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Human Medicines Research and Development Support

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".

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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.

Table of Content

1. Type IA Variations

1.1. When shall I submit my Type IA / IA$_{IN}$ variation(s)? Rev. July 2013

Commission Regulation (EC) No 1234/2008 ('the Variations Regulation') and the "Commission guidelines on the details of the various categories of variations, on the operation of the procedures laid down in Chapters II, IIa, III and IV of Commission Regulation (EC) No 1234/2008 and on the documentation to be submitted pursuant to those procedures" ('the Classification Variations Guidelines') 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 ('IA$_{IN}$')

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).

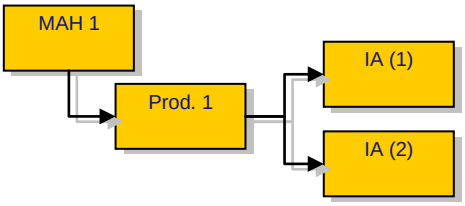
For product information, it is when the Company internally approves the revised product information. The revised product information will then be used in the next packaging run.

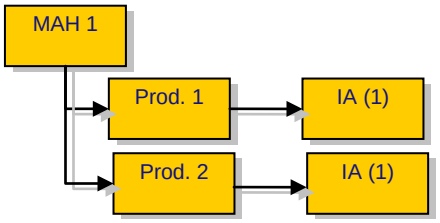
1.2. Can I group the submission of Type IA / IA_{IN} variations? Can they be grouped with other types of variations? Rev. Sep 2014

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.

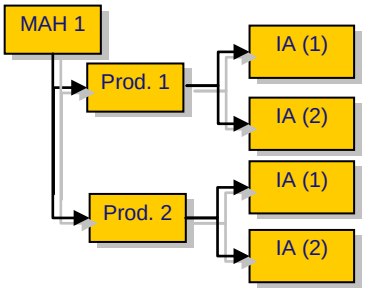
Possible grouping of Type IA/IA_{IN} changes only:

- 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.





- Several Type IA and/or IA_{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.



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

[1] For example the type IAIN 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/IA$_{IN}$ 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 Agency 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/ 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.

1.3. Is the (Co-) Rapporteur involved in the review of Type IA/ IA$_{IN}$ Variations Rev. Aug 2014

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/ IA$_{IN}$ notification must be submitted to the Rapporteur and other Committee members at the time of submission (for information) to maintain the life cycle of the eCTD dossier (See also "How shall I present and submit my Type IA/ IA$_{IN}$ Variation").

The same principle applies whether a single or a group of Type IA/ IA$_{IN}$ variations is being submitted.

However, if the Type IA/ IA$_{IN}$ 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/IA$_{IN}$ 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/ IA$_{IN}$ changes in the group.

1.4. How shall I present and submit my Type IA/ IA$_{IN}$ Variation(s)? Rev. Jul 2015

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 "Variations Guidelines" 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. Also, in order to facilitate the completion of the application form, MAHs are advised to consult the EMA/CMDh Explanatory Notes on Variation Application Form and the EMA Practical Guidance on the Application Form for Centralised type IA and IB variations.

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 single

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_{IN} variation notification, as specified in the Variations Guidelines:

- **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.
- Procedure number – The procedure number will be assigned by the EMA only upon receipt of an eCTD application. For further details please refer to EMA pre-submission guidance "How is an EMA application/procedure number attributed?"
- The completed electronic **EU variation application form** (eAF), including the details of the marketing authorisation(s) concerned, as well as a description of all variations submitted together with their date of implementation. As of 1 July 2015, the use of the Electronic Application Form is mandatory for all centralised procedures. Information on the electronic Application Form for variations can be found in the eSubmissions eAF webpage. 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 variation code** as laid down in the Annex to the Variations Guidelines, 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 Annex.
- 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.

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 Variations guidelines.

Grouped Type IA/ IA_{IN} variations

- For grouped Type IA/ IA_{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_{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.

For procedural matters related to a type IA/ IAIN Variation for a specific product and in order to avoid rejection, please contact IAquery@ema.europa.eu.

For more detailed queries on technical matters please contact the PA-BUS department (PA-BUS@ema.europa.eu)

Submission of Type IA/ IA_{IN} Variation Notifications

Please refer to question 22.5 Other - How and to whom shall I submit my application?

References

- Commission Regulation (EC) No 1234/2008
- Commission Regulation (EU) No 712/2012 amending Regulation (EC) No 1234/2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products
- Guidelines on the details of the various categories of variations, on the operation of the procedures laid down in Chapters II, IIa, III and IV of 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 and on the documentation to be submitted pursuant to those procedures
- Electronic Variation application form
- Variation application form, The Rules governing Medicinal Products in the European Union, Notice to Applicants, Volume 2C
- EMA/CMDh Explanatory Notes on Variation Application Form (CMDh/EMA/133/2010)

- EMA Practical Guidance on the Application Form for Centralised Type IA and IB Variations (EMA/233564/2014
- Pre-notification checklist for Type IA variations
- Template for cover letter
- Article 5 Recommendation

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/ IA_{IN} 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/ IA_{IN} 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/ IA_{IN} 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/ IA_{IN} 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/ IA_{IN} be part of worksharing? Rev. Jun 2014

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

However, the submission of one or several Type IA/ IA_{IN} 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/ IA_{IN} variations? Can they be grouped with other types of variations?”

This type of grouping is referred to as ’ IG’ by the Agency.

In addition, it is also possible to group a 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 Rapporteur will be asked to confirm

whether the non-acceptance of (part of) the change(s) leads to non-acceptance of Type IA/IA_{IN} in the group.

1.7. What should I do in case of an unfavourable outcome for my Type IA/ IA_{IN} variation(s)? Rev. July 2013

A Type IA/ IA_{IN} variation will be rejected when:

- The classification of the proposed change(s) in incorrect
- not all of the conditions for the Type IA/ IA_{IN} variation are met
- the submitted documentation as required by the Variations 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_{IN} variation? Rev. Feb 2013

For information on the fee applicable for Type IA/ IA_{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_{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_{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

- Council Regulation (EC) No 297/95 (OJ L 35 of 15 February 1995), as amended
- Explanatory note on fees payable to the European Medicines Agency

1.9. Do I have to submit mock-ups and specimens? Rev. July 2013

For information concerning submission of mock-ups and specimens in the framework of post-authorisation procedures, please refer to the document 'Checking process of mock-ups and specimens of outer/immediate labelling and package leaflet of human medicinal products in the centralised procedure, 3.4 Other post-authorisation procedures.

References

- 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. What changes will trigger new EU number(s) (additional presentation(s))? New Apr 2015

Any changes in the number of units of medicinal product or medical device being an integral part of the medicinal product (e.g. prefilled syringes) will trigger a different EU number.

Differentiation should be made between the addition of a presentation where the two presentations will co-exist on the market on a long-term basis versus a replacement of a presentation where the new presentation will replace the previous one (it is expected that for a certain period of time, the two presentations will co-exist on the market until the stock of the previous presentation runs out).

In principle, a **replacement** of one presentation by another presentation does not trigger a new EU number, unless the number of units of medicinal product or medical device being an integral part of the medicinal product (e.g. prefilled syringes) is changed.

Examples of changes in presentations for replacement, not triggering a new EU number (this is not an exhaustive list):

- Replacement of the primary or secondary packaging,
- Changes in the number of medical devices not being integral part of the medicinal product,

- Change in composition (e.g. change in excipients),
- Change in units per blisters (without change to the total number of units per pack).

Examples of changes in presentations for replacement, triggering a new EU number (this is not an exhaustive list):

- 30 to 60 tablets,
- 2 prefilled syringes containing the medicinal product instead of one prefilled syringe.

In case of **addition**, as the presentations will co-exist on the market, two packs with different contents cannot be covered by the same EU number and will be considered as different presentations.

Changes in the number of any unit (not restricted to the medicinal product) or changes in the specifications of any unit (not restricted to the medicinal product) contained in the pack will trigger a new EU number.

Examples of changes that will trigger new EU numbers (this is not an exhaustive list):

- Introduction of an alternative injection kit with a different number of syringes or swabs,
- Introduction of an alternative syringe of different volume or an alternative syringe with a needle guard,
- Introduction of an alternative immediate (primary) packaging made from a different material,
- Introduction of an alternative shape/dimension of a pharmaceutical form (pre-rolled sealant matrix versus flat, change in size of patch).

If you have any questions on any upcoming submission, please contact us using the relevant email addresses: IAquery@ema.europa.eu, IBquery@ema.europa.eu or IIquery@ema.europa.eu

1.11. How to obtain new EU sub-numbers for Type IA_{IN} variation concerning an additional presentation (e.g. new pack-size)? Rev. Aug 2014

In the specific case of a Type IA_{IN} 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 newEUnumber@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.

1.12. When do I have to submit revised product information? In all languages? Rev. Aug 2014

In case the Type IA/ IA_{IN} 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. 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 on-going 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/ IA_{IN} 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/ IA_{IN} **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 PDF format and EN tracked Word, 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 IA_{IN} 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.

1.13. How and when will the updated product information Annexes become part of the Marketing Authorisation? Rev. Oct 2012

For Type IA/ IA_{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_{IN} change(s) agreed during the past year together with a line-listing of those Type IA/ IA_{IN} notification(s). The Commission will subsequently issue a Commission Decision on the Type IA/ IA_{IN} notification(s) concerned.

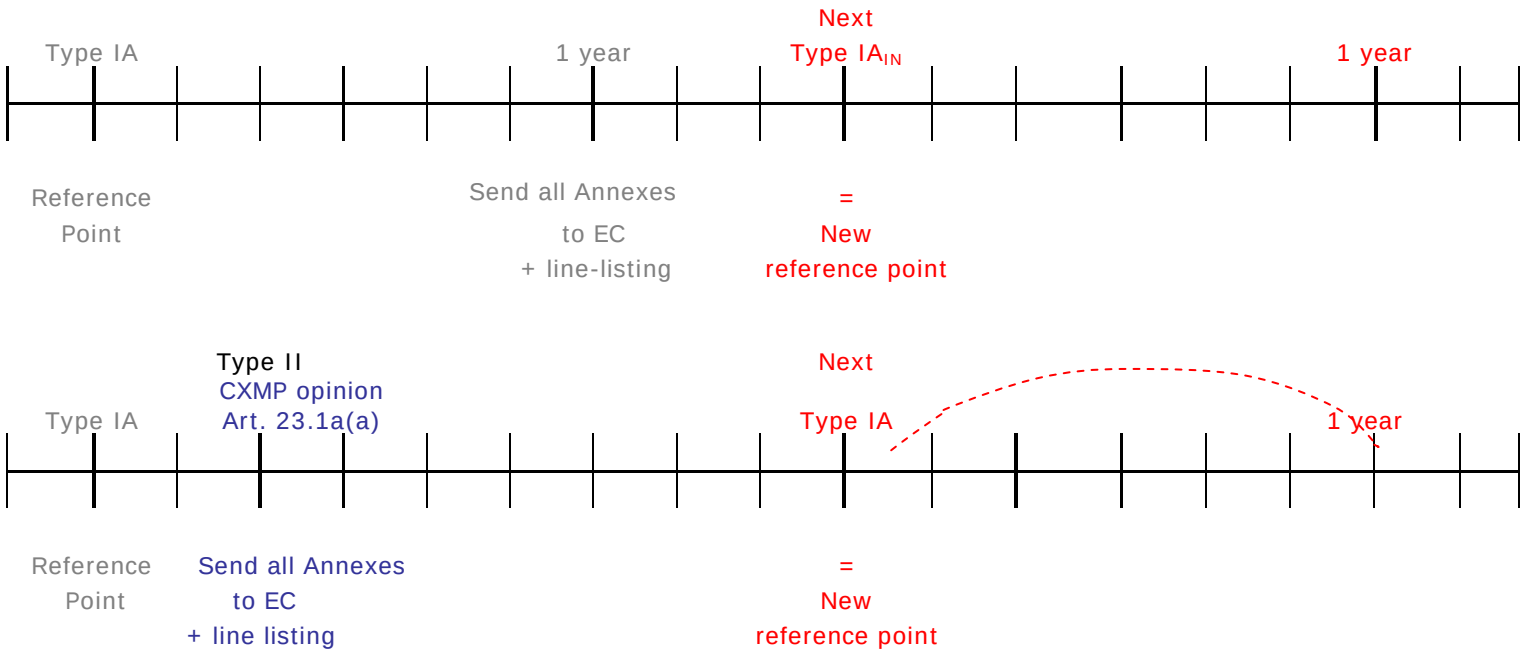
However, where an Opinion affecting the Annexes which is followed by an immediate Commission Decision, e.g. listed in the Article 23.1a(a), is transmitted to the Commission within this yearly period the changes of the Type IA/ IA_{IN} notification(s) concerned will already be included in the Annexes 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_{IN} notification(s) concerned.

At the occasion of the next Type IA/ IA_{IN} variation affecting the Annexes, the procedure outlined above will be repeated based on the new 'Reference point' of the next Type IA/ IA_{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_{IN} notification concerns several marketing authorisations, the Commission will update the marketing authorisation with one Decision per marketing authorisation concerned.



1.14. What should be the date of revision of the text for Type IA Variations? New Oct 2010

Type IA/IA$_{IN}$ 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 ('IA$_{IN}$') 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/IA$_{IN}$ variation(s)?

1.15. What can be considered an editorial change and how can it be submitted as part of a type iA/IB/II variation? NEW May 2015

The European Commission 'Variations Guidelines' 2013/C 223/01 specifies that "If amendments to the dossier only concern editorial changes, such changes should generally not be submitted as a separate variation, but they can be included in a variation concerning that part of the dossier.". Changes that can be classified as a variation as per Variations Guidelines are not considered editorial changes and should be submitted under the appropriate variation category.

1.15.1. Editorial changes in module 3

Provided that the above condition is fulfilled, the following changes to the Module 3 may be considered editorial: adding headers for ease of use, reordering of existing information without changing the meaning, alignment of information among/within the sections provided that it can be demonstrated what is the correct reference that had been previously agreed (e.g. alignment of information in flow charts to process description), punctuation changes and grammar/orthographic corrections that do not alter the meaning of the text.

Examples of changes that cannot be considered editorial: removal of specification parameters or manufacturing description, update of information to bring the dossier content in line with the current manufacturing process, etc.

In practice for the Agency, "that part of the dossier" can cover sections up to the fourth level of the eCTD, as follows "3.2.S.x" or "3.2.P.x". For example, if a variation affects section 3.2.S.2.1 editorial changes can be submitted in sections from 3.2.S.2.1 to 3.2.S.2.7.

Editorial changes should always be clearly identified in the application form as following: A brief description of the editorial changes should be provided in the Precise Scope. All the editorial changes should be listed in the **present/proposed table**, and a **justification** as to why the holder considers them 'editorial' (i.e. why they should not trigger a specific variation) should be provided for each change.

In addition, the MAH should provide a **declaration** in the 'Precise scope and background…' section of the application form confirming that the changes proposed as editorial do not change the content of

the concerned part(s) of the dossier beyond the scope of the variation submitted within which the editorial changes are being submitted.

If the editorial changes affect sections not impacted by any upcoming variation, the MAH may consider submitting these changes as a separate type IB variation (B.I.z or B.II.z respectively).

1.15.2. Editorial changes in module 4 and 5

Editorial changes in module 4 and 5 are not foreseen. Please contact us (IAquery@ema.europa.eu, IBquery@ema.europa.eu or IIquery@ema.europa.eu as relevant) in advance of an upcoming submission.

1.15.3. Editorial changes to the product information in module 1.3.1

Formatting changes, correction of typographical errors and/or mistakes to the English Product Information or other linguistic versions of the Product Information are considered editorial changes provided that the meaning of the text is not altered. These changes can be included within the scope of any upcoming variation impacting the product information.

Changes in the scientific content cannot be accepted as an editorial change. These changes should be classified under the scope of the relevant variation as per Variations Guidelines (e.g. Type II C.I.4). If no relevant scope is available, a variation type IB C.I.z may be appropriate.

Proposed changes that may require confirmation by the rapporteur or linguistic review will only be accepted by the Agency when submitted within the scope of an upcoming variation type IB or type II under chapter C which impacts the product information.

Editorial changes should generally not be submitted as a separate variation and therefore no reference to a variation category is required. Should there be no upcoming variation to include the editorial changes, these could also be submitted as a stand-alone IB C.I.z if they affect the English SmPC or an Art. 61(3) notification if they only affect the PIL/labelling. If other languages are affected and in case no variation affecting the product information is upcoming, the applicants are advised to contact the Agency to discuss how to handle these necessary changes.

The MAH should liaise with the Agency without delay if the mistake concerns an incorrect or missing important information (e.g. contra-indication or adverse event) that could affect the safe and effective use of the medicinal product and/or lead to a potential medication errors (e.g. wrong strength, wrong posology, wrong route of administration).

The editorial changes should be clearly identified in the application form as editorial changes. A brief description of the editorial changes should be provided in the precise scope of the application form. Furthermore, editorial changes should be presented in the **present / proposed table** or provided as a separate Annex. A statement confirming that the proposed editorial change(s) do(es) not change the content of the previously approved Product information should be provided.

Any changes proposed by the applicants as editorial will be carefully considered by the Agency at time of submission and may be subject to further assessment at the same time as the variation. Proposed editorial changes that cannot be accepted as such will be rejected. In case of doubt, applicants can contact the Agency in advance of the planned submission using the appropriate pre-submission query email address IAquery@ema.europa.eu, IBquery@ema.europa.eu or IIquery@ema.europa.eu as relevant.

References

- Commission Regulation (EC) No 1234/2008 (OJ L334 of 12 December 2008)
- Commission Regulation (EU) No 712/2012 amending Regulation (EC) No 1234/2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products
- Guidelines on the details of the various categories of variations, on the operation of the procedures laid down in Chapters II, IIa, III and IV of 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 and on the documentation to be submitted pursuant to those procedures
- Practical questions and answers to support the implementation of the variations guidelines in the centralised procedure (EMA/427505/2013)
- CMDh Recommendation for classification of unforeseen variations according to Article 5 of Commission Regulation (EC) 1234/2008

1.16. Who should I contact if I have a question when preparing my application? NEW Apr 2014

If you cannot find the answer to your question in the Q&A when preparing your application, please contact us using the following email address: IAquery@ema.europa.eu

The Agency aims to respond to your query within 5 working days. To help us deal with your enquiry, please provide as much information as possible including the name of the product in your correspondence.

You should submit your query once and it is important that you submit it only to one dedicated email address. If you are uncertain on a classification of a variation as type IA or type IB please choose one of the relevant email addresses available to you (either IAquery@ema.europa.eu or IBquery@ema.europa.eu). Your query will be channelled internally to the relevant service(s) that will respond to you.

The above email address is only applicable when you have a pre-submission query. A dedicated Procedure Manager (PM) will be assigned to the procedure once your application has been validated. You will be able to contact this PM throughout the procedure.

1.17. Who is my contact at the European Medicines Agency during post-authorisation procedures? NEW Apr 2015

Please refer to question 22.8 Other - Who is my contact at the European Medicines Agency during post-authorisation procedures?

2. Type IB variations

2.1. What changes are considered Type IB Variations? Rev. Oct 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 guidelines on the details of the various categories of variations, on the operation of the procedures laid down in Chapters II, IIa, III and IV of Commission Regulation (EC) No 1234/2008 and on the documentation to be submitted pursuant to those procedures" ('the Variations Guidelines'), 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

- Commission Regulation (EC) No 1234/2008 (OJ L334 of 12 December 2008)
- Commission Regulation (EU) No 712/2012 amending Regulation (EC) No 1234/2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products
- Guidelines on the details of the various categories of variations, on the operation of the procedures laid down in Chapters II, IIa, III and IV of 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 and on the documentation to be submitted pursuant to those procedures
- Practical questions and answers to support the implementation of the variations guidelines in the centralised procedure
- CMDh recommendation for classification of unforeseen variations according to Article 5 of Commission Regulation (EC) 1234/2008

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)”?

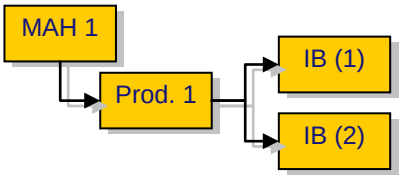
The Co-Rapporteur is not involved in Type IB variations. However, a copy of the complete Type IB notification must also be submitted to the Co-Rapporteur.

