ask the applicants to avoid sending multiple copies of the same cover letter, even if the letter is addressed to multiple recipients.

The cover letter should include identical information to the “eCTD envelope” and printed on the CD/DVD. It is also very useful to include the history of the lifecycle sequences of the product up to the enclosed submission as an annex to the cover letter.

Replacement sequences of a previously submitted eCTD application (e.g. following corrections) are not acceptable. Instead corrected eCTD applications should always be submitted as a new eCTD sequence. Replacements should always be accompanied by an updated cover letter explaining the reason of the re-submission. Upon validation, the final data package should be submitted to the CHMP members only, there is no need to send it again to the European Medicines Agency and to relevant (Co)-Rapporteurs.

The submission of reformatted documentation (commonly referred to as a ‘baseline’ submission), should preferably occur simultaneously (but separately) with the submission of a variation, line extension or renewal. A clear distinction between the reformatted (unchanged) information and the documentation supporting the simultaneously submitted variation / line extension or renewal should be made.

An eCTD baseline submission is expected at day 0 of the application procedure, and subsequent sequences should then be provided in accordance with the corresponding milestones for that procedure, through to approval. Please note that once the product starts an eCTD lifecycle, all subsequent submissions should follow this mandatory format.

Further details on implementation of the eCTD are provided on the European Medicines Agency e-submission website (http://esubmission.emea.europa.eu/), in particular in the European Medicines Agency Q&A relating to Practical and Technical aspects of eCTD implementation

References

• EMA statement of intent
• Q&A relating to strategic and general aspects of the implementation
• Q&A on practical/technical aspects of eCTD implementation


Article 5(12) of the Orphan Regulation provides for a designated orphan medicinal product to be removed from the Community register of orphan medicinal products at the end of the period of market exclusivity, as laid down in Article 8.

This means that once the market exclusivity for an authorised orphan medicinal product expires, the medicinal product will be removed from the Community register of orphan medicinal products and, therefore, will no longer be considered as an orphan medicinal product. Consequently, it will not benefit from incentives applicable to orphan medicinal products.

References

• Regulation (EC) No 141/2000 on orphan medicinal products