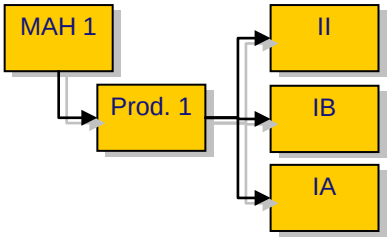
2.3. Can I group the submission of Type IB variations? Can they be grouped with other types of variations? Rev. Oct 2013

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

- Commission Regulation (EC) No 1234/2008 (OJ L334 of 12 December 2008)
- Commission Regulation (EU) No 712/2012 amending Regulation (EC) No 1234/2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products
- Guidelines on the details of the various categories of variations, on the operation of the procedures laid down in Chapters II, IIa, III and IV of 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 and on the documentation to be submitted pursuant to those procedures

2.4. How shall I present and submit my Type IB Variation? Rev. Nov 2015

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.

In order to help MAHs ensuring that their type IB 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 IB variation.

In order to facilitate the completion of a correct application form before submission to the Agency, MAHs are advised to consult the EMA/CMDh Explanatory Notes on the Variation Application Form and the EMA Practical Guidance on the Application Form for Centralised type IA and IB variations.

The Commission 'Variations Guidelines' 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 MAH should indicate when the exact same change is submitted for different products in separate IBs.
- Procedure number – The procedure number will be assigned by the EMA only upon receipt of an eCTD application. For further details please refer to EMA pre-submission guidance "How is an EMA application/procedure number attributed?"
- 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 variation code as laid down in the Annex to the Variations Guidelines, 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 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 Annex.
- 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 Variations Guidelines. 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 IBquery@ema.europa.eu (see also Question 12. “Who should I contact if I have a question when preparing my application?”).

Submission of Type IB Notifications

Please refer to question 22.5 Other – How and to whom shall I submit my application?

References

- Commission Regulation (EC) No 1234/2008
- Commission Regulation (EU) No 712/2012 amending Regulation (EC) No 1234/2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products
- Guidelines on the details of the various categories of variations, on the operation of the procedures laid down in Chapters II, IIa, III and IV of 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 and on the documentation to be submitted pursuant to those procedures
- Electronic Variation application form / Variation application form, The Rules governing Medicinal Products in the European Union, Notice to Applicants, Volume 2C

- EMA/CMDh Explanatory Notes on Variation Application Form (CMDh/EMA/133/2010)
- EMA Practical Guidance on the Application Form for Centralised Type I variations (EMA/233564/2014)
- Template for cover letter
- Article 5 Recommendation

2.5. When shall I submit my Type IB Variation? Rev. July 2013

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 include 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 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

- Commission Regulation (EC) No 1234/2008 (OJ L334 of 12 December 2008)
- Commission Regulation (EU) No 712/2012 amending Regulation (EC) No 1234/2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products

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

2.6. How shall my Type IB variation be handled (timetable)? Rev. Aug 2014

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 7 calendar days whether the variation is correct and complete ('validation') before the start of the evaluation procedure.

Day	Action
Day x	Receipt of Type IB variation
Day x+1	Start of Agency validation
Day x+7 (in case of missing information, this period will be extended)	Agency validation

Issues identified during validation will be notified to the MAH via e-mail. The MAH will be requested to provide responses to the issues raised within 5 working days. Delayed or insufficient responses will lead to complete or partial invalidation (in case of groupings) of the application as only one request for supplementary information will be issued during the validation phase.

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

Day	Action
Day 1	Start of evaluation
by Day 20	Receipt of Assessment Report
by Day 30	(Non-)acceptance of the variation

Within 30 calendar 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 calendar days, the notification shall be deemed acceptable.

In case of an unfavourable outcome the MAH may, within 30 calendar 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 calendar 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 7 calendar 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 correspondence.

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

- Council Regulation (EC) No 297/95 (OJ L 35 of 15 February 1995), as amended
- Fees payable to the European Medicines Agency

2.8. Do I have to submit mock-ups and specimens? Rev. July 2013

For information concerning submission of mock-ups and specimens in the framework of post-authorisation procedures, please refer to the document 'Checking process of mock-ups and specimens of outer/immediate labelling and package leaflet of human medicinal products in the centralised procedure, 3.4 Other post-authorisation procedures.

References

- The 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. Aug 2014

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. 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.

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 on-going 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. What changes will trigger new EU number(s) (additional presentation(s))? New Apr 2015

Any changes in the number of units of medicinal product or medical device being an integral part of the medicinal product (e.g. prefilled syringes) will trigger a different EU number.

[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)

Differentiation should be made between the addition of a presentation where the two presentations will co-exist on the market on a long-term basis versus a replacement of a presentation where the new presentation will replace the previous one (it is expected that for a certain period of time, the two presentations will co-exist on the market until the stock of the previous presentation runs out).

In principle, a **replacement** of one presentation by another presentation does not trigger a new EU number, unless the number of units of medicinal product or medical device being an integral part of the medicinal product (e.g. prefilled syringes) is changed.

Examples of changes in presentations for replacement, not triggering a new EU number (this is not an exhaustive list):

- Replacement of the primary or secondary packaging,
- Changes in the number of medical devices not being integral part of the medicinal product,
- Change in composition (e.g. change in excipients),
- Change in units per blisters (without change to the total number of units per pack).

Examples of changes in presentations for replacement, triggering a new EU number (this is not an exhaustive list):

- 30 to 60 tablets,
- 2 prefilled syringes containing the medicinal product instead of one prefilled syringe.

In case of **addition**, as the presentations will co-exist on the market, two packs with different contents cannot be covered by the same EU number and will be considered as different presentations.

Changes in the number of any unit (not restricted to the medicinal product) or changes in the specifications of any unit (not restricted to the medicinal product) contained in the pack will trigger a new EU number.

Examples of changes that will trigger new EU numbers (this is not an exhaustive list):

- Introduction of an alternative injection kit with a different number of syringes or swabs,
- Introduction of an alternative syringe of different volume or an alternative syringe with a needle guard,
- Introduction of an alternative immediate (primary) packaging made from a different material,
- Introduction of an alternative shape/dimension of a pharmaceutical form (pre-rolled sealant matrix versus flat, change in size of patch).

If you have any questions on any upcoming submission, please contact us using the relevant email addresses: IAquery@ema.europa.eu, IBquery@ema.europa.eu or IIquery@ema.europa.eu

2.11. How to obtain new EU sub-numbers for a Type IB variation concerning an additional presentation (e.g. new pack-size)? Rev. Aug 2014

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 newEUnumber@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.

2.12. 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.

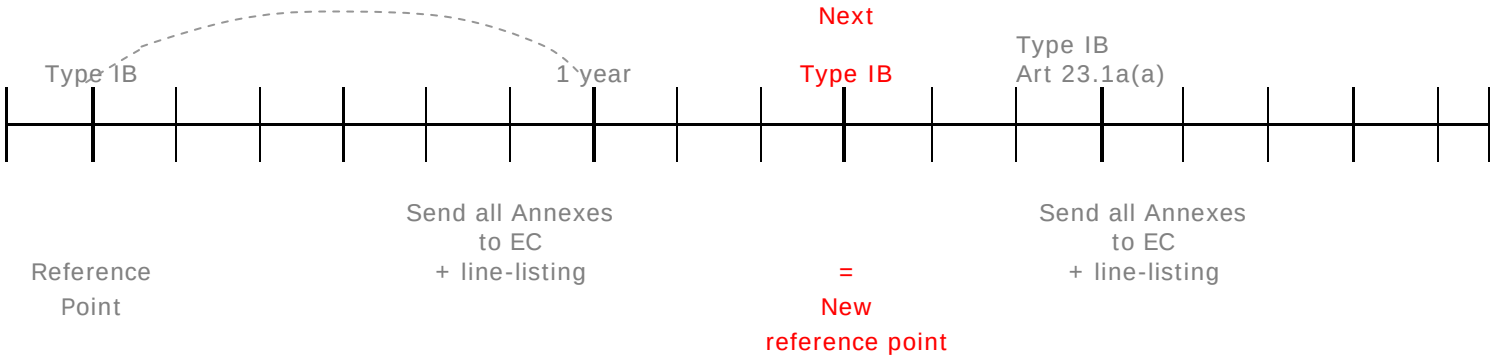
For type IB variations subject to yearly update of the respective Commission decision, at the end of this yearly period, the Agency will send the complete set of Annexes, based on the latest approved Annexes and reflecting the Type IB change(s) introduced during the past year as well as a line-listing of those variations pending update of the Commission decision.

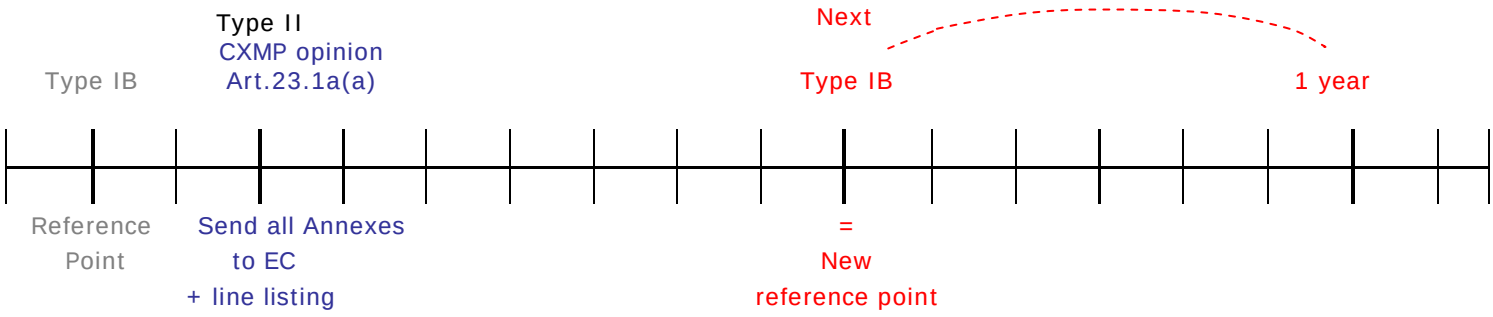
Where a notification contained several Type IB variations concerning one marketing authorisation, the Commission will update the marketing authorisation with one single decision to cover all the approved minor variations.

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)





2.13. What can be considered an editorial change and how can it be submitted as part of a type IA/IB/II variation? NEW May 2015

The European Commission 'Variations Guidelines' 2013/C 223/01 specifies that “If amendments to the dossier only concern editorial changes, such changes should generally not be submitted as a separate variation, but they can be included in a variation concerning that part of the dossier.”. Changes that can be classified as a variation as per Variations Guidelines are not considered editorial changes and should be submitted under the appropriate variation category.

2.13.1. Editorial changes in module 3

Provided that the above condition is fulfilled, the following changes to the Module 3 may be considered editorial: adding headers for ease of use, reordering of existing information without changing the meaning, alignment of information among/within the sections provided that it can be demonstrated what is the correct reference that had been previously agreed (e.g. alignment of information in flow charts to process description), punctuation changes and grammar/orthographic corrections that do not alter the meaning of the text.

Examples of changes that cannot be considered editorial: removal of specification parameters or manufacturing description, update of information to bring the dossier content in line with the current manufacturing process, etc.

In practice for the Agency, “that part of the dossier” can cover sections up to the fourth level of the eCTD, as follows “3.2.S.x” or “3.2.P.x”. For example, if a variation affects section 3.2.S.2.1 editorial changes can be submitted in sections from 3.2.S.2.1 to 3.2.S.2.7.

Editorial changes should always be clearly identified in the application form as following: A brief description of the editorial changes should be provided in the Precise Scope. All the editorial changes should be listed in the **present / proposed table**, and a **justification** as to why the holder considers them 'editorial' (i.e. why they should not trigger a specific variation) should be provided for each change.

In addition, the MAH should provide a **declaration** in the 'Precise scope and background…' section of the application form confirming that the changes proposed as editorial do not change the content of the concerned part(s) of the dossier beyond the scope of the variation submitted within which the editorial changes are being submitted.

If the editorial changes affect sections not impacted by any upcoming variation, the MAH may consider submitting these changes as a separate type IB variation (B.I.z or B.II.z respectively).

2.13.2. Editorial changes in module 4 and 5

Editorial changes in module 4 and 5 are not foreseen. Please contact us (IAquery@ema.europa.eu, IBquery@ema.europa.eu or IIquery@ema.europa.eu as relevant) in advance of an upcoming submission.

2.13.3. Editorial changes to the product information in module 1.3.1

Formatting changes, correction of typographical errors and/or mistakes to the English Product Information or other linguistic versions of the Product Information are considered editorial changes provided that the meaning of the text is not altered. These changes can be included within the scope of any upcoming variation impacting the product information.

Changes in the scientific content cannot be accepted as an editorial change. These changes should be classified under the scope of the relevant variation as per Variations Guidelines (e.g. Type II C.I.4). If no relevant scope is available, a variation type IB C.I.z may be appropriate.

Proposed changes that may require confirmation by the rapporteur or linguistic review will only be accepted by the Agency when submitted within the scope of an upcoming variation type IB or type II under chapter C which impacts the product information.

Editorial changes should generally not be submitted as a separate variation and therefore no reference to a variation category is required. Should there be no upcoming variation to include the editorial changes, these could also be submitted as a stand-alone IB C.I.z if they affect the English SmPC or an Art. 61(3) notification if they only affect the PIL/labelling. If other languages are affected and in case no variation affecting the product information is upcoming, the applicants are advised to contact the Agency to discuss how to handle these necessary changes.

The MAH should liaise with the Agency without delay if the mistake concerns an incorrect or missing important information (e.g. contra-indication or adverse event) that could affect the safe and effective use of the medicinal product and/or lead to a potential medication errors (e.g. wrong strength, wrong posology, wrong route of administration).

The editorial changes should be clearly identified in the application form as editorial changes. A brief description of the editorial changes should be provided in the precise scope of the application form. Furthermore, editorial changes should be presented in the **present / proposed table** or provided as a separate Annex. A statement confirming that the proposed editorial change(s) do(es) not change the content of the previously approved Product information should be provided.

Any changes proposed by the applicants as editorial will be carefully considered by the Agency at time of submission and may be subject to further assessment at the same time as the variation. Proposed editorial changes that cannot be accepted as such will be rejected. In case of doubt, applicants can contact the Agency in advance of the planned submission using the appropriate pre-submission query email address IAquery@ema.europa.eu, IBquery@ema.europa.eu or IIquery@ema.europa.eu as relevant.

References

- Commission Regulation (EC) No 1234/2008 (OJ L334 of 12 December 2008)
- Commission Regulation (EU) No 712/2012 amending Regulation (EC) No 1234/2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products
- Guidelines on the details of the various categories of variations, on the operation of the procedures laid down in Chapters II, IIa, III and IV of 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 and on the documentation to be submitted pursuant to those procedures
- Practical questions and answers to support the implementation of the variations guidelines in the centralised procedure (EMA/427505/2013)
- CMDh Recommendation for classification of unforeseen variations according to Article 5 of Commission Regulation (EC) 1234/2008

2.14. Who should I contact if I have a question when preparing my application? NEW Apr 2014

If you cannot find the answer to your question in the Q&A when preparing your application, please contact us using the following email address: IBquery@ema.europa.eu

The Agency aims to respond to your query within 5 working days. To help us deal with your enquiry, please provide as much information as possible including the name of the product in your correspondence.

You should submit your query once and it is important that you submit it only to one dedicated email address. If you are uncertain of on a classification of a variation as type IB or type II please choose one of the relevant email addresses available to you (either IBquery@ema.europa.eu or IIquery@ema.europa.eu). Your query will be channelled internally to the relevant service(s) that will respond to you.

The above email address is only applicable when you have a pre-submission query. A dedicated Procedure Manager (PM) will be assigned to the procedure once your application has been validated. You will be able to contact this PM throughout the procedure.

2.15. Who is my contact at the European Medicines Agency during post-authorisation procedures? NEW Apr 2015

Please refer to question 22.8 Other - Who is my contact at the European Medicines Agency during post-authorisation procedures?

3. Type II variations

3.1. What changes are considered Type II Variations? Rev. Feb 2015

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 Variations Guidelines 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 "How shall my Type IB variations be handled (timetable)?".

References

- Commission Regulation (EC) No 1234/2008 (OJ L334 of 12 December 2008)
- Commission Regulation (EU) No 712/2012 amending Regulation (EC) No 1234/2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products
- Guidelines on the details of the various categories of variations, on the operation of the procedures laid down in Chapters II, IIa, III and IV of 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 and on the documentation to be submitted pursuant to those procedures (so-called "Variations Guidelines")
- Practical questions and answers to support the implementation of the variations guidelines in the centralised procedure (EMA/427505/2013)
- CMDh recommendation for classification of unforeseen variations according to Article 5 of Commission Regulation (EC) 1234/2008

3.2. Is the Co-Rapporteur involved in Type II Variations? Rev. Feb 2015

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 SmPC changes.

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

The MAH should therefore inform the Agency (IIquery@ema.europa.eu) of an upcoming Type II application for a new indication at least 2 months before submission, so that the CHMP is informed of the future submission and can agree on the Co-Rapporteur's involvement.

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.

At the time of validation the Agency will inform the MAH of the involvement of the CHMP Co-Rapporteur and/or PRAC Rapporteur through the assessment timetable which will refer to the relevant assessment reports expected from the Co-Rapporteur and/or PRAC Rapporteur, as appropriate.

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

3.3. Can I group the submission of Type II variations? Can they be grouped with other types of variations? Rev. Feb 2015

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) (e.g. Type IB or IA variations) or extension applications. Such grouped submissions will follow the assessment timetable 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(s) 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

- Commission Regulation (EC) No 1234/2008 (OJ L334 of 12 December 2008)
- Commission Regulation (EU) No 712/2012 amending Regulation (EC) No 1234/2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products
- Guidelines on the details of the various categories of variations, on the operation of the procedures laid down in Chapters II, IIa, III and IV of 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 and on the documentation to be submitted pursuant to those procedures (so-called "Variations Guidelines")

3.4. How shall I present my Type II Variation application? Rev. Jul 2015

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 'Variations Guidelines' 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.
- Procedure number – The procedure number will be assigned by the EMA only upon receipt of an eCTD application. For further details refer to EMA pre-submission guidance "How is an EMA application/procedure number attributed?"
- 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 variation code as laid down in the Annex to the Variations Guidelines 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 SmPC, 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. Please also refer to "Who should I contact if I have a question when preparing my application?".

Please also refer to the following questions which address orphan and paediatric related aspects 'What specific requirements apply to my Type II variation for a new orphan indication?', 'What should I consider in case I wish to add a new non-orphan therapeutic indication to my orphan medicinal product?' and 'Do I need to address any paediatric requirements in my type II variation application?'.

References

- Commission Regulation (EC) No 1234/2008 (OJ L334 of 12 December 2008)
- Commission Regulation (EU) No 712/2012 amending Regulation (EC) No 1234/2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products

- Guidelines on the details of the various categories of variations, on the operation of the procedures laid down in Chapters II, IIa, III and IV of 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 and on the documentation to be submitted pursuant to those procedures
- 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? Rev. Aug 2014

See question 22.5 Other – How and to whom shall I submit my application?

3.6. Which submission dates (weekly or monthly) are applicable for my type II variation and when shall I submit my application? Rev. Feb 2015

As of March 2015 the Agency has introduced weekly start dates for the assessment of type II variations applications, in addition to the already existing monthly start dates. The aim of the new timetables (hereafter called 'weekly-start timetables', as opposed to 'monthly-start timetables') is to increase submission flexibility and allowing certain types of type II variation to start and conclude independently of the CHMP meeting periodicity.

The weekly-start timetables are applicable for the majority of the Type II variation applications that are received by the Agency.

The following minority of type II variations applications will continue to follow the monthly-start timetables:

- extensions of indication
- variations involving PRAC, CAT in addition to the CHMP (e.g. variations including an RMP update, assessment of non-interventional PASS results or variations for ATMPs) and
- other variations requiring amendment of the Commission Decision granting the Marketing Authorisation within two months from CHMP Opinion (*See also question 'Which post-opinion steps apply to my Type II variation and when can I implement the approved changes?').*

Opinions for these variations will be adopted during the CHMP plenary meetings.

For variations following the weekly-start timetable, should the need for discussion at plenary meeting or for immediate EC decision arise during the procedure, the Agency will accommodate the need for committee discussion and/or adoption of the Opinion at the CHMP plenary.

In case there is uncertainty before submission as to which timetables and submission deadlines are to be followed, MAHs can request the advice of the Agency using the pre-submission query service (IIquery@ema.europa.eu). In exceptional cases when a variation application is only identified as falling in one of the above three categories during validation, the Agency shall inform the MAH that the monthly start timetable will apply. For more information see also q*uestion 'How shall my Type II application be handled (timetable)?'*.

In the case of both weekly and monthly start assessment timetables, the MAH shall submit their application 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 of their legal obligation to submit forthwith any information that becomes available which might entail the variation of the MA.

Where the CHMP requests the submission of a variation following the assessment of a post-authorisation measure (PAM), Specific Obligation (SO) or signal, MAHs must submit the corresponding variation application within the requested timeframe.

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

- Commission Regulation (EC) No 1234/2008 (OJ L334 of 12 December 2008)
- Commission Regulation (EU) No 712/2012 amending Regulation (EC) No 1234/2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products
- Guidelines on the details of the various categories of variations, on the operation of the procedures laid down in Chapters II, IIa, III and IV of 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 and on the documentation to be submitted pursuant to those procedures

3.7. How shall my Type II application be handled (timetable)? Rev. Jul 2015

Assessment of type II variations following a 60 day timetable may, depending on whether they need to follow the CHMP plenary meeting periodicity or not (see above question "*Which submission dates (weekly or monthly) are applicable for my type II variation and when shall I submit my application?"*), either start on a weekly basis or on specific monthly dates. Type II variation procedures following a 30-day timetable (e.g. urgent safety issues) or a 90-day timetable (i.e. new indication or amendment of an existing one) will always follow the monthly-start timetable.

For variations following a weekly-start timetable, the opinion or request for supplementary information will be adopted by the CHMP independently of the plenary meetings.

Upon receipt of a technically valid application, a dedicated Procedure Manager (PM) will be assigned to the procedure. The PM will perform validation of the content of the application. Supplementary information may be requested in order for the validation to be finalised and the procedure will commence at the next available start date after resolution of issues identified during validation. The Agency will inform the MAH of the outcome of the validation and timetable.

Variations following a 60 day TT (= standard timetable)

Condition:

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

Variations assessed by the CHMP only

Day	Action
Day 1	Start of evaluation
Day 36	Receipt of CHMP Rapporteur's Assessment Report
Day 50	Comments by other CHMP members
Day 53	Receipt of CHMP Rapporteur's updated Assessment Report*
Day 60	Adoption of the CHMP Opinion *[or Request for supplementary information]*

*Updated assessment reports are optional, depending on comments received by other committee members.

Variations assessed by PRAC^ and CHMP

Day	Action
Day 1	Start of evaluation
Day 30	Receipt of CHMP# Rapporteur's Assessment Report
Day 33	Receipt of PRAC Rapporteur's Assessment Report
Day 38	Comments by other PRAC members
Day 39	Receipt of PRAC Rapporteur's updated Assessment Report*
Day 46	PRAC outcome
Day 50	Comments by other CHMP members
Day 53	Receipt of CHMP* Rapporteur's updated assessment report*
Day 60	Adoption of the CHMP Opinion *[or Request for supplementary information]*

* Updated assessment reports are optional, depending on comments received by other committee members.

^The PRAC is involved in the assessment of a type II variation, e.g. when a RMP is submitted within the variation.

#There is(are) no CHMP Rapporteur's assessment report(s) in case of PRAC-led variations.

Variations following 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

Variations assessed by the CHMP only

Day	Action
Day 1	Start of evaluation
Day 15	Receipt of CHMP# Rapporteur's Assessment Report
Day 20	Comments by other CHMP Members
Day 23	Receipt of CHMP# and PRAC Rapporteur's updated Assessment Report*
Day 30	Adoption of the CHMP Opinion *[or Request for supplementary information]*

*Updated assessment reports are optional, depending on comments received by other committee members.

Variations assessed by PRAC^ and CHMP

Day	Action
Day 1	Start of evaluation
Day 6	Receipt of PRAC Rapporteur's Assessment Report
Day 8	Comments by other PRAC Members
Day 9	Receipt of PRAC Rapporteur's updated Assessment Report*
Day 15	Receipt of CHMP Rapporteur's assessment report
Day 16	PRAC outcome
Day 20	Comments by other CHMP members

Day 23	Receipt of CHMP Rapporteur's updated assessment report*
Day 30	Adoption of the CHMP Opinion *[or Request for supplementary info]*

* Updated assessment reports are optional, depending on comments received by other committee members.

^The PRAC is involved in the assessment of a type II variation, e.g. when a RMP is submitted within the variation.

#There is(are) no CHMP Rapporteur's assessment report(s) in case of PRAC-led variations.

In exceptional cases, this timetable could be further shortened.

Variations following a 90 day TT

Condition:

- For variations concerning changes to or addition of therapeutic indications

Day	Action
Day 1	Start of evaluation
Day 56	Receipt of and CHMP (Co-) Rapporteur's assessment report
Day 63	Receipt of PRAC^ Rapporteur's Assessment Report
Day 68	Comments by other PRAC members
Day 76	PRAC outcome
Day 80	Comments by other CHMP members
Day 83	Receipt of CHMP Rapporteur's joint assessment report
Day 90	Adoption of the CHMP Opinion *[or Request for supplementary info]*

^The PRAC is normally involved in the assessment of type II variation applications following the 90-day TT because an (updated) RMP is usually expected to be submitted as part of the application. Absence of an RMP update should be justified at the time of submission.

In case issues which prevent the adoption of an Opinion are identified, the CHMP will adopt a request for supplementary information together with a deadline for submission of the requested data by the MAH and a timetable for the assessment of the MAH's responses. The MAH will receive the adopted

timetable together with the request for supplementary information. The clock will be stopped until the receipt of the requested supplementary information.

Any response to a request for supplementary information must be sent to the Agency, the (Co) Rapporteur and all CHMP members, as well as PRAC members where appropriate.

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 at the latest before the adoption of the request for supplementary information. 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.

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. Upon receipt of the responses from the MAH, the procedure will be re-started following a weekly-start or monthly-start timetable according to the same principles as the ones applied at the initial start of procedure.

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

References

- Commission Regulation (EC) No 1234/2008 (OJ L334 of 12 December 2008)
- Commission Regulation (EU) No 712/2012 amending Regulation (EC) No 1234/2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products
- Guidelines on the details of the various categories of variations, on the operation of the procedures laid down in Chapters II, IIa, III and IV of 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 and on the documentation to be submitted pursuant to those procedures

3.8. Which post-opinion steps apply to my Type II variation and when can I implement the approved changes? Rev. Feb 2015

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 Scientific Advisory Group (SAG) in connection with the re-examination, the applicant should inform the CHMP as soon as possible of this request.

The CHMP will appoint different (Co-) Rapporteurs, 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 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.

Linguistic review

Where the product information is affected, a linguistic review of the Product Information changes will be performed. The linguistic review will start 5 days after the CHMP plenary meeting following the adoption of the CHMP opinion on the variation. The monthly linguistic review will cover all procedures affecting the annexes concluded since the latest linguistic review. The EPAR update will also consolidate all procedures concluded since the latest EPAR update.

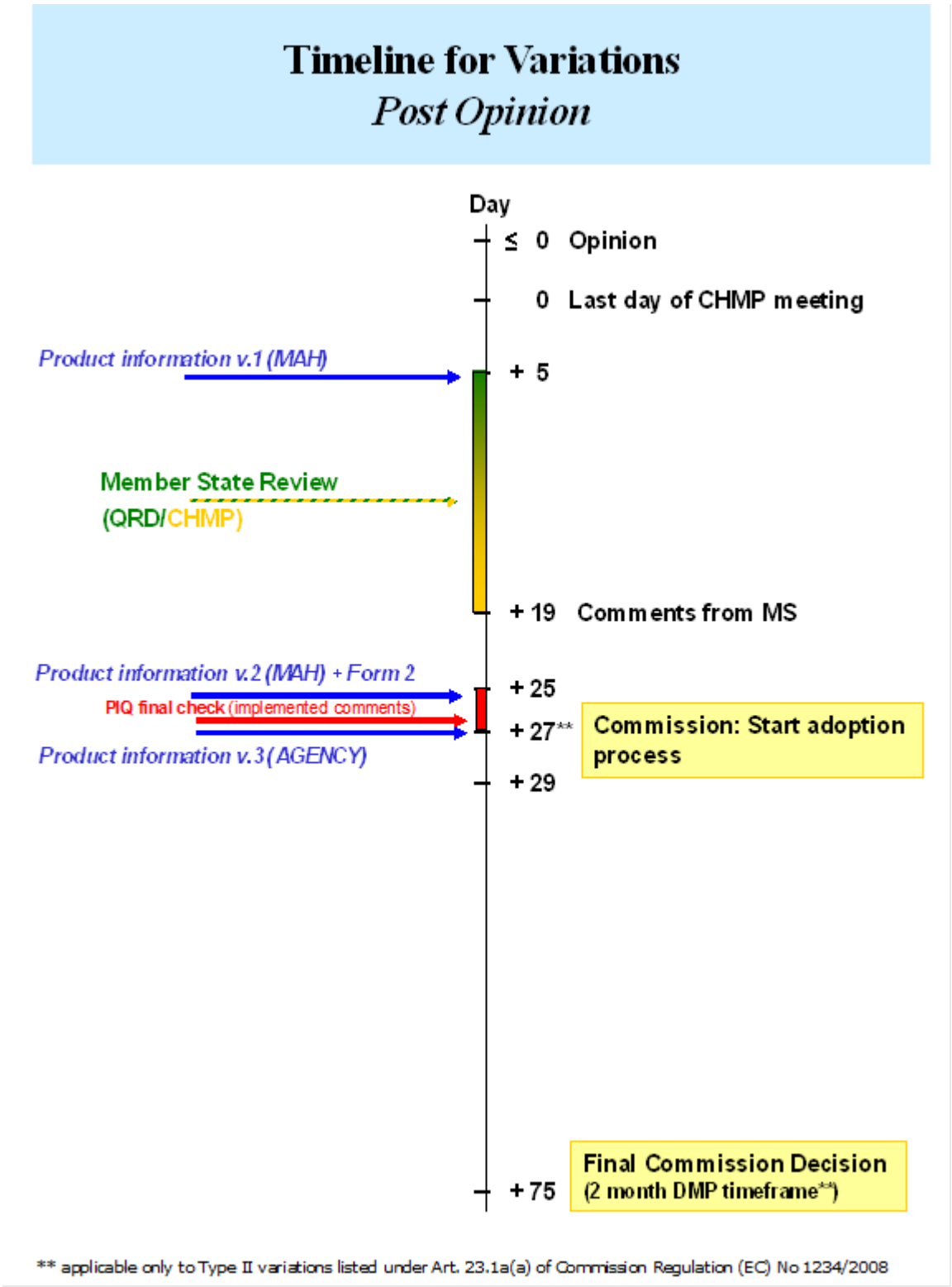
Decision-Making Process

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

All the other type II variations will follow a yearly timeframe for update of the respective Commission decision.



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 MAH 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 Product Information 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.

This date corresponds to the date of EC decision or CHMP opinion when that specific annex was affected.

References

- Commission Regulation (EC) No 1234/2008 (OJ L334 of 12 December 2008)
- Commission Regulation (EU) No 712/2012 amending Regulation (EC) No 1234/2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products
- Guidelines on the details of the various categories of variations, on the operation of the procedures laid down in Chapters II, IIa, III and IV of 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 and on the documentation to be submitted pursuant to those procedures
- 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

- Council Regulation (EC) No 297/95 (OJ L 35 of 15 February 1995), as amended
- Fees payable to the European Medicines Agency

3.10. Do I have to submit mock-ups and specimens? Rev. July 2013

For information concerning submission of mock-ups and specimens in the framework of post-authorisation procedures, please refer to the document 'Checking process of mock-ups and specimens of outer/immediate labelling and package leaflet of human medicinal products in the centralised procedure, 3.4 Other post-authorisation procedures.

References

- The 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. Feb 2015

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

At submission

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

At CHMP Opinion (Day 0)

- English language: complete set of finally agreed Annexes electronically only in Word format (highlighted and clean)

After CHMP Opinion (Day +5, for variations on a weekly-start timetable, this is 5 days after the CHMP plenary meeting following the adoption of the CHMP opinion)

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

After Linguistic check (Day +25, for variations on a weekly-start timetable, this is 25 days after theCHMP plenary meeting following the adoption of the CHMP opinion)

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

Overview

Day	Lang.*	Post-opinion linguistic review Timetable
0	EN	Electronically Word format (highlighted)
+5	All EEA	Electronically Word format (highlighted)
+25	All EEA	Electronically Word format (highlighted)

* = 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 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 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. 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, *for variations on a weekly-start timetable, this is 5 days after the CHMP plenary meeting following the adoption of the CHMP opinion*) 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 changes will trigger new EU number(s) (additional presentation(s))? New Apr 2015

Any changes in the number of units of medicinal product or medical device being an integral part of the medicinal product (e.g. prefilled syringes) will trigger a different EU number.

Differentiation should be made between the addition of a presentation where the two presentations will co-exist on the market on a long-term basis versus a replacement of a presentation where the new presentation will replace the previous one (it is expected that for a certain period of time, the two presentations will co-exist on the market until the stock of the previous presentation runs out).

In principle, a **replacement** of one presentation by another presentation does not trigger a new EU number, unless the number of units of medicinal product or medical device being an integral part of the medicinal product (e.g. prefilled syringes) is changed.

Examples of changes in presentations for replacement, not triggering a new EU number (this is not an exhaustive list):

- Replacement of the primary or secondary packaging,

- Change in composition (e.g. change in excipients),

In case of **addition**, as the presentations will co-exist on the market, two packs with different contents cannot be covered by the same EU number and will be considered as different presentations.

Changes in the number of any unit (not restricted to the medicinal product) or changes in the specifications of any unit (not restricted to the medicinal product) contained in the pack will trigger a new EU number.

Examples of changes that will trigger new EU numbers (this is not an exhaustive list):

- Introduction of an alternative immediate (primary) packaging made from a different material,
- Introduction of an alternative shape/dimension of a pharmaceutical form (pre-rolled sealant matrix versus flat, change in size of patch).

If you have any questions on any upcoming submission, please contact us using the relevant email addresses: IAquery@ema.europa.eu, IBquery@ema.europa.eu or IIquery@ema.europa.eu

3.13. 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.

3.14. 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.

3.15. What specific requirements apply to my Type II variation for a new orphan indication? Rev. Feb 2015

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 in module 1.7.1 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 in module 1.7.2 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.

References

- Regulation (EC) No 141/2000
- Regulation (EC) No 847/2000
- 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
- Community Register - website of the European Commission

3.16. 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.

References

- Regulation (EC) No 141/2000 on orphan medicinal products

3.17. 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':

- 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"

3.18. What can be considered an editorial change and how can it be submitted as part of a type IA/IB/II variation? NEW May 2015

The European Commission 'Variations Guidelines' 2013/C 223/01 specifies that "If amendments to the dossier only concern editorial changes, such changes should generally not be submitted as a separate variation, but they can be included in a variation concerning that part of the dossier.". Changes that can be classified as a variation as per Variations Guidelines are not considered editorial changes and should be submitted under the appropriate variation category.

3.18.1. Editorial changes in module 3

Provided that the above condition is fulfilled, the following changes to the Module 3 may be considered editorial: adding headers for ease of use, reordering of existing information without changing the meaning, alignment of information among/within the sections provided that it can be demonstrated what is the correct reference that had been previously agreed (e.g. alignment of information in flow charts to process description), punctuation changes and grammar/orthographic corrections that do not alter the meaning of the text.

Examples of changes that cannot be considered editorial: removal of specification parameters or manufacturing description, update of information to bring the dossier content in line with the current manufacturing process, etc.

In practice for the Agency, “that part of the dossier” can cover sections up to the fourth level of the eCTD, as follows “3.2.S.x” or “3.2.P.x”. For example, if a variation affects section 3.2.S.2.1 editorial changes can be submitted in sections from 3.2.S.2.1 to 3.2.S.2.7.

Editorial changes should always be clearly identified in the application form as following: A brief description of the editorial changes should be provided in the Precise Scope. All the editorial changes should be listed in the **present / proposed table**, and a **justification** as to why the holder considers them ‘editorial’ (i.e. why they should not trigger a specific variation) should be provided for each change.

In addition, the MAH should provide a **declaration** in the ‘Precise scope and background…’ section of the application form confirming that the changes proposed as editorial do not change the content of the concerned part(s) of the dossier beyond the scope of the variation submitted within which the editorial changes are being submitted.

If the editorial changes affect sections not impacted by any upcoming variation, the MAH may consider submitting these changes as a separate type IB variation (B.I.z or B.II.z respectively).

3.18.2. Editorial changes in module 4 and 5

Editorial changes in module 4 and 5 are not foreseen. Please contact us (IAquery@ema.europa.eu, IBquery@ema.europa.eu or IIquery@ema.europa.eu as relevant) in advance of an upcoming submission.

3.18.3. Editorial changes to the product information in module 1.3.1

Formatting changes, correction of typographical errors and/or mistakes to the English Product Information or other linguistic versions of the Product Information are considered editorial changes provided that the meaning of the text is not altered. These changes can be included within the scope of any upcoming variation impacting the product information.

Changes in the scientific content cannot be accepted as an editorial change. These changes should be classified under the scope of the relevant variation as per Variations Guidelines (e.g. Type II C.I.4). If no relevant scope is available, a variation type IB C.I.z may be appropriate.

Proposed changes that may require confirmation by the rapporteur or linguistic review will only be accepted by the Agency when submitted within the scope of an upcoming variation type IB or type II under chapter C which impacts the product information.

Editorial changes should generally not be submitted as a separate variation and therefore no reference to a variation category is required. Should there be no upcoming variation to include the editorial changes, these could also be submitted as a stand-alone IB C.I.z if they affect the English SmPC or an Art. 61(3) notification if they only affect the PIL/labelling. If other languages are affected and in case no variation affecting the product information is upcoming, the applicants are advised to contact the Agency to discuss how to handle these necessary changes.

The MAH should liaise with the Agency without delay if the mistake concerns an incorrect or missing important information (e.g. contra-indication or adverse event) that could affect the safe and effective use of the medicinal product and/or lead to a potential medication errors (e.g. wrong strength, wrong posology, wrong route of administration).

The editorial changes should be clearly identified in the application form as editorial changes. A brief description of the editorial changes should be provided in the precise scope of the application form.

Furthermore, editorial changes should be presented in the **present / proposed table** or provided as a separate Annex. A statement confirming that the proposed editorial change(s) do(es) not change the content of the previously approved Product information should be provided.

Any changes proposed by the applicants as editorial will be carefully considered by the Agency at time of submission and may be subject to further assessment at the same time as the variation. Proposed editorial changes that cannot be accepted as such will be rejected. In case of doubt, applicants can contact the Agency in advance of the planned submission using the appropriate pre-submission query email address IAquery@ema.europa.eu, IBquery@ema.europa.eu or IIquery@ema.europa.eu as relevant.

References

- Commission Regulation (EC) No 1234/2008 (OJ L334 of 12 December 2008)
- Commission Regulation (EU) No 712/2012 amending Regulation (EC) No 1234/2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products
- Guidelines on the details of the various categories of variations, on the operation of the procedures laid down in Chapters II, IIa, III and IV of 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 and on the documentation to be submitted pursuant to those procedures
- Practical questions and answers to support the implementation of the variations guidelines in the centralised procedure (EMA/427505/2013)
- CMDh Recommendation for classification of unforeseen variations according to Article 5 of Commission Regulation (EC) 1234/2008

3.19. Who should I contact if I have a question when preparing my application? NEW Apr 2014

If you cannot find the answer to your question in the Q&A when preparing your application, please contact us using the following email address: IIquery@ema.europa.eu

The Agency aims to respond to your query within 5 working days. To help us deal with your enquiry, please provide as much information as possible including the name of the product in your correspondence.

You should submit your query once and it is important that you submit it only to one dedicated email address. If you are uncertain of on a classification of a variation as type IB or type II please choose one of the relevant email addresses available to you (either IBquery@ema.europa.eu or IIquery@ema.europa.eu). Your query will be channelled internally to the relevant service(s) that will respond to you.

The above email address is only applicable when you have a pre-submission query. A dedicated Procedure Manager (PM) will be assigned to the procedure once your application has been validated. You will be able to contact this PM throughout the procedure.

3.20. Who is my contact at the European Medicines Agency during an application procedure for extension of indication? NEW Apr 2015

The management of an application procedure for extension of indication follows the principles outlined for initial marketing authorisation application (MAA) evaluations (see separate Q&A).

The procedure manager (PM) is the primary contact for the applicant prior to submission and throughout the procedure until the decision is granted by the European Commission. The MAH will be notified of the allocated PM at time of confirmation of validation of the application.

The PM will serve as the main liaison person between the EMA product team, the Rapporteurs and the applicant. The PM, in close co-operation with the EMA product lead (EPL) and the rapporteurs, will ensure that the applicant is kept informed of all aspects related to the MAA evaluation.

The applicant should contact the **PM** for all questions regarding the evaluation procedure, including

- Requests for guidance in the pre-submission phase, such as the pre-submission meeting;
- Any type of procedural questions during the evaluation, such as availability of assessment reports and opinion documents;
- Discussion on timetables including requests for extension of clock-stops etc.
- Any question where guidance related to the evaluation procedure is needed; in such cases the PM will address or liaise and redirect as appropriate.

At certain milestones during the evaluation procedure, the **EPL** will contact the applicant for a direct exchange to facilitate the discussion on the scientific evaluation. These include:

- Preparation and conduct of clarification meetings (where applicant requests such meeting);
- Immediate feedback regarding scientific aspects from committee plenary discussions, where required;
- Expectations relating to the oral explanation, including topics to be addressed;
- Discussion of required post-authorisation measures;
- Late-stage revisions of the product information before adoption of the final opinion.

These interactions occur in close co-operation with the Rapporteurs. Occasionally other members from the EMA Product team may contact the applicant directly to facilitate the discussion on specific aspects (e.g. risk management).

Where the applicant is in direct contact with the EPL or another member of the EMA Product Team the PM should always be copied in the correspondence.

Please see other relevant questions and answers in the EMA pre-authorisation guidance “What is the role of the EMA product team? and Who is my contact at the European Medicines Agency during a marketing authorisation application (MAA) evaluation procedure?” and in the EMA post-authorisation guidance “Who is my contact at the European Medicines Agency during post-authorisation procedures?” and “Who is my contact at the European Medicines Agency during the post-authorisation phase outside any evaluation procedures?”.

4. Extension applications

4.1. When will my variation application be considered a Type II variation or an Extension application? Rev. Oct 2013

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 Variations Guidelines 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

- Commission Regulation (EC) No 1234/2008 (OJ L334 of 12 December 2008)
- Commission Regulation (EU) No 712/2012 amending Regulation (EC) No 1234/2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products
- Guidelines on the details of the various categories of variations, on the operation of the procedures laid down in Chapters II, IIa, III and IV of 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 and on the documentation to be submitted pursuant to those procedures
- Guideline on the categorisation of New Applications versus Variations Applications, The Rules governing Medicinal Products in the European Union, Notice to Applicants, Volume 2C
- Regulation (EC) No 1901/2006
- EDQM Guidance – 'Standard Terms – Introduction and Guidance for use'

4.2. Extension Applications - Will my invented name change? Rev. Aug 2014

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. The addition of a qualifier (suffix) (e.g. Invented name + qualifier) is not possible within the same Marketing Authorisation as this would result in a different (invented) name.

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

- Commission Regulation (EC) No 1234/2008 (OJ L334 of 12 December 2008)
- "Guideline on the acceptability of invented names for human medicinal products processed through the centralised procedure (CHMP/328/98)"
- A Guideline on Summary of Product Characteristics, The Rules governing Medicinal Products in the European Union, Notice to Applicants, Volume 2C
- 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.

4.4. How shall I present my Extension Application? Rev. Feb 2013

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? Rev. Sep 2014

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 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? Rev. Oct 2013

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

- Commission Regulation (EC) No 1234/2008 (OJ L334 of 12 December 2008)
- Commission Regulation (EU) No 712/2012 amending Regulation (EC) No 1234/2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products
- Guidelines on the details of the various categories of variations, on the operation of the procedures laid down in Chapters II, IIa, III and IV of 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 and on the documentation to be submitted pursuant to those procedures

4.7. How, when and to whom shall I submit my Extension Application? Rev. Aug 2014

See question 22.5 Other – How and to whom shall I submit my application?

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").

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

DAY	ACTION
1	Start of the procedure
80	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.
100	Rapporteur, other CHMP members and Agency receive comments from Members of the CHMP.
115	CHMP members and Agency receive a draft list of questions (including draft overall conclusions and draft overview of the scientific data) from Rapporteur.
120	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.
Clock stop.	
121*	Submission of the responses and restart of the clock.

*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:

DAY	ACTION
150	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.
170	Comments from CHMP Members to Rapporteur.
180	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.
181	Restart of the clock and oral explanation.

185	Final draft of English SmPC, labelling and package leaflet sent by MAH to the Rapporteur, Agency and other CHMP members.
By 210	Adoption of CHMP Opinion + CHMP Assessment Report.

In cases where the PRAC is involved in an extension application, e.g. when a RMP is submitted within the extension, the following time tables with PRAC mile stones will apply:

DAY	ACTION
1	Start of the procedure
80	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.
87	PRAC Rapporteur circulates the RMP assessment report and proposed RMP LoQ
100	Rapporteur, other CHMP members and Agency receive comments from Members of the CHMP.
101-104	PRAC adopts PRAC RMP Assessment Overview and Advice for D120 LOQ
115	CHMP members and Agency receive a draft list of questions (including draft overall conclusions and draft overview of the scientific data) from Rapporteur.
120	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.
Clock stop.	
121*	Submission of the responses and restart of the clock.

*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:

DAY	ACTION
150	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.
167	PRAC adopts PRAC RMP Assessment Overview and Advice for D180 LoOI
170	Comments from CHMP Members to Rapporteur.
180	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.
181	Restart of the clock and oral explanation.

181 to 210	Final draft of English SmPC, labelling and package leaflet sent by MAH to the Rapporteur, Agency and other CHMP members.
197	PRAC adopts the final PRAC RMP Assessment Overview and Advice
By 210	Adoption of CHMP Opinion + CHMP Assessment Report.

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
- Commission Regulation (EC) No 1234/2008 (OJ L334 of 12 December 2008)
- Commission Regulation (EU) No 712/2012 amending Regulation (EC) No 1234/2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products
- "Centralised procedure", The Rules governing Medicinal Products in the European Union, Notice to Applicants, Volume 2A, chapter 4.

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

- Council Regulation (EC) No 297/95 (OJ L 35 of 15 February 1995), as amended
- Fees payable to the European Medicines Agency
- Guideline on the categorisation of New Applications versus Variations Applications, The Rules governing Medicinal Products in the European Union, Notice to Applicants, Volume 2C

4.10. Do I have to submit mock-ups and specimens? Rev. July 2013

For information concerning submission of mock-ups and specimens in the framework of extension applications, please refer to the document 'Checking process of mock-ups and specimens of outer/immediate labelling and package leaflet of human medicinal products in the centralised procedure, 3.1 New marketing authorisation applications and extensions applications.

References

- The 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. Aug 2014

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 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.

References

- The new product information linguistic review process for new applications in the Centralised Procedure (EMEA/5542/02)

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"

4.15. Who should I contact if I have a question when preparing my application? NEW Sep 2014

If you cannot find the answer to your question in the Q&A when preparing your application, please contact us using the following email address: Extensionapplicationquery@ema.europa.eu.

The Agency aims to respond to your query within 5 working days. To help us deal with your enquiry, please provide as much information as possible including the name of the product in your correspondence.

The above email address is only applicable when you have a pre-submission query. A dedicated Procedure Manager (PM) will be assigned to the procedure once your application has been received. You will be able to contact this PM throughout the procedure.

4.16. Who is my contact at the European Medicines Agency during post-authorisation procedures? NEW Apr 2015

Please refer to question 22.8 Other - Who is my contact at the European Medicines Agency during post-authorisation procedures?.

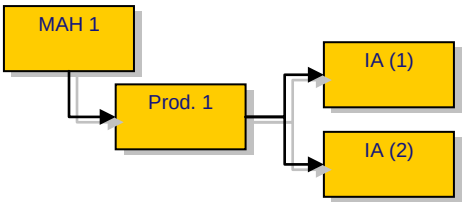
5. Grouping of variations

5.1. What types of variations can be grouped? Rev. Oct 2013

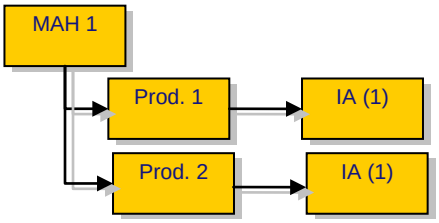
Article 7.2(a) of the Variations Regulation sets out the possibility for a marketing authorisation holder to group several Type IA/ IA_{IN} variations under a single notification to the same relevant authority:

- **Several** Type IA or IA_{IN} affecting **one** medicinal product.

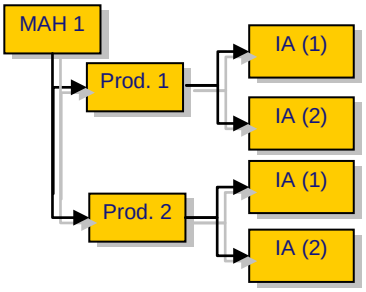
  This means for instance that a Type IA variation which is normally not subject to immediate notification can be included in the submission of a Type IA_{IN} variation.



- **one** Type IA or IA_{IN} affecting **several** medicinal products from the same MAH.



- **several** Type IA and/or IA_{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.

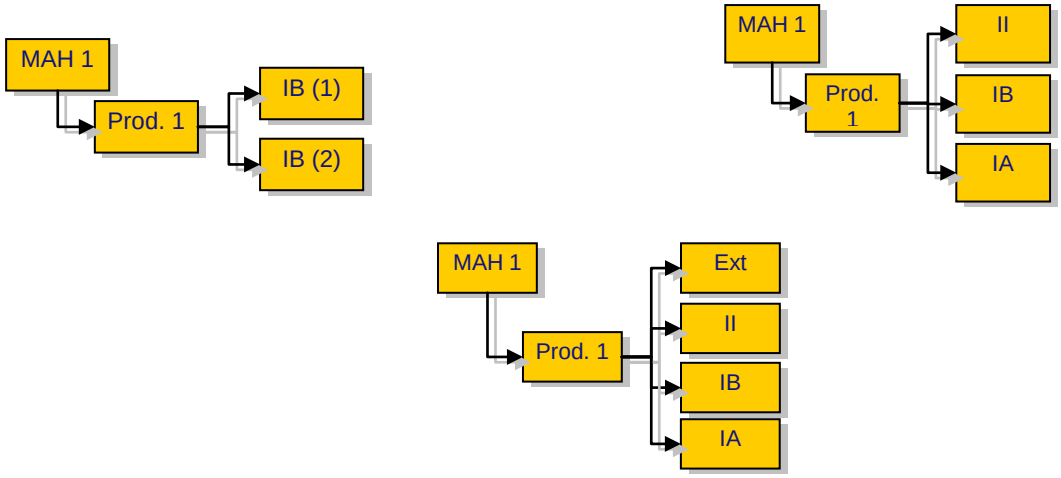


Applicants belonging to the same mother company or group of companies and applicants having concluded agreements or exercising concerted practices concerning the placing on the market of the medicinal product(s) concerned, have to be taken as "the same marketing authorisation holder".[3]

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

[3] See Commission Communication 98/C 229/03 OJ C 229, 22.7.1998, p. 4.

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

- Commission Regulation (EC) No 1234/2008 (OJ L334 of 12 December 2008)
- Commission Regulation (EU) No 712/2012 amending Regulation (EC) No 1234/2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products
- Guidelines on the details of the various categories of variations, on the operation of the procedures laid down in Chapters II, IIa, III and IV of 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 and on the documentation to be submitted pursuant to those procedures

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)

1	One of the variations in the group is an extension of the marketing authorisation.	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. Example: Extension for a new strength/pharmaceutical form + Type II for new indication to be used with this new strength form
2	One of the variations in the group is a major variation of type II; all other variations in the group are	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.

	variations which are consequential to this major variation of type II.	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.
12	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)

Grouping of several drug-drug interaction studies e.g. 1 Type II - interaction study with Rifampicin 1 Type II - interaction study with oral contraceptive	 Grouping acceptable 1 Type II per interaction study, but Type IIs can be grouped in 1 application
Grouping of variations for change of indication + legal status e.g. Type II to change the indication Type II to change the legal status (switch to OTC) , linked to the new wording of the indication	 Grouping acceptable Type IIs can be grouped in 1 application
Grouping of Type IB variations and Type IA variations *Quality* e.g. Type IB – extension of re-test period of the active substance Type IB – changes in the storage conditions of the active substance e.g. Type IB – changes to a test procedure of the active substance Type IA – deletion of a non-significant IPC of the finished product *Quality + Administrative* e.g. Type IB Extension of the shelf life of the finished product Type IA_{IN} Change in the name of a manufacturer responsible for batch release	 Grouping acceptable (both related to active substance) Grouping acceptable (finished product change linked to active substance change) Grouping acceptable (admin change can be combined with quality change as PI Annexes are affected)

Type IA Change in ATC Code	
Implementation of agreed wording change(s) requested by the CHMP for which no new additional data are submitted by the MAH	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.
Grouping of variations for extensions of indication e.g. Data package supportive of 2 different indications e.g. renal cell carcinoma + non-small cell lung cancer	Not acceptable for grouping
Grouping of variations affecting different aspects of the product information e.g. Type II to update safety information in section 4.8 Type II to update section 5.2 of the SPC with PK data	Not acceptable for grouping

5.3. How shall I present a grouped variations application? Rev. Oct 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/ IA_{IN} 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

- Guidelines on the details of the various categories of variations, on the operation of the procedures laid down in Chapters II, IIa, III and IV of 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 and on the documentation to be submitted pursuant to those procedures
- eCTD Variations Q&A document
- Template for cover letter
- TIGes Harmonised Guidance for eCTD Submissions in the EU

5.4. What procedure number will be given to grouped variation applications? Rev. Oct 2013

- Several Type IA/ IA_{IN} 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 IA_{IN}.

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

- One or more Type IA/ IA_{IN} 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/ IA_{IN} variations i.e. "IG". As the 'high-level' number cannot 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 mandatory for submissions sent via the eSubmission Gateway or Web Client since this number has to be included in the 'naming convention of the file 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/IG0002/nn which was submitted as part of a Type IA/ IA_{IN} group affecting several medicinal products "IG0002")

- 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_{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.

5.6. How will grouped variation applications be handled (timetable)? What will be the outcome of the evaluation of a grouped variation application? Rev. Feb 2015

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.

When the group follows the timetable of the Type II variation, weekly-start timetables may apply to the assessment following the same principles as those applied to the assessment of Type II variations. For more information please refer to the following questions and answers from the post-authorisation guidance for Type II variations: '*Which submission dates (weekly or monthly) are applicable for my type II variation and when shall I submit my application?*' and '*How shall my Type II application be handled (timetable)?*'

In case of grouped Type IA/ IA_{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. July 2013

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), for which the amendments to the decision granting the marketing authorisation will follow a two month timeframe;

Where a group of Type IA/ IA_{IN} 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/ IA_{IN} 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 to 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

- Council Regulation (EC) No 297/95 (OJ L 35 of 15 February 1995), as amended
- More information about fees and fee payment in the Centralised Procedure

6. Worksharing of variations

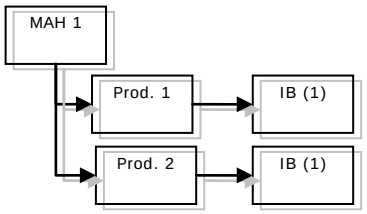
6.1. What is worksharing and what types of variations can be subject to worksharing? Rev. Oct 2013

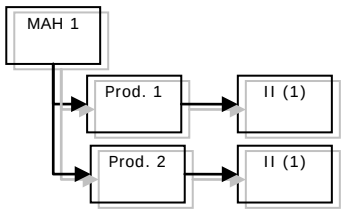
Article 20 of Commission Regulation (EC) N° 1234/2008 (the 'Variations Regulation') sets-out the possibility for a MAH to submit the same Type IB or Type II variation, or the same group of variations affecting more than one marketing authorisation from the same MAH in one application.

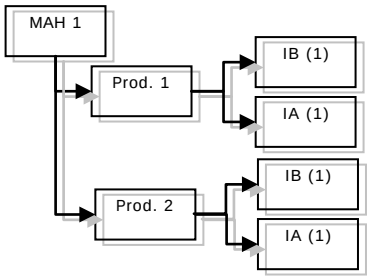
Applicants belonging to the same mother company or group of companies and applicants having concluded agreements or exercising concerted practices concerning the placing on the market of the medicinal product(s) concerned, have to be taken as "the same marketing authorisation holder" .

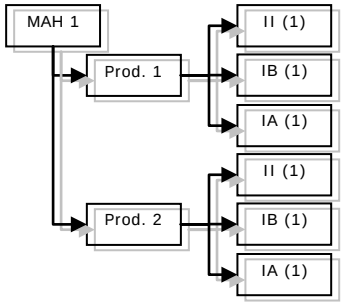
Extensions are excluded from worksharing.

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 can be included in worksharing procedures submitted as of 4th August 2013.

References

- Commission Regulation (EC) No 1234/2008 (OJ L334 of 12 December 2008)
- Commission Regulation (EU) No 712/2012 amending Regulation (EC) No 1234/2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products (OJ L209 of 4 August 2012)
- Guidelines on the details of the various categories of variations, on the operation of the procedures laid down in Chapters II, IIa, III and IV of 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 and on the documentation to be submitted pursuant to those procedures

6.2. What variation(s) would be considered acceptable for worksharing? Rev. July 2013

In order to benefit from a worksharing procedure, it is required 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

- 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
- Introduction or changes to the pharmacovigilance system

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. May 2015

In order to facilitate the planning of a worksharing procedure, MAHs are advised to inform the Agency at least 2 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, Reference Member States (RMS) and National Competent Authorities 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.

Upon receipt of the letter of intent, the Agency will appoint a Procedure Manager 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 or National Competent Authorities 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.

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 submit such variations as usual and a procedure manager will be appointed at the time of validation. A worksharing procedure number will be assigned at the same time.

6.4. How shall I present a variation application under worksharing? Rev. Jul 2015

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 electronic 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 nationally authorised medicinal products 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, RMSs and National Competent Authorities, as applicable, 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 nationally authorised medicinal products 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 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 nationally authorised medicinal products only is available on the Agency's website.
- One completed electronic 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 nationally authorised medicinal products 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.

References

- Guidelines on the details of the various categories of variations, on the operation of the procedures laid down in Chapters II, IIa, III and IV of 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 and on the documentation to be submitted pursuant to those procedures

- eCTD Variations Q&A document
- Template cover letter for worksharing procedures including CAPs and MRP only
- Template for Annex B

6.5. How and to whom shall I submit my variation application under worksharing? Rev. Jul 2015

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

From 1 March 2014, the use of the eSubmission Gateway or web client is mandatory for all electronic Common Technical Document (eCTD) submissions through the centralised procedure. The European Medicines Agency (EMA) no longer accepts submissions on CD or DVD. This applies to all applications for human medicines.

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 European Medicines Agency eSubmission Gateway: Questions and answers relating to practical and technical aspects of the implementation and the eSubmission Gateway web client: Guidance for applicants. Applicants must not send duplicate submissions electronically or via CD-ROM or DVD as this might lead to delays in the handling of applications.

An automated acknowledgement email is sent from the system confirming whether the submission has passed the relevant technical validation criteria and whether it has been uploaded to the Agency's review tool and made available via the Common Repository. There is no need to send any accompanying hard media or separate paper cover letter as the cover letter will be in the relevant part of eCTD module 1 in PDF format.

Where applicable, revised product information Annexes (including Annex A, if applicable) should be included in electronic (Word and PDF) format in the same eSubmission Gateway and eSubmission Web Client package within a folder called 'working documents'. Where applicable changes in Word documents should be indicated using 'Tools-Track Changes'. Clean PDF versions should have all changes 'accepted'.

For Centrally Authorised medicinal products (eCTD mandatory)

An electronic copy containing the relevant eCTD sequence for each product, should be submitted to the Agency. The coordinating Procedure Manager should be indicated in copy ("cc") on the cover letter.

For nationally authorised medicinal products (eCTD not mandatory)

eSubmission Gateway / Web Client package 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
- Commission Regulation (EU) No 712/2012 amending Regulation (EC) No 1234/2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products (OJ L209 of 4 August 2012)
- 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)
- Guidelines on the details of the various categories of variations, on the operation of the procedures laid down in Chapters II, IIa, III and IV of 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 and on the documentation to be submitted pursuant to those procedures
- 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 2013

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 cannot 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/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/nn which was submitted as part of the 3rd worksharing procedure received by the Agency "WS0003"

Worksharing applications for a group of variations will include the suffix "/G" e.g. EMEA/H/C/xxxx/WS/0004/G and EMEA/H/C/prod_nb/WS0004/nn/G.

For all worksharing procedures, including those which contain nationally authorised medicinal products, the 'high-level' procedure number should be systematically 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 meantime.

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. Feb 2015

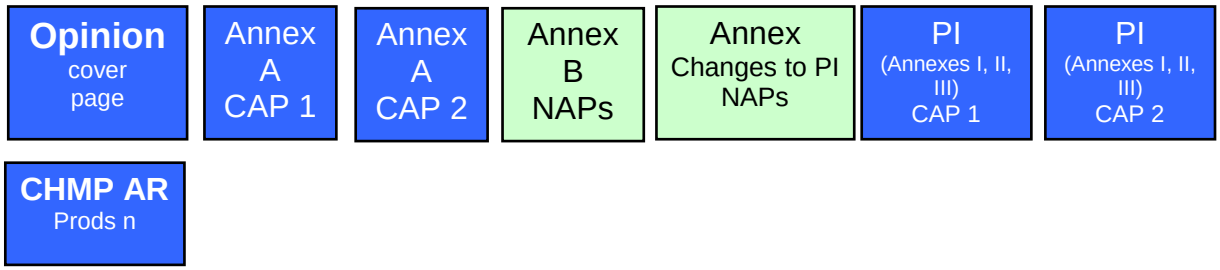
The MAH must submit the variation application for worksharing, at the latest by the recommended submission dates published on the Agency's website (See also Human Medicines – Procedural Timetables / Submission dates).

In general, variations submitted for worksharing will follow the 60-day evaluation timetable of Type II variations and weekly-start timetables may apply to the assessment following the same principles as those applied to the assessment of Type II variations. The 60-day period may 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)?" For more information on the weekly-start timetables, please refer to "Which submission dates (weekly or monthly) are applicable for my type II variation and when shall I submit my application?"

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:



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. Feb 2015

Upon adoption of the CHMP Opinion on the worksharing procedure, the Agency will inform the MAH 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.

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 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 the 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 day timeframe.

Decision-Making Process for centrally authorised medicinal products

Upon receipt of a favourable CHMP opinion which requires amendments to the decision granting the marketing authorisation, the Commission shall amend the marketing authorisation for each centrally

authorised medicinal product to reflect the approved variation(s) within 2 months, for the variations listed under Article 23(1a)(a) or within one year for the other variations. A single decision will be issued for each centrally authorised medicinal product.

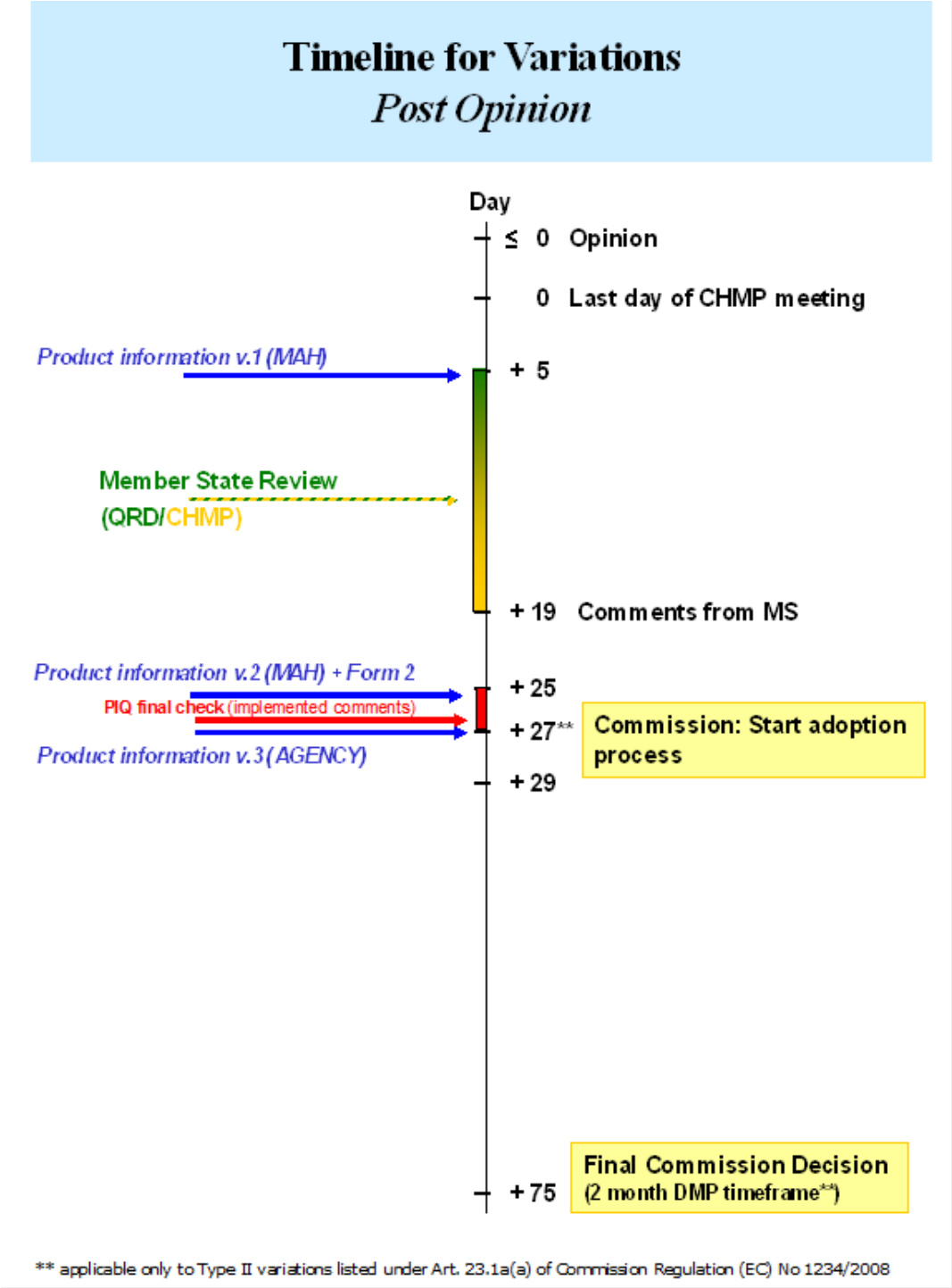
Article 23(1a)(a) provides for a two month timeframe for amending the decision granting the marketing authorisation for the following variations:

- 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 variations will follow a yearly timeframe for update of the respective Commission decision.

The Agency applies 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 MAH 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?").



MA updating Process for nationally authorised medicinal products (if applicable)

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 60 days.

Implementation

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

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.

Type II variations approved via a worksharing procedure, which do not require any amendment of the marketing authorisation or which follow a yearly update of the respective Commission Decision can be implemented 30 days after receipt of the favourable CHMP opinion. The agreed change(s) should be included in the Annexes of any subsequent regulatory procedure.

Variations related to safety issues, including urgent safety restrictions, must be implemented within a timeframe agreed by the marketing authorisation holder and the Agency.

References

- Commission Regulation (EC) No 1234/2008 (OJ L334 of 12 December 2008)
- Commission Regulation (EU) No 712/2012 amending Regulation (EC) No 1234/2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products (OJ L209 of 4 August 2012)
- Guidelines on the details of the various categories of variations, on the operation of the procedures laid down in Chapters II, IIa, III and IV of 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 and on the documentation to be submitted pursuant to those procedures

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 cannot 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

- Council Regulation (EC) No 297/95 (OJ L 35 of 15 February 1995), as amended
- 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. Aug 2014

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.

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:

Day	Lang.*	Type II variation(s)	Type IB variation(s)
0	EN	Electronically Word format (highlighted) All CAPs	Electronically Word format (highlighted) All CAPs
	Other EEA	/	Electronically Word format (highlighted)

			One CAP
+5	All EEA	**After opinion** Electronically Word format (highlighted) One CAP	/
+25	All EEA	**After opinion** Electronically Word format (highlighted) PDF format (clean) All CAPs	**After start of procedure** Electronically Word format (highlighted) PDF format (clean) All CAPs

* = 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 Gateway/Web Client. 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. Pre-submission queries service NEW Jul 2015

7.1. What is the pre-submission queries service?

The pre-submission queries service is a service set up to respond to pre-submission queries that marketing authorisation holders (MAHs) may have in relation to the following post authorisation procedures: types IA, IB and II variations, PSURs, renewal applications (including annual re-assessment and annual renewal procedures), extension applications, post-authorisation measures (PAMs), post-authorisation safety studies (under Article 107n/q), marketing authorisation transfers and Article 61(3) notifications.

The service aims to provide timely regulatory procedural pre-submission guidance to MAHs to facilitate the validation of these post-authorisation applications. It allows MAHs to receive specific regulatory guidance on planned applications and to discuss any pre-submission questions with a procedure manager before submitting an application.

This service does not address pre-submission queries for initial marketing authorisation applications; for these applications, a procedure manager is assigned at the eligibility stage of the application and may be contacted for any pre-submission queries.

7.2. How should I send queries to the pre-submission queries service?

You should send queries via email using one the following email addresses:

- Type IA variations: IAquery@ema.europa.eu
- Type IB variations: IBquery@ema.europa.eu
- Type II variations: IIquery@ema.europa.eu
- PSURs: PSURquery@ema.europa.eu
- Marketing authorisation transfers: MATransferquery@ema.europa.eu
- Article 61(3) notifications: 61.3.query@ema.europa.eu
- Renewal applications, including annual re-assessment and annual renewal procedures: renewalquery@ema.euopa.eu
- Extension applications: Extension application@ema.europa.eu
- Post-authorisation measures, PAMs: PAMquery@ema.europa.eu
- Post-authorisation safety studies: PASS.107n_q@ema.europa.eu

To help the service deal with your query, please provide as much relevant information as possible in your correspondence, not forgetting to include the name of the product.

If you are uncertain about the type of intended submission, send your query to the email address most likely related to your procedure. If the pre-submission query is related to more than one procedure (e.g. both a type IB and type II variation), send the query to only one of the relevant email addresses. We will provide a consolidated response.

The pre-submission queries service should always be the first point of contact, including for products with a high number of upcoming post-authorisation procedures requiring detailed discussion where the product team would be involved.

7.3. How will my query be handles by the pre-submission queries service?

A team of procedure managers with in-depth regulatory knowledge of procedures monitors all queries we receive. Your query will be assigned to a procedure manager specialising in the procedure concerned by your query. An internal peer review process of the response is in place to ensure consistency in the advices provided.

Queries received & advice provided to the MAHs are also recorded to ensure consistency of the responses provided and identify areas for improvement of the existing post-authorisation guidance published on the Agency website.

7.4. When can I expect to receive a response to my query?

The procedure manager will endeavour to send a response within 5 working days of the receipt of the query. You will receive along with your response the contact details of the procedure manager who handled your query in case you need further clarification, such as teleconference, related to the same query.

For complex queries where more internal consultation than usual is required, it may take more than 5 days to send a response. In those cases, you will be informed of the extra consultation and of the delay in sending you a response.

8. Changing the (Invented) Name of a Centrally Authorised Medicinal Product

8.1. Can I change the (Invented) Name of my CAP? Rev. Oct 2013

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_{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_{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_{IN} variation notification to the Agency for review (see PAG on Type IA variations).

References

- Commission Regulation (EC) No 1234/2008 (OJ L334 of 12 December 2008)
- Commission Regulation (EU) No 712/2012 amending Regulation (EC) No 1234/2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products (OJ L209 of 4 August 2012)
- Guidelines on the details of the various categories of variations, on the operation of the procedures laid down in Chapters II, IIa, III and IV of 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 and on the documentation to be submitted pursuant to those procedures
- Guideline on the acceptability of invented names for human medicinal products processed through the centralised procedure

8.2. Is the Invented Name (IN) checking procedure mandatory for the new proposed IN? Rev. Oct 2013

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_{IN} variation application since a final positive outcome of the checking procedure is required before implementation and submission of the Type IA_{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

- Commission Regulation (EC) No 1234/2008 (OJ L334 of 12 December 2008)
- Commission Regulation (EU) No 712/2012 amending Regulation (EC) No 1234/2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products (OJ L209 of 4 August 2012)
- Guideline on the acceptability of invented names for human medicinal products processed through the centralised procedure

8.3. How shall I present my IN change application? Rev. Jul 2015

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 with the following attachments:
	c.	A copy of the relevant page(s) of the annex to the Variations 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?"

For more information on how to submit please refer to question 22.5 Other – How and to whom shall I submit my application?

References

- Commission Regulation (EC) No 1234/2008
- Commission Regulation (EU) No 712/2012 amending Regulation (EC) No 1234/2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products (OJ L209 of 4 August 2012)
- Guidelines on the details of the various categories of variations, on the operation of the procedures laid down in Chapters II, IIa, III and IV of 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 and on the documentation to be submitted pursuant to those procedures

- 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

8.4. Do I need to submit amended mock-ups/specimens with my variation? Rev. Oct 2013

For information concerning submission of mock-ups and specimens in the framework of post-authorisation procedures, please refer to checking process of mock-ups and specimens of outer/immediate labelling and package leaflet of human medicinal products in the centralised procedure, 3.4 other post authorisation procedures.

References

- 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)

9. Annual Re-assessment

9.1. What is the Annual Re-assessment? Rev. Mar 2013

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

- Directive 2001/83/EC, Article 22 and its Annex I, Part II.6
- Regulation (EC) No 726/2004, Article 14(8)
- Guideline on procedures for the granting of a marketing authorisation under exceptional circumstances

9.2. Are the CHMP Co-Rapporteur and the PRAC involved in the assessment? Rev. March 2013

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.

9.3. How shall I present my annual re-assessment application? Rev. Aug 2014

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

- Directive 2001/83/EC, Article 22 and its Annex I, Part II.6
- Regulation (EC) No 726/2004 (EEC), Article 14(8)
- Template cover letter

9.4. Can I submit PSUR or an RMP with my annual re-assessment application? Rev. Mar 2013

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.

9.5. When, how and to whom shall I submit my annual re-assessment application? Rev. Aug 2014

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).

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.

Please refer to question 22.5 Other – How and to whom shall I submit my application?

9.6. How shall my annual re-assessment be handled (timetable)? Rev. Mar 2013

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:

DAY	ACTION
D 1	Start of procedure
D 30	CHMP Rap AR circulated to both CHMP/PRAC
D 35	PRAC Rap (draft) advice circulated to both CHMP/PRAC
D 46	Adoption of PRAC Advice (with PRAC divergent views appended)
D 60	Comments by CHMP members
D 80	Updated CHMP Rap AR considering PRAC advice and CHMP comments
D 90	Adoption of CHMP opinion and CHMP AR (or List of Outstanding Issues)

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.

9.7. What could be the outcome of my annual re-assessment? Rev. Mar 2013

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
- Annex I to Directive 2001/83/EC, Part II.6
- Regulation (EC) 726/2004

9.8. Can I submit my annual re-assessment within the renewal? Rev. Mar 2013

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

9.9. Do I have to pay fees for an annual re-assessment? Rev. Mar 2013

There is no fee payable for the annual re-assessment.

9.10. What impact do ongoing Variation(s) (Type IA / IB or Type II) have on the annual re-assessment? Rev. Sep 2014

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.

MAH is advised to contact the Agency in advance of the annual re-assessment submission, in order to discuss how to optimally handle the above issue.

9.11. Do I have to submit mock-ups and specimens? Rev. Mar 2013

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.

9.12. When do I have to submit (revised) product information? In all languages? Rev. Sep 2014

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:

Day	Language	
At submission:	EN	- Electronically - Word format (highlighted)
	Other EEA	- /
Day 5 after CHMP opinion	All EEA	- Electronically - Word format (highlighted)
Day 25 after CHMP opinion	All EEA	- Electronically - Word format (highlighted) - PDF format (clean)

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. 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 on-going 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.

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.

9.13. Will there be any publication on the outcome of my annual re-assessment? Rev. Mar 2013

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

9.14. Who should I contact if I have a question when preparing my application? NEW Sep 2014

If you cannot find the answer to your question in the Q&A when preparing your application, please contact us using the following email address: Renewalquery@ema.europa.eu

The Agency aims to respond to your query within 5 working days. To help us deal with your enquiry, please provide as much information as possible including the name of the product in your correspondence.

The above email address is only applicable when you have a pre-submission query. A dedicated Procedure Manager (PM) will be assigned to the procedure once your application has been received. You will be able to contact this PM throughout the procedure.

9.15. Who is my contact at the European Medicines Agency during post-authorisation procedures? NEW Apr 2015

Please refer to question 22.8 Other - Who is my contact at the European Medicines Agency during post-authorisation procedures?.

10. Renewal

10.1. How long is my marketing authorisation valid? Rev. Mar 2013

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 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)

10.2. When shall I submit my renewal application? Rev. Sep 2014

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 the key to ensure a timely start and finalisation of the renewal procedure, MAHs are strongly advised to contact the Agency 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

10.3. How shall I present my renewal application? Rev. Jul 2015

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), including the details of the marketing authorisation concerned, with the following annexes (the electronic application form is available on the eSubmission website:

- 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)

1.5.1 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.

1.5.2 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 has 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

- Variation application form, The Rules governing Medicinal Products in the European Union, Notice to Applicants, Volume 2C
- Template for cover letter

10.4. How and to whom shall I submit my renewal application? Rev. Aug 2014

Please refer to question 22.5 Other – How and to whom shall I submit my application?

10.5. How shall my renewal application be handled (timetable)? Rev. Mar 2013

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.

Day 1	Start of procedure (see published dates on EMA website)
Day 45	CHMP Rapporteur's Assessment Report sent to CHMP Co-Rapporteur and PRAC Rapporteur
Day 60	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 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 day timeframe.

References

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

10.6. What fee do I have to pay for a renewal? Rev. Mar 2013

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

10.7. Can other non-renewal specific changes be included in the renewal application? Rev. Mar 2013

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)

10.8. How to handle other ongoing variation applications during the renewal procedure and what impact may ongoing procedures have on the renewal procedure? Rev. Mar 2013

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 on-going 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? Rev. Sep 2014

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
30 Churchill Place
Canary Wharf
London E14 5EU
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 (muspecimens@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 Agency 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

10.10. When do I have to submit revised product information? In all languages? Rev. Sep 2014

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 Procedure Manager 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, IIIB, 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)

10.11. When will the linguistic checking of the product information take place? Rev. Sep 2014

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 EMA Procedure Manager secretary.

The following **checks post-opinion** will apply:

Check by	When	Who	Scope
QRD/ 'Member State'	Day +5 to +19	Member States	Detailed review of (highlighted changes in) all translations
PIQ	Day +25 to +27	EMA	Review of implementation of Member States comments

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

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? Rev. Mar 2013

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

10.13. Will there be any publication on the outcome of my renewal application? Rev. Mar 2013

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

10.14. Who should I contact if I have a question when preparing my application? NEW Sep 2014

If you cannot find the answer to your question in the Q&A when preparing your application, please contact us using the following email address: Renewalquery@ema.europa.eu

The Agency aims to respond to your query within 5 working days. To help us deal with your enquiry, please provide as much information as possible including the name of the product in your correspondence.

The above email address is only applicable when you have a pre-submission query. A dedicated Procedure Manager (PM) will be assigned to the procedure once your application has been received. You will be able to contact this PM throughout the procedure.

10.15. Who is my contact at the European Medicines Agency during post-authorisation procedures? NEW Apr 2015

Please refer to question 22.8 Other - Who is my contact at the European Medicines Agency during post-authorisation procedures?.

11. Annual renewal of conditional marketing authorisations

11.1. How long is my conditional marketing authorisation valid? NEW Mar 2013

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
- Commission Regulation (EC) No 507/2006

11.2. When shall I submit my annual renewal application? Rev. Sep 2014

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 the Agency for a pre-renewal - submission dialogue.

References

- Article 6 of Commission Regulation (EC) No 507/2006
- Community Register of medicinal product : website of the European Commission

11.3. How shall I present my annual renewal application? Rev. Sep 2014

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[4]:

- 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

[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

- 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, 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 Agency 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).

11.4. How and to whom shall I submit my annual renewal application? Rev. Aug 2014

Please refer to question 22.5 Other – How and to whom shall I submit my application?

11.5. How shall my annual renewal application be handled (timetable)? NEW Mar 2013

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.

DAY	ACTION
D 1	Start of procedure
D 30	CHMP Rapp AR circulated to both CHMP/PRAC
D 46	Adoption of PRAC Advice (with PRAC divergent views appended)
D 50	CHMP members' comments
D 55	Updated CHMP Rap AR considering PRAC advice and CHMP comments
D 60	Adoption of CHMP opinion and CHMP AR (or RSI without a clock stop)

DAY	ACTION
D 66	Responses to RSI
D 77	CHMP Rapp AR on responses circulated to both CHMP/PRAC
D 81	Comments by both CHMP and PRAC members
D 83	Updated CHMP Rap AR considering comments
D 90	Adoption of the CHMP Opinion

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.

11.6. What fee do I have to pay for a renewal? NEW Mar 2013

There is no fee payable for the annual renewal of a conditional marketing authorisation.

References

- Fees payable to the European Medicines Agency

11.7. Can other non-renewal specific changes be included in the annual renewal application? NEW Mar 2013

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.

11.8. How to handle other ongoing variation applications during the renewal procedure and what impact may ongoing procedures have on the renewal procedure? NEW Mar 2013

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.

11.9. Do I have to submit mock-ups and specimens? NEW Mar 2013

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.

11.10. When do I have to submit revised product information? In all languages? Rev. Sep 2014

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 Procedure Manager 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)

11.11. When will the linguistic checking of the product information take place? Rev. Sep 2014

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 EMA Procedure Manager secretary.

The following **checks post-opinion** will apply:

Check by	When	Who	Scope
QRD/ 'Member State'	Day +5 to +19	Member States	Detailed review of (highlighted changes in) all translations
PIQ	Day +25 to +27	EMA	Review of implementation of Member States comments

Comments will be sent directly by the Member States to the MAH at the latest by Day +19, with a copy to the EMA Procedure Manager secretary.

The MAH will send the final translations with tracked changes, incorporating the Member States' comments, electronically to the EMA Procedure Manager 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.

11.12. What do I need to do if I do not want to renew the Marketing authorisation of certain product presentations or the entire product? NEW Mar 2013

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

11.13. 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? NEW Mar 2013

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

- Article 7 of Commission Regulation (EC) No 507/2006

11.14. Will there be any publication on the outcome of my annual renewal application? NEW Mar 2013

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

11.15. Who should I contact if I have a question when preparing my application? NEW Sep 2014

If you cannot find the answer to your question in the Q&A when preparing your application, please contact us using the following email address: Renewalquery@ema.europa.eu

The Agency aims to respond to your query within 5 working days. To help us deal with your enquiry, please provide as much information as possible including the name of the product in your correspondence.

The above email address is only applicable when you have a pre-submission query. A dedicated Procedure Manager (PM) will be assigned to the procedure once your application has been received. You will be able to contact this PM throughout the procedure.

11.16. Who is my contact at the European Medicines Agency during post-authorisation procedures? NEW Apr 2015

Please refer to question 22.8 Other - Who is my contact at the European Medicines Agency during post-authorisation procedures?.

12. Post Authorisation Safety Study (PASS)

12.1. What is a PASS? Rev. Jul 2013

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.

12.2. Is a meta-analysis of safety data a non-interventional PASS? Rev. Jul 2013

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.

12.3. How will an imposed non-interventional PASS be handled? Rev. Jul 2013

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.

References

- Directive 2001/83/EC
- Regulation (EC) No 726/2004
- Commission implementing Regulation No 520/2012 of 19 June 2012 on the performance of pharmacovigilance activities provided for in Regulation (EC) No 726/2004 of the European Parliament and of the Council and Directive 2001/83/EC of the European Parliament and of the Council
- Guideline on good pharmacovigilance practices – Module VIII – Post-authorisation Safety Studies

- European Commission Question and Answers on transitional arrangements concerning the entering into force of the new pharmacovigilance rules provided by Directive 2010/84/EU amending Directive 2001/83/EC and Regulation (EU) No 1235/2010 amending Regulation (EC) No 726/2004 (SANCO/D5/FS/(2012)1014848)
- HMA-EMA Questions and answers on practical transitional measures for the implementation of the pharmacovigilance legislation (EMA/228816/2012 – v.2)

12.4. How will my imposed non-interventional PASS protocol be assessed? Rev. Sep 2014

Before an imposed non-interventional PASS 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.

12.4.1. How will my imposed non-interventional PASS protocol be evaluated (time table)?

The PRAC evaluation of the PASS protocol is a 60 day procedure, which follows the time tables available from the following webpage.

12.4.2. What are the possible outcomes of the PRAC evaluation of an imposed 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.

12.4.3. 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 the Agency and/or PRAC Rapporteurs beforehand. The email address should include the Procedure Manager's email and the product specific mailbox.

12.5. How will my imposed non-interventional PASS results be assessed? Rev. Jul 2013

Upon completion of the study, a final study report shall be submitted to PRAC within 12 months of the end of data collection unless a written waiver has been granted by PRAC, as appropriate.

The PRAC will assess the final study report and, based on the results of the study, will make recommendations concerning the marketing authorisation, stating the reasons on which they are based. The PRAC may recommend the maintenance of the terms of the marketing authorisation. In such cases the PRAC recommendation will be the final step in the procedure and the MAH will be informed as such.

Should the PRAC however recommend the variation, suspension or revocation of the marketing authorisation, this recommendation will be forwarded to the CHMP. The CHMP will then adopt an Opinion taking into account the recommendation. Should the CHMP Opinion uphold the PRAC recommendation, it will be forwarded to the Commission, who will then adopt a Decision in accordance with this Opinion.

12.5.1. How is an imposed non-interventional PASS final study report evaluated (time table)?

Time tables for the PRAC (/CHMP) evaluation of a PASS final study report procedure are currently under development and will be shortly available from the EMA web-site.

12.6. What if I, as the MAH, am of the opinion that the imposed non-interventional PASS results make a variation necessary? Rev. Jul 2013

The results of the PASS should be evaluated by the MAH, who should consider whether the results have an impact on the marketing authorisation. If the MAH concludes that this is indeed the case, the MAH should submit the results directly as a variation to the Agency.

Independently from the MAH evaluation of the need for a 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.

12.7. To whom should I submit my PASS protocol or study report? Rev. Aug 2014

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.

Please refer to question 22.5 Other – How and to whom shall I submit my application?

12.8. Who should I contact if I have a question when preparing my application? New Sep 2014

If you cannot find the answer to your question in the Q&A when preparing your application, please contact us using the following email address: PASS.107n_q.query@ema.europa.eu

The Agency aims to respond to your query within 5 working days. To help us deal with your enquiry, please provide as much information as possible including the name of the product in your correspondence.

The above email address is only applicable when you have a pre-submission query. A dedicated Procedure Manager (PM) will be assigned to the procedure once your application has been received. You will be able to contact this PM throughout the procedure.

12.9. Who is my contact at the European Medicines Agency during post-authorisation procedures? NEW Apr 2015

Please refer to question 22.8 Other - Who is my contact at the European Medicines Agency during post-authorisation procedures?.

12.10. Scientific advice for safety studies NEW Jul 2015

12.10.1. What is this pilot on scientific advice for safety studies about?

The Agency will run a 12 month pilot to encourage scientific advice on safety studies. This pilot will focus on protocols for non-imposed Post-Authorisation Safety Studies (PASS) i.e. Category III. Scientific advice is elaborated through the Scientific Advice Working Party (SAWP) with the

Pharmacovigilance Risk Assessment Committee (PRAC) endorsing the scientific advice letters in the case of PASS protocols.

Scientific advice on safety studies is a voluntary option for Marketing Authorisation Holders (MAH) or Applicants, and complementary to existing procedures.

12.10.2. Why is this pilot of scientific advice for PASS being run?

This pilot aims to encourage scientific advice on safety studies, to further develop an integrated lifecycle approach to advice on medicines across safety, quality, efficacy pre- and post-authorisation, and to support proactive pharmacovigilance planning. Procedural enhancements have also been put in place to strengthen the PRAC–SAWP interaction in order to meet these goals, and to better deliver on the Agency's mandate to provide advice on studies to determine the quality, safety and efficacy of medicinal products.

12.10.3. Why should I consider seeking scientific advice on PASS?

By engaging in scientific advice on PASS, Applicants or Marketing Authorisation Holders (MAH) can benefit from

- a strengthened PRAC-SAWP interaction
- a lifecycle approach to medicines advice with integrated advice on all aspects of medicines development from involved Committees
- support for proactive pharmacovigilance planning
- advice at an early or late stage of the protocol development
- targeted advice on key issues
- a well-defined procedural timetable
- a presubmission interaction with Agency secretariat to consider suitability and validity of the dossier
- a face to face meeting with involved regulators during the procedure
- engagement with patient representatives
- options to include other stakeholders such as HTAs or FDA further supporting optimised evidence generation
- the possibility of seeking follow-up advice

12.10.4. Which post-authorisation safety studies are in the focus of this PASS-SAWP pilot?

The pilot will focus on category III PASS protocols. Protocols of PASS imposed as conditions to the marketing authorisation (i.e category I and II) and protocols of joint imposed PASS conducted by a consortium of MAH will be assessed and endorsed by the PRAC under the provisions of article 107n of Directive 2001/83/EC; however, applicants/MAHs wishing to request scientific advice from the Agency on specific aspects of the protocol, in advance of its final submission under article 107n, can submit a SA request under this pilot.

12.10.5. Does EMA expect all PASS studies to go through scientific advice? If not, what advice can be given to sponsors on how to target studies for which a scientific advice should be sought?

Scientific advice is a voluntarily procedure and it is the choice of the MAHs or Applicant to submit or not the PASS protocol for scientific advice. Advice is frequently sought for complex or controversial issues, or for innovative approaches or methodologies. Scientific advice can also be valuable where MAHs or Applicants would value expert advice.

12.10.6. Are Post-Authorisation Efficacy Studies (PAES) part of this pilot?

Post-authorisation efficacy studies can already be submitted for EMA scientific advice. However, these are not the focus of this particular pilot.

12.10.7. Could requests for 'mixed' advice be submitted e.g. questions on pre-marketing and post-marketing phases, or questions on PASS and pivotal phase III studies, or questions on interventional and non-interventional studies?

Yes, such mixed advices are possible.

12.10.8. Can a draft PASS protocol be submitted for scientific advice although the marketing authorisation application is still under assessment?

Early submissions of PASS protocols for scientific advice are possible. However, Applicants should duly consider the best timing for their request for scientific advice, i.e. whether at the moment of the submission there are sufficient certainties about the status and the objectives of the study.

12.10.9. Can scientific advice be sought for nationally as well as centrally authorised products?

Yes, scientific advice can be sought for nationally as well as centrally authorised products.

12.10.10. Can a follow up advice be requested?

Yes. Follow up procedures are possible.

12.10.11. How long will the pilot last?

The pilot will run for a 12 month period and will start in Q3 2015.

12.10.12. When will the pilot start?

PASS protocols can be submitted for scientific advice from the date of this document in line with published scientific procedural timelines. Please see the published scientific advice timelines for subsequent procedures here.

12.10.13. Who will assess the non-imposed PASS protocols for SAWP?

As per existing scientific advice procedures, the assessment is led by SAWP delegates acting as SAWP coordinators. Two SAWP members/alternates are appointed as coordinators for each scientific advice procedure. A further PRAC expert is appointed to provide additional product specific PRAC input.

12.10.14. How will the PRAC Rapporteur for the product be involved in the scientific advice?

The PRAC Rapporteur for a specific product is involved through either the SAWP coordinators (i.e. assessment team from the same member state) or appointed as the PRAC expert for a specific scientific advice procedure.

12.10.15. Is the necessary expertise available in SAWP to evaluate non-imposed PASS protocols?

Expertise in pharmacoepidemiology, needed to evaluate the PASS protocol within this pilot, is available through the extension of the SAWP to at least 2 joint SAWP- PRAC delegates who can also act as SAWP coordinators for a specific scientific advice product procedure.

12.10.16. What is the role of the PRAC within the scientific advice procedure for non-imposed PASS protocols?

Scientific advice procedures for PASS will involve PRAC systematically at all the stages of the procedure. All scientific advice documents will be available to the PRAC during the procedure. The PRAC will endorse the advice relating to PASS, and a Final Advice Letter will be issued.

Each procedure will have a named PRAC expert appointed to provide product specific PRAC input. The PRAC Rapporteur for a product will be systematically involved either through the SAWP coordinatorship or as PRAC expert roles to ensure continuity across procedures through the lifecycle of the products.

12.10.17. For PASS within the focus of this pilot (category III), is it mandatory for companies to submit non-imposed PASS protocols to PRAC?

For category III studies, there is no legal obligation for companies to submit the protocol to the PRAC. However, the PRAC may request to review the protocol of some of these category III studies which are of interest for the committee and for which such submission of protocol is reflected as a milestone in the Risk Management Plan.

Please note that the advice provided within this pilot is without prejudice to any national requirement regarding the PASS protocols that might be in place is some Member states.

The SA provided within this pilot is without prejudice to any national requirement regarding the PASS protocols that may exist in Member States.

12.10.18. What about non-imposed PASS protocols required to be submitted by the PRAC that have not been through an EMA scientific advice procedure?

The final protocols for non-imposed PASS required by the PRAC can continue to be submitted to the PRAC as a Post-authorisation measure (PAM).

12.10.19. How do I apply for scientific advice on a PASS protocol?

A letter of intent for scientific advice should be submitted to the Agency at the mailbox scientificadvice@ema.europa.eu together with a briefing document in accordance with published EMA scientific advice guidance and timelines. See link here.

12.10.20. What is the format of the briefing document?

The MAH or Applicant provides questions and an accompanying justification of the approach taken with the relevant introduction, background, annexes and references. Please see the published scientific advice template.

12.10.21. What kinds of annexes are required?

Protocols or synopses, SmPCs, Risk Management Plans and assessment reports pertinent to the topic should be annexed as appropriate. Ready availability of relevant documents and references facilitates assessment.

12.10.22. What type of question is expected to be raised for the concerned study protocols?

In general, any question pertaining to the draft protocol can be posed in the draft briefing document. Feedback on whether the MAH or Applicant's draft questions can be validated as posed or reworded will be given at the validation stage.

12.10.23. Could questions be asked about the choice of the adverse reactions of interest?

In general, any question pertaining to the draft protocol can be posed in the draft briefing document. Feedback on whether questions can be validated as posed or reworded will be given at the validation stage. Specifically scientific advice can be sought for the selection of adverse reactions of interest.

12.10.24. How will scientific advice procedures for safety studies be run?

In summary, scientific advice will follow the same procedure as other scientific advice with the exception of involvement of PRAC, the appointment of PRAC expert, and endorsement of the letter by PRAC.

The EMA Secretariat should be formally notified of the intent to submit a scientific advice or protocol assistance request via a Letter of Intent. A Letter of Intent should be sent by email to scientificadvice@ema.europa.eu in advance of the anticipated start of the procedure. The latest PDF letter of Intent form provided on the EMA scientific advice website should be used.

The draft package should be presented in line with published template for scientific advice. A pre-submission meeting with Agency staff will be arranged to consider the suitability and validity of the submission. Following the pre-submission meeting and validation, an amended electronic final package is submitted and circulated to the appointed coordinators and experts in line with agreed timelines.

The SAWP Coordinators will then draft preliminary reports in response to the scientific advice or protocol assistance requests taking into account the timetable for evaluation of such requests. In addition to the SAWP coordinators and the joint PRAC SAWP delegate, a PRAC expert is appointed to

follow the procedure. The preliminary reports are discussed in the scientific advice plenary meeting and are made available to the involved Working Parties, Committees, and experts as appropriate. A list of issues for discussion at the Discussion meeting is sent to the MAH/Applicant (See figure 1 below SAWP 2). A face to face discussion meeting with the MAH/Applicant and members of the SAWP is held the following month (See figure 1 below SAWP 3).

Following the discussion meeting with the MAH/Applicant, and further to the SAWP plenary discussion, the SAWP Coordinators issue a draft joint report for comments by the involved participants. The joint report and the draft final advice letter are adopted by the SAWP through a written procedure.

All submission documents and reports are available to all PRAC members throughout the procedure. The final advice letter is endorsed by the PRAC and sent to the MAH/Applicant. SAWP will report to PRAC at each phase of the procedure.

Figure 1: Overview of scientific advice procedure on PASS.

Further details on routine scientific advice procedure are available.

12.10.25. Is a pre-submission meeting always expected or can the MAH/Applicant choose not to have one?

It is proposed that during the pilot phase, all procedures would have pre-submission meetings; optional pre-submission meetings could be envisaged further to review of experience gained during the pilot.

12.10.26. Is a discussion meeting with the MAH/Applicant during the procedure always expected?

It is proposed that during the pilot phase, all procedures would have a discussion meeting with the MAH/Applicant during the procedure; more targeted discussion meetings could be envisaged depending on the need for such discussions further to review of experience.

12.10.27. What is the nature of the discussion meeting?

Information regarding the discussion meeting is provided in the FAQ 21 “How do I prepare for a Discussion meeting?” in the published scientific advice guidance.

12.10.28. Can additional data or amended protocols be submitted during the procedure?

Additional data or amended protocols can be submitted at a specific point during the scientific advice procedure further to the SAWP list of issues. The MAH/Applicant may also propose in writing to the

Agency additional points for discussion that are not part of the adopted list of issues and submit these in writing ahead of the Discussion meeting. Any amendment/change to the development programme should be notified to the Agency /SAWP ahead of the discussion meeting.

12.10.29. Will the EMA support for these protocols be different from any other scientific advice?

Procedures for non-imposed PASS protocols will not be handled any differently than for existing scientific advice procedures except the extension to and inclusion of PRAC interactions and relevant Agency staff, such as the Risk Management Specialist.

12.10.30. Will fees be levied for scientific advice provided for non-imposed PASS protocols?

Yes, in accordance with the Agency's Fee Regulation and its corresponding Implementing Rules, fees will be levied on MAH/Applicants seeking scientific advice on PASS protocols.

In this context, two different types of scientific advice fees are applied depending on whether the request is an 'initial request' or a 'follow-up'. For further details on fees and fee incentives/reductions please consult the Explanatory Note on fees payable to the EMA and the section on fees on the Agency's website.

12.10.31. Where can I find further information about scientific advice?

Please see the published EMA scientific advice guidance for many FAQs.

13. Post-authorisation efficacy study (PAES) NEW Nov 2015

13.1. What is a PAES imposed in accordance with the Commission Delegated Regulation?

PAES imposed in accordance with the Commission Delegated Regulation (EU) No 357/2014 it is meant an efficacy study which is requested by a Competent Authority pursuant to at least one of the situations set out in this said regulation. The data resulting from such a PAES conducted within an authorised therapeutic indication are required to be submitted as they are considered important for complementing available efficacy data in the light of well-reasoned scientific uncertainties on aspects of the evidence of benefits that is to be, or can only be, addressed post-authorisation. The results of the PAES have the potential to impact on the benefit-risk of the medicinal product or product information.

Such efficacy study conducted post-authorisation can be imposed either:

- at the time of granting the initial marketing authorisation (MA) where concerns relating to some aspects of the efficacy of the medicinal product are identified and can be resolved only after the medicinal product has been marketed; or
- after granting of a MA where the understanding of the disease or the clinical methodology or the use of the medicinal product under real-life conditions indicate that previous efficacy evaluations might have to be revised significantly.

It is also possible to impose the conduct of post-authorisation efficacy studies in the specific situations of a conditional MA, a MA granted in exceptional circumstances, a MA granted to an advanced therapy medicinal product, the paediatric use of a medicinal product, a referral procedure initiated under Article 31 or Article 107i of Directive 2001/83/EC or Article 20 of Regulation (EC) No 726/2004, however these fall outside the scope of the Delegated Regulation.

References

- Regulation (EC) No 726/2004
- Directive 2001/83/EC
- Commission Delegated Regulation (EU) No 357/2014
- Draft scientific guidance on post-authorisation efficacy studies

13.2. How and where the PAES imposed in accordance with the Commission Delegated Regulation will be reflected in the marketing authorisation?

For centrally authorised medicinal products (“CAPs”), a PAES imposed as a condition to the MA is reflected in Annex II under section D “Obligation to conduct post-authorisation measures”.

The study objective and the deadline for the submission of the final study results are specified in the Annex II. At the beginning of the description of the study, such efficacy study imposed in accordance with the Delegated Regulation is explicitly named ‘Post-Authorisation Efficacy Study (PAES)’.

The imposition of such PAES shall meet one of the criteria set out in the Delegated Regulation. A justification will be provided in the CHMP assessment report.

If the MAH has to submit the protocol for endorsement by the European Medicines Agency, this will be reflected in Annex II in the wording of the condition (e.g. “according to an agreed protocol”).

Any post-approval amendments to the conditions in Annex II (objective and/or due date) should be duly justified and submitted as a variation, type IB C.I.11.z) for change in the due date or type II C.I.11.b) for changes other than the due date, for further details, please refer to ‘Practical questions and answers to support the implementation of the variations guidelines in the centralised procedure’.

As for any imposed post-authorisation efficacy studies, those imposed in accordance with the Delegated Regulation should also be reflected in the risk management plan (“RMP”), part IV ‘*Plans for post-authorisation efficacy studies*’ and if applicable under part III in case of important safety concerns addressed by this study as well.

References

- Commission Delegated Regulation (EU) No 357/2014
- GVP module on RMP
- EMA Practical questions and answers to support the implementation of the variations guidelines in the centralised procedure

13.3. Following which procedure will my imposed PAES protocol be assessed?

If the review of the imposed PAES protocol has been reflected in the Annex II, the MAH will have to submit a draft protocol to the European Medicines Agency as a post-authorisation measure (“PAM”). Otherwise, the review of the protocol is not deemed necessary.

The MAH is generally advised to consider seeking scientific advice on the study design irrespective of whether the submission of the protocol has been requested, in order to discuss the design of the study and ensure that it meets the intended objectives.

In case the PAES is a clinical trial, it falls under the scope of Directive 2001/20/EC (to be superseded by the Clinical Trial Regulation (EU) No 536/2014) and is subject to the national clinical trial authorisations.

References

- Scientific advice procedure
- EMA post-authorisation procedural advice for users of the centralised procedure (PAG) – Post-authorisation measures (PAMs)
- Directive 2001/20/EC
- Regulation (EU) No 536/2014 on clinical trials for medicinal products for human use

13.4. When should I submit my imposed PAES protocol?

If the submission of the protocol has been requested in the Annex II, the MAH should submit the protocol in accordance with the timeframe specified in the RMP, part IV as timelines for protocol submission are not specified in the Annex II.

At time of imposition, the MAH is asked to propose appropriate dates for the submission of the protocol and the post-authorisation data that are proportionate to the uncertainty to be addressed. The proposed dates for submission are subject to agreement with the Agency's Committee(s).

If the MAH would be unable to provide the protocol by the specified deadline, the MAH must inform the Agency and the Rapporteur in writing as early as possible in advance of the submission due time. The delay must be duly justified and a new submission date should be proposed. Such request should be sent to PAMquery@ema.europa.eu and will be subject to agreement by the Committee(s).

If the submission date of the final study results mentioned in the Annex II is impacted, this requires the submission of a type IB variation C.I.11.z).

References

- EMA Practical questions and answers to support the implementation of the variations guidelines in the centralised procedure

13.5. In which timeframe will my imposed PAES protocol be evaluated (timetable)?

The evaluation of the PAES protocol will be led by the CHMP with consultation of other committees where foreseen. The evaluation will be handled as a 60 day PAM procedure, which follows the timetables available on the Agency's website.

The protocol assessment will start in accordance with the published timetable for PAMs which is available on the following webpage.

13.6. What are the possible outcomes of the evaluation of an imposed PAES protocol?

The CHMP, taking into account advice of other committees where provided, will conclude the assessment of the protocol according to the following options:

- endorsement of the protocol;
- objection to the protocol;

In case of endorsement, the assessment report may still include recommendations for amendments to the protocol. These recommendations are for consideration by the MAH and do not require resubmission of the protocol.

In case of objection, resubmission of an amended protocol for reassessment will be required.

13.7. Do I have to submit interim results?

There is no obligation to submit interim results, unless it has been requested by the Committee(s).

However, when requested, interim results should be submitted as a PAM (see: *Under which procedure should I submit my PAM*?) unless there is an impact on the product information. In such case a variation should be submitted.

13.8. Do I have to submit the final results of my imposed PAES?

Upon completion of the study, a final study report shall be submitted by the deadline specified in Annex II via the appropriate variation procedure irrespective of changes to the product information.

The MAH should consider whether the final results have an impact on the marketing authorisation. If the MAH concludes that this is the case, the MAH should submit the results together with the proposed changes to the product information.

The classification of the variation will depend on whether there are proposed changes to the product information. Please refer to the EMA Practical questions and answers to support the implementation of the variations guidelines in the centralised procedure for further details.

With the application submitted, the MAH should indicate in the table of the cover letter of the application which post-authorisation measure is being addressed and the full description of the relevant measure.

The CHMP will lead on the assessment of the study results and will conclude, taking into account advice of other Committees where provided.

In addition, it is reminded that the MAH should provide in the PSUR, as usual, a summary of the clinically important efficacy and safety findings obtained from the study during the reporting interval.

References

- Template for cover letter
- EMA Practical questions and answers to support the implementation of the variations guidelines in the centralised procedure

13.9. Do I have to pay fees for the protocol and final study results submission?

There is no fee payable for the protocol submission as a PAM procedure.

For the final study results submission, there are fees applicable to the related variation procedure.

13.10. How is a PAES enforced?

The Agency will keep a record of the post-authorisation measure and its due date in its database.

In case of overdue condition or a MAH being found non-compliant in satisfying such condition, the competent authorities will consider the need for appropriate actions to be taken.

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 medicinal product(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 the MAH to the Committee
- Initiation of a referral procedure with a view to vary/suspend/revoke the MA
- Inspection to be performed upon request of the Committee(s)

Such regulatory action in regards to non-compliance of the MAH may be made public on the Agency website, e.g. in the EPAR(s) of the affected medicinal product(s).

References

- Directive 2001/83/EC
- Regulation (EC) No 726/2004

13.11. Will there be any publication on the outcome of my PAES protocol and final study results assessment?

Outcome of protocol assessment are not published on the EMA Website. However, in case of a clinical trial the protocol and summary will be available in the clinical trials database, as per usual procedure.

Outcome of final study results will be published in the EPAR under 'Procedural steps taken and scientific information after the authorisation'. Relevant results of the study will be included in the SmPC.

To support transparency on PAES that are outside the scope of Directive 2001/20/EC, study information (including for studies conducted outside the EU) should be made available in the EU electronic register of post-authorisation studies (EU PAS Register) maintained by the Agency.[5]

References

- EPARs

13.12. Who should I contact if I have a question when preparing my application?

If you cannot find the answer to your question in this Q&A when preparing your application, please contact the following email address, as appropriate: PAMquery@ema.europa.eu (in case of submission of a PAM) or IIquery@ema.europa.eu (in case of submission of a type II).

You should submit your query once and it is important that you submit it only to one dedicated email address. If you are uncertain of on a classification of the change, please choose one of the relevant email addresses. Your query will be channelled internally to the relevant service(s) that will respond to you.

[5] http://www.encepp.eu/encepp_studies/indexRegister.shtml

The Agency aims to respond to your query within 5 working days. To help us deal with your enquiry, please provide as much information as possible including the name of the medicinal product in your correspondence.

The above email address is only applicable when you have a pre-submission query. A dedicated Procedure Manager ("PM") will be assigned to the procedure once your application has been received. You will be able to contact this PM throughout the procedure.

14. Post-Authorisation Measures (PAMs)

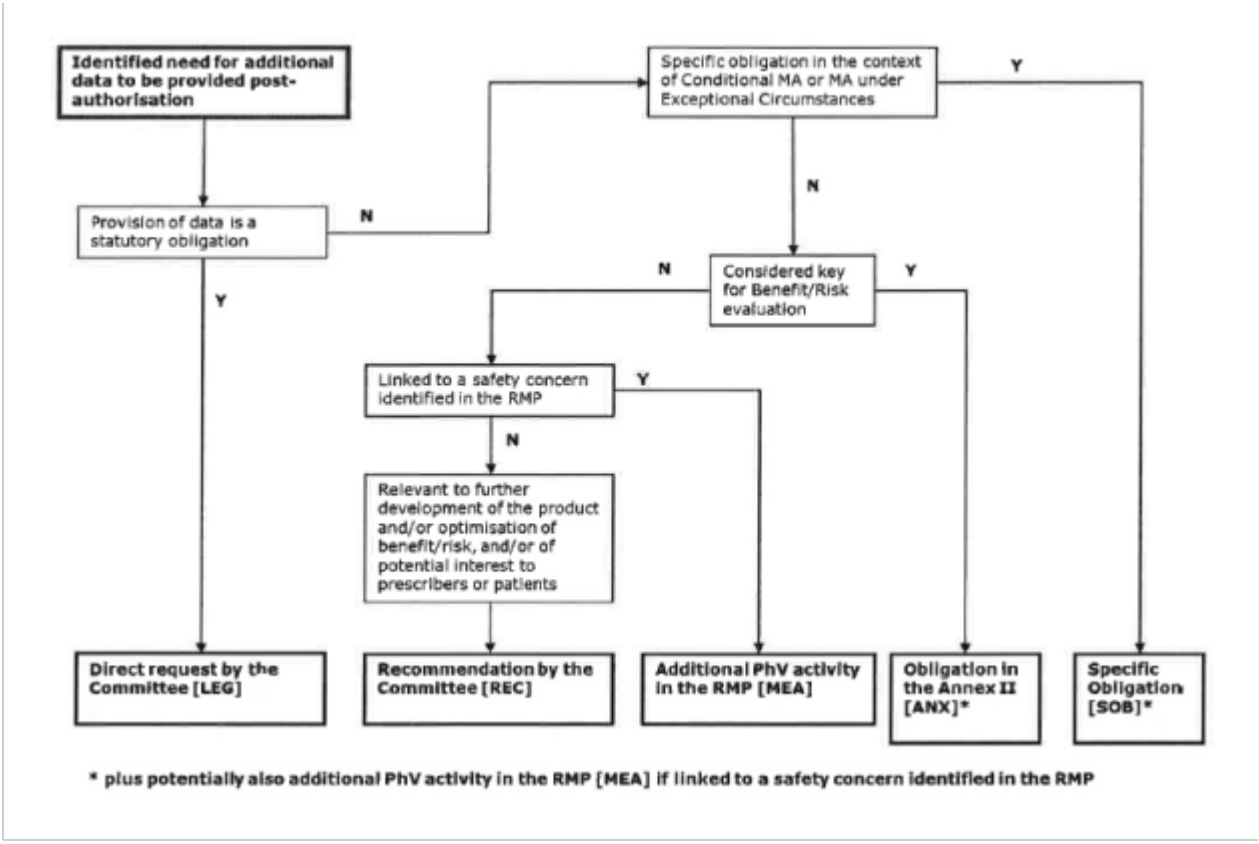
14.1. What are PAMs? Rev. Apr 2015

At the time of finalising a procedure or in follow up of a signal evaluation, the Agency's Committee(s) may agree that the applicant/MAH should provide 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 or quality of authorised medicinal products. Such post-authorisation measures (PAMs) may be aimed at collecting or providing data to enable the assessment of the safety or efficacy of medicinal products in the post-approval setting.

The existence of such a system of PAMs 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, which will present 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



Consequently, PAMs fall within one of the following categories [EMA codes[6]]:

- specific obligation [SOB]
- annex II condition [ANX]
- additional pharmacovigilance activity in the risk-management plan RMP [MEA] (e.g. interim results of imposed/non-imposed interventional/non-interventional clinical or nonclinical studies)
- legally binding measure [LEG] (e.g. cumulative review following a request originating from a PSUR or a signal evaluation [SDA], Corrective Action/Preventive Action (CAPA), paediatric [P46] submissions, MAH's justification for not submitting a requested variation)
- recommendation [REC] e.g. quality improvement

Only certain medicinal products can be subject to specific obligations (see also '*What is a Specific Obligation?*'). 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 during post-authorisation.

The wording of the PAM will describe the issue under investigation that has led to the request together with a clear outline of the studies 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

14.2. What is a specific obligation ['SOB']? Rev. Apr 2015

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. These may also be additional Pharmacovigilance activity and will be included as well in the RMP (category 2 studies). 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.

[6] These codes relate to the Agency's product and procedures tracking 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

As specific obligations are binding conditions to the marketing authorisation, any modification proposal by the MAH with regards to their **description or due date** (as described in Annex II of the product information) has to be submitted within an appropriate procedure , i.e. either within the annual re-assessment, the annual renewal or a variation application. (For further details, please refer to 'Practical questions and answers to support the implementation of the variations guidelines in the centralised procedure'.)

Interim results not impacting on the product information or on the description of the specific obligation can be submitted as a PAM as described below, if they are not part of the annual reassessment or annual renewal. (see: *How and to whom shall I submit my PAM data*?).

In case of interim results impacting on the product information, a variation should be submitted without waiting for the annual re-assessment or annual renewal.

Final results leading to the **fulfilment of the specific obligation** should be submitted within an appropriate procedure, i.e. either within the annual re-assessment, the annual renewal or a variation application. (For further details, please refer to 'Practical questions and answers to support the implementation of the variations guidelines in the centralised procedure')

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 imposed PASS protocol and results as described in the Agency's post-authorisation procedural advice on PASS and in the corresponding guideline on good pharmacovigilance practices (GVP) Module VIII - PASS.

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
- Practical questions and answers to support the implementation of the variations guidelines in the centralised procedure" EMA/427505/2013

14.3. What is an Annex II condition ['ANX']? Rev. Apr 2015

The European Commission can impose on the marketing authorisation holder (MAH) the obligation to conduct post-authorisation measures. These obligations can be imposed at the time of the granting of the marketing authorisation or later, as conditions to the marketing authorisation. These are conditions to the marketing authorisation included in Annex II.D of the marketing authorisation. These may also be additional Pharmacovigilance activity and will be included in the RMP (category 1 studies).

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. These can consist of post-authorisation safety or efficacy study.

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 as a variation application.(For further details, please refer to the 'Practical questions and answers to support the implementation of the variations guidelines in the centralised procedure.').

Interim results not impacting on the product information or on the condition as stated in the Annex II can be submitted as a PAM as described in question *How and to whom shall I submit my PAM data?*.

Final results leading to the fulfilment of the Annex II condition should be submitted as a variation application. (For further details, please refer to 'Practical questions and answers to support the implementation of the variations guidelines in the centralised procedure'.)

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 imposed PASS protocol and results as described in the Agency's post-authorisation procedural advice on PASS and in the corresponding guideline on good pharmacovigilance practice (GVP) Module VIII - 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
- Practical questions and answers to support the implementation of the variations guidelines in the centralised procedure EMA/427505/2013

14.4. What is an additional Pharmacovigilance (PhV) activity in the RMP ['MEA']? Rev. Apr 2015

Additional pharmacovigilance activities in the RMP (category 3 studies) 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.

All relevant milestones, 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 pharmacovigilance 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.) should be submitted via the appropriate variation procedure to amend the RMP (For further details, please refer to 'Practical questions and answers to support the implementation of the variations guidelines in the centralised procedure').

Information not impacting on the product information or description/due date of the measure itself, (e.g. interim results, can be submitted as a self-standing PAM as described in question 'How and to whom shall I submit my PAM data?').

Submissions of final study reports leading to the fulfilment of a MEA should be addressed via the appropriate variation procedure. (see also: *Should I submit a variation to fulfil a PAM?*).

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
- Practical questions and answers to support the implementation of the variations guidelines in the centralised procedure EMA/427505/2013

14.5. What is a legally binding measure ['LEG']? Rev. Apr 2015

Some post-authorisation measures are already defined as statutory obligations in pharmaceutical legislation. As such, they have to be fulfilled by the MAH upon request of the Agency and its committees. Examples for such directly binding legal measures evaluated as PAMs are:

- Requests for provision of data as a stand-alone submission (e.g. cumulative review following a PSUR assessment).
- Requests for supplementary information to evaluate a signal (see EMA's questions and answers on signal management)
- Request for updates of the product information
- Obligations to submit any data requested in relation to CAPA (corrective action or preventive action) in the context of inspections
- Submission of final results of study involving paediatric patients submitted in fulfilment of Article 46 of the paediatric regulation

Where requested, these are directly addressed to the MAH by the Agency, either within the assessment report of the committee(s) or within a letter informing about the committee(s)'(s) conclusions, and have to be responded to within the stated time frame.

Requests for updates of the product information should be addressed via a variation; a scientific justification for not submitting a requested variation should be submitted as a PAM.

When responding to these requests, the MAH should select the "LEG" PAM type in point 12 of the template table of the cover letter except for:

- Submission of final results of study involving paediatric patients submitted in fulfilment of Article 46 of the paediatric where the MAH should select the "P46" PAM type in point 12 of the cover letter.

- Provision of supplementary information to evaluate a signal or a scientific justification for not submitting a requested variation following a signal assessment, where the MAH should select the "SDA" PAM type in point 12 of the cover letter.

In accordance with the Paediatric legislation, MAHs should submit paediatric studies within six months of their completion and irrespective of whether it is part of a PIP (completed or not yet completed) or not, or whether it is intended for submission later on as part of a variation, extension or new stand-alone marketing-authorisation application.

References

- Directive 2001/83/EC
- Regulation (EC) No 726/2004
- Questions and answers on signal management
- Submission of Article-46 paediatric studies: questions and answers
- Communication from the Commission — Guideline on the format and content of applications for agreement or modification of a PIP and requests for waivers or deferrals and concerning the operation of the compliance check and on criteria for assessing significant studies
- Practical questions and answers to support the implementation of the variations guidelines in the centralised procedure EMA/427505/2013

14.6. What is a recommendation ['REC']? Rev. Apr 2015

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.

This information can be submitted as a PAM however 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 (see: *How and to whom shall I submit my PAM data?*).

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.)

References

- Directive 2001/83/EC
- Regulation (EC) No 726/2004

14.7. Can the classification of my PAM change during its life-cycle? Rev. Apr 2015

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 information that has become available and will be justified in the assessment report where the measure is, as a consequence, up- or downgraded.

14.8. When shall I submit my PAM? Rev. Apr 2015

The MAH shall submit the PAM data according to the timeframe specified by the Agency's committee(s) as specified either in the annex II, the RMP or the respective committee assessment. When requested, the MAHs should propose due dates for the submission of the post-authorisation data that are realistic and proportionate to the uncertainty to be addressed which are then subject to agreement with the Agency's committee(s).

Data submitted as PAM should be submitted as per the deadline specified by the Committee(s), and will start 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 start in accordance with the start date of the following month.

If the MAH is unable to provide the required data by the specified deadline, he 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 is subject to agreement by the committee(s). These submissions should be done as follows:

- Changes to the due date for a SOB, Annex II condition or category 3 study in the RMP should be submitted as type IB variation category C.I.11.z, include the updated RMP and/or product information as applicable (one variation per change of due date is required).
- Changes to category 4 studies listed in the RMP can be updated in the context of any other RMP update.
- Proposals for changes to directly legally binding measures (LEG including SDA) have to be notified in writing, together with an appropriate justification, and have to be agreed as well by the Agency's Committee(s). Such requests should be sent to PAMquery@ema.europa.eu.

In the case of a non-justifiable delay, the Agency's Committee will consider taking regulatory action (see also next question).

References

- Directive 2001/83/EC
- Regulation (EC) No 726/2004
- Guidelines on the details of the various categories of variations, on the operation of the procedures laid down in Chapters II, IIa, III and IV of 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 and on the documentation to be submitted pursuant to those procedures (Guidelines on Variations)
- Practical questions and answers to support the implementation of the variations guidelines in the centralised procedure EMA/427505/2013

14.9. Under which procedure should I submit my PAM? NEW Apr 2015

The procedure under which the PAM should be submitted will depend on the content and type of information submitted as part of the PAM, as summarised in the table below:

PAM	Submission	Procedure/Type of application
Specific obligation (category 2) [SOB]	Non-interventional PASS	See Post Authorisation Safety Study
	• Protocol and substantial amendments	Article 107n-o
	• Interim results	See below as for other SOBs
	• Final results	Article 107p-q
	Others SOB than non-interventional PASS	
	• Protocol (where requested to be submitted)	Stand-alone PAM *Where a protocol is not requested to be submitted by the Agency's Committee, the MAH should consider to seek scientific advice*
	• Interim results	Conditional renewal, annual re-assessment *(Note: if submission of interim results is requested outside of the timelines of the renewal or annual re-assessment, these can be submitted as stand-alone PAM, if no changes to the PI are proposed), alternatively a type II would be required.*
	• Final results	Conditional renewal, annual re-

		assessment or type II variation, depending on the timelines.
Annex II condition (category 1, PAES) [ANX]	Non-interventional PASS and results	See Post Authorisation Safety Study
	• Protocol and substantial amendments	Article 107n-o
	• Interim results	See below as for other studies
	• Final results	Article 107p-q
	Others studies than non-interventional PASS (including PAES)	
	• Protocol (where requested to be submitted)	Stand-alone PAM *Where a protocol is not requested to be submitted by the Agency's Committee, the MAH should consider to seek scientific advice*
	Interim results • No changes to PI • Changes to PI	 Stand-alone PAM Type II variation
	Other studies: Final results	Type II variation
Additional Pharmacovigilance activity in the RMP (category 3) [MEA]	Protocol (as requested by Committee and reflected as a milestone in the RMP)	Stand-alone PAM *Where a protocol is not requested to be submitted by the Agency's Committee, the MAH should consider to seek scientific advice*
	Interim results • No changes to PI • Changes to PI	 Stand-alone PAM Type II variation
	Final results	Type II variation
Legally binding measure [LEG] (including [SDA] and [P46])	Provision of data requested by the Committee (e.g. cumulative review, CAPA, interim study results) *([SDA] when related to a signal assessment)*	
	• with no changes to the PI	Stand-alone PAM
	• with PI changes	Type II variation
	Final study report	Type II variation
	Justification for not submitting a variation *([SDA] when related to a signal assessment, otherwise [LEG])*	Stand-alone PAM
	Submission of final results of study involving paediatric patients in	

	accordance with Article 46 of the paediatric regulation [P46]	
	• No changes to PI	Stand-alone PAM [P46]
	• Changes to PI	Type II variation
Recommendation [REC]	Interim results • No changes to PI • Changes to PI	 Stand-alone PAM Type II variation
	Final results	Type II variation
	ERA study results with no impact to PI	Type IB C.I.z variation

Where the deliverable of a measure is submitted as part of another procedure, the structure of the submission package should follow the requirements of this procedure and the MAH should indicate in the template table of cover letter of the application which PAM is being addressed, including the EMA reference number and the full description of the relevant PAM. The MAH does not need to submit a separate 'stand-alone' submission of the PAM data.

References

- Directive 2001/83/EC
- Regulation (EC) No 726/2004
- EMA post-authorisation procedural advice - variations
- Guidelines on the details of the various categories of variations, on the operation of the procedures laid down in Chapters II, IIa, III and IV of 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 and on the documentation to be submitted pursuant to those procedures (Guidelines on Variations)
- Practical questions and answers to support the implementation of the variations guidelines in the centralised procedure EMA/427505/2013

14.10. How shall I structure my PAM submission dossier? Rev. Apr 2015

The Agency will check PAM submissions with respect to the Guidelines on Variations to ensure that it does not fall within one of the classifications. In this regard, the Agency will reject any PAM submission that should be filed as a variation application (see also the 'Practical Questions and Answers to support the implementation of the Variations Guidelines in the centralised procedure'). In such cases, the eCTD submission of the variation application should provide a reference to the PAM eCTD submission for this sequence to be closed. Where the MAH is requested to resubmit as a variation application, the start of the variation procedure will be upon receipt of the complete application according to the next upcoming starting date as per published time table for Type II.

'Stand-alone' PAM submission should include:

- A cover letter indicating the full description and – as available - the reference number(s) of the PAM(s) (The number(s) to be quoted are the number(s) attributed by the Agency at the time of adoption of the PAM including – for SDAs – the EPITT number). The letter should mention the due date including any agreed extension of it. The cover letter should also contain the template table to facilitate submission and registration. In this table, the MAH should indicate whether the PAM relates to quality, pre-clinical, clinical or pharmacovigilance, whether it fulfils Article 46 of the paediatric regulation or is a response to a signal, among others. The completed table should also indicate whether the submission relates to protocol/ interim results of interventional/ non-interventional studies or follow-up queries further to the review of data by the PRAC or the CHMP. The MAH should describe from which procedure this PAM originates (initial MA, type II variation, PSUR/PSUSA, etc) and whether it is a follow-up to a previous PAM (responses to questions raised during the assessment of a PAM). This information will allow the involvement of the appropriate Committee(s) and identification of the timetable to be applied.
- All supportive documentation relevant to the fulfilment of the PAM should be presented in accordance with the appropriate headings and numbering of the European Common Technical Document (EU-eCTD) format.
- Any scientific advice or protocol assistance obtained in relation to the fulfilment of PAMs concerned should be included.

References

- Template for cover letter
- EMA post-authorisation procedural advice - variations
- Regulatory and procedural guidance on dossier format

14.11. How and to whom shall I submit my PAM data? Rev. Aug 2014

Please refer to question 22.5 Other – How and to whom shall I submit my application?

14.12. How shall my submission of PAM be handled (timetable), and what could be the outcome of the evaluation? Rev. Apr 2015

This section only applies to submissions of PAM data as a ‘stand-alone’ submission.

Most PAMs will be evaluated by CHMP (and CAT if an advanced therapy medicinal product).

However, PRAC will lead the review of protocols or interim results of non-interventional safety studies and in any follow-up PAM to a procedure primarily assessed by PRAC (e.g: cumulative safety review requested further to the assessment of PSUR [LEG] or a signal [SDA]).

PAMs will be handled using one of the three timetables:

- CHMP led PAM assessment timetable
- PRAC led PAM assessment timetable

- Urgent PRAC led PAM assessment timetable, e.g. for urgent signal PAMs [SDA]

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 Agency will inform the MAH of the outcome of the committee's evaluation in writing. The following may be envisaged depending on committee's conclusion:

- the PAM is fulfilled and no further action is required
- the PAM is not yet fulfilled, as further clarifications or additional data are required. A request for supplementary information to be addressed by the MAH within a given time frame will be issued and a follow-on PAM (such as MEA 00X.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 fulfilled but follow-up regulatory action is required, e.g. a request for variation and this will result in a new PAM being issued.

References

- Directive 2001/83/EC
- Regulation (EC) No 726/2004

14.13. Do I have to pay fees for the PAM data submission? Rev. Apr 2015

There is no fee payable for a PAM stand-alone submission.

14.14. How are PAMs enforced? Rev. Apr 2015

The Agency will keep a record of the post-authorisation measure and its due date in its database.

In case of overdue measures or a MAH being found non-compliant in satisfying a post-authorisation measure, the responsible committee will consider the need for appropriate actions to be taken including involvement of the relevant committee(s).

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

14.15. Will there be any publication on the outcome of my PAM? Rev. Apr 2015

Outcome of PAMs are not published in the EPAR 'Procedural steps taken and scientific information after the authorisation'. However, assessment reports for data submitted in accordance with Article 46 of the paediatric regulation and PRAC recommendations on signals are published on the Agency's website.

Reference

- EPARs

14.16. Who should I contact if I have a question when preparing my application? NEW Sep 2014

If you cannot find the answer to your question in the Q&A when preparing your application, please contact us using the following email address: PAMquery@ema.europa.eu

The Agency aims to respond to your query within 5 working days. To help us deal with your enquiry, please provide as much information as possible including the name of the product in your correspondence.

The above email address is only applicable when you have a pre-submission query. A dedicated Procedure Manager (PM) will be assigned to the procedure once your application has been received. You will be able to contact this PM throughout the procedure.

14.17. Who is my contact at the European Medicines Agency during post-authorisation procedures? NEW Apr 2015

Please refer to question 22.8 Other - Who is my contact at the European Medicines Agency during post-authorisation procedures?.

15. PSURs

15.1. What is a Periodic Safety Update Report (PSUR)? Rev. Sep 2014

Periodic safety update reports are pharmacovigilance documents intended to provide a safety update resulting in an evaluation of the impact of the reports on 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 the Regulation (EC) No 726/2004 and the Directive 2001/83/EC

The format of PSURs shall follow the structure described in the Commission implementing Regulation (EU) No 520/2012.

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 Module VII "Periodic safety update report" of the Guideline on good pharmacovigilance practices (GVP) and in the following questions and answers.

References

- Regulation (EC) No 726/2004
- Directive 2001/83/EC
- Commission implementing Regulation (EU) No 520/2012 on the performance of pharmacovigilance activities
- Guideline on good pharmacovigilance practices (GVP) – Module VII – Periodic safety update report
- European Commission Question and Answers on transitional arrangements concerning the entering into force of the new pharmacovigilance rules
- EMA - HMA Questions and answers on practical transitional measures for the implementation of the pharmacovigilance legislation
- ICH guideline E2C (R2) Periodic benefit-risk evaluation report (PBRER)
- Guideline on good pharmacovigilance practices, Annex I - Definitions

15.2. What is the scope of PSUR assessment under the EU single assessment? Rev. Jul 2015

The Pharmacovigilance Risk Assessment Committee (PRAC) is in charge of issuing recommendation on the PSUR assessment for a single centrally authorised product and of the EU PSUR single assessment.

The EU PSUR single assessment, referred also as PSUSA, 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 and for which the frequency and dates of submission of PSURs have been harmonised in the list of EU reference dates (referred also as EURD list). These PSURs will

be jointly assessed by the PRAC or a Member State appointed by the CMDh and result in one single assessment report, which will be shared amongst all the Marketing Authorisation Holders (MAHs) whose medicinal product(s) are part of the PSUR single assessment procedure. Hence, the data presented in the PSUR(s) should be solely for the purposes of the concerned procedure, as the single assessment report will not be redacted with respect to individual products before it is shared. Of note, PSUR related data presented in agreement with GVP module VII on PSURs as such are not considered to be commercially confidential.

Overall, the PRAC will issue a recommendation for the assessment of the following PSURs:

- PSURs of centrally authorised product(s);
- PSURs of any mix of centrally authorised products and nationally authorised products (including through the mutual recognition and decentralised procedures);
- PSURs of nationally authorised products.

Please note that, for nationally authorised medicinal products which are marketed in only one Member State and whose active substance or combination of active substances is included in the EURD list, the MAH should submit a PSUR as part of PSUSA procedure. Note that a PSUSA is foreseen for each active substance or combination of active substances registered in the EURD list.

The PSUSA involving only nationally authorised medicinal products will start at the end of 2014 i.e. products with data lock points (DLPs) falling on or after the 01/09/2014. Until the single assessment procedure involving only nationally authorised medicinal products starts MAHs should follow where applicable the “List of substances under PSUR Work Sharing scheme and other substances contained in Nationally Authorised Products with DLP synchronised”. For more information about this list please refer to the CMDh webpage for the PSUR Work sharing and Synchronisation Project.

For purely nationally authorised medicinal products, containing substances or combination of actives substances not included in the EURD list, for which no PSUSA procedure has been established, the assessment of the PSURs will remain at national level.

Purely nationally authorised medicinal products are considered those which contain substances or a combination of actives substances which are only authorised in one Member State.

Reference

- Guideline on good pharmacovigilance practices (GVP) – Module VII – PSUR

15.3. How shall I present my PSUR and in which format? Rev. Jul 2015

The format and content of the PSUR, is legally required according to Commission implementing Regulation (EU) No 520/2012 since January 2013 and is further described in the Guideline on good pharmacovigilance practices (GVP) Module VII – Periodic safety update report.

In addition, the required format and content of PSURs in the EU are based on those for the Periodic Benefit Risk Evaluation Report (PBRER) described in the ICH-E2C(R2) guideline (see Annex IV ICH-E2C(R2). To keep the terminology consistent with the one used in the EU legislation, the new PBRER continues to be described as PSUR.

Unless otherwise requested by competent authorities, the marketing authorisation holder shall prepare a single PSUR for all its medicinal products containing the same active substance with information covering all the authorised indications, route of administration, dosage forms and dosing regiments, irrespective of whether authorised under different names and through separate procedures. Even if a single PSUR is prepared for several products, please note that for medicinal products with documentation previously submitted in eCTD format, PSURs should be presented in a new eCTD sequence in the respective eCTD lifecycle of the concerned product. Where relevant, data relating to a particular indication, dosage form, and route of administration or dosing regimen, shall be presented in a separate section of the PSUR and any safety concerns shall be addressed accordingly.

Within the PSUR, the marketing authorisation holder is required to consider the impact of the data and evaluations presented within the report, on the marketing authorisation. Based on the evaluation of the cumulative safety data and the risk-benefit analysis, the marketing authorisation holder shall draw conclusions in the PSUR as to the need for changes to the product information of the products covered by the PSUR. For the purpose of analysing the impact of the PSUR data, the MAH can establish a so-called reference product information which should include “core safety” and “authorised indications” components, as explained in the GVP module VII on PSURs (section VII.B.4. ‘Reference information’). The changes proposed to the labelling can be based on the reference product information. However as the reference product information might be different for the various EU product information, it is therefore essential that the MAH considers the proposed changes for the reference product information in the context of the different EU product information for the products covered by the submitted PSUR and this should be clearly discussed in both the conclusions and actions section of the body of the PSUR as well as in the EU regional appendix.

In the EU regional appendix, sub-section “Proposed product information” of the PSUR, the marketing authorisation holder should provide their proposal for product information (SmPC and package leaflet) changes based on the above mentioned evaluation. These should take into account all EU authorised indications for products containing that active substance or combination of active substances. For marketing authorisation holders of nationally authorised products with a large number of marketing authorisations with different product information, the Agency will also accept that the core message of the proposed changes to the product information be included in the EU regional appendix as described below (see also question below “How can I propose changes to the Product Information within the PSUR for NAPs which are part of an EU single assessment?”.

The submission should include a cover letter containing the following formatted table template to facilitate the registration of the submission. This table should be completed in accordance with the published EURD list, where the procedure number is the combination of a unique ID and the applicable Data Lock Point (DLP) in YYYYMM format. For any medicinal product which is nationally authorised (i.e. through MRP, DCP or National procedures) it is important to highlight in Annex I of the cover letter the legal basis under which the product was authorised, in particular for those medicinal products authorised under Articles 10(1), 10a, 14 and 16a of Directive 2001/83/EC.

All the entries in the EURD list have been assigned a procedure number presented in the column “Procedure number of the PSUR single assessment”. This procedure number was initially only applicable to PSUSA procedures containing CAPs and NAPs. The number should be applied now to all procedures starting from October 2014 onwards which contain single CAPs, a mixture of CAPs, a mixture of NAPs or a mixture of CAPs and NAPs.

In order to facilitate the identification of procedures containing centrally and/or nationally authorised substances, the extra columns “Centrally Authorised Product (CAP) and “Nationally authorised product (NAP)” have been added in the EURD list”.

In line with article 57(2) of Regulation (EU) No 1235/2010 all holders of marketing authorisations for medicines in the European Union and the European Economic Area must submit information to the European Medicines Agency on authorised medicines and keep this information up-to-date. This is a legally binding requirement from the EU pharmaceutical legislation. The Agency uses this information to support the analysis of data, regulatory activities and communication. In relation to the submission of PSURs, this will facilitate the processing of the submissions in the upcoming PSUR Repository.

Please see question "*To whom should I submit my PSUR?"* for further details on submission requirements.

References

- Directive 2001/83/EC
- Guideline on good pharmacovigilance practices (GVP) – Module VII – Periodic safety update report
- Commission implementing Regulation (EU) No 520/2012 on the performance of pharmacovigilance activities
- ICH guideline E2C (R2) Periodic benefit-risk evaluation report

15.4. How can I submit the proposed changes tot the Product Information within the PSUR for NAPs which are part of an EU single assessment? NEW Dec 2014

According to the guidance set out in the GVP module VII on PSURs, proposed changes to the EU labels as a result of the PSUR data should be provided under Section VII.C.5.1. PSUR EU regional appendix, sub-section "Proposed product information" of the PSUR.

It should be presented as a tracked change version of each EU SmPCs and package leaflets of the products concerned and each product information should be translated into English language including the tracked changes proposed, in order to enable the EU single assessment.

However, this can result in having to submit a large number of sets of tracked change Product Information with the additional burden of providing translations. Hence MAHs can consider the option to focus on the proposed amendments to SmPC and Package Leaflet. In such case, only the amended parts of the SmPC and Package Leaflet should be provided in track changes and in English language under the EU regional appendix.

In case no changes to the Product Information are being proposed as part of the PSUR, the MAH should not include any product information within the EU regional appendix.

Reference

- Guideline on good pharmacovigilance practices (GVP) – Module VII –Periodic safety update report

15.5. What is the List of European Union reference dates (EURD list) and frequency of submission of PSURs? Rev. Sep 2014

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 European Union reference date (EURD) corresponds to the date of the first or the earliest known date of the marketing authorisation in the EU of a medicinal product containing the active substance or combination of active substances.

In addition to the EU reference dates and frequencies of PSURs, the EURD list also provides the Data Lock Point (DLP) of the next PSUR submissions.

The EURD list facilitates 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 one single assessment of PSURs for products containing the same active substance.

The PSUR frequency as published on the EURD list for a given active substance or combination of active substances overrules the standard submission cycle (i.e. 6-monthly, yearly and thereafter 3-yearly) set out in the legislation and any condition related to the frequency of submission of PSURs included in the Marketing Authorisation. However, National Competent Authorities (NCAs) may still request the submission of a PSUR at any given time.

The EURD list is a living document, meaning 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 or requests from the marketing authorisation holders.

Full information on the EURD list is included in the GVP Module VII – Periodic safety update report and the introductory cover note to the EURD list.

For guidance on submission of requests for amendment of the EURD list, please refer to the question "*How can I request to amend the list of EU reference dates?*".

References

- Directive 2001/83/EC
- Guideline on good pharmacovigilance practices – Module VII – Periodic safety update report
- List of European Union reference dates and frequency of submission of Periodic Safety Update Reports Introductory cover note

15.6. When does the EURD list become legally binding? Rev. Sep 2014

The EURD list is updated on a monthly basis and changes in the PSUR submission frequencies and dates of submission come into force 6 months after its publication. This publication occurs after adoption of the EURD list by the CHMP and CMDh following consultation of the PRAC.

Since changes become binding 6 months after publication, there might be situations where "*ad hoc*" PSUR submissions would be necessary prior to the new frequency taking effect.

A note on this "*ad hoc*" PSUR will also be included in the EURD list.

Reference

- Directive 2001/83/EC

15.7. How can I request to amend the list of EU reference dates? Rev. Mar 2013

Marketing authorisation holders can submit requests to the CHMP or the CMDh, as appropriate, to determine the Union reference dates or to change the frequency of submission of PSURs 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 medicine's website.

For more details on how to submit amendments to the list, please refer to the EURD list cover note (sections 2 and 5).

References

- Directive 2001/83/EC
- Guideline on good pharmacovigilance practices (GVP) Module VII – Periodic safety update report

15.8. Do I have to submit a PSUR if the active substance/combination of active substances of my medicinal product is not on the EURD list? Rev. Sep 2014

If the active substance contained in the medicinal product is not included in the EURD list, the MAH should continue to submit PSUR to the National Competent Authority (NCA) where the product is authorised in accordance with the conditions specified in the marketing authorisation (MA), or otherwise according to the standard submission schedule of PSURs (i.e. 6-monthly intervals, yearly and thereafter 3-yearly). Marketing authorisation holders for certain medicinal products, such as medicinal products authorised under Article 10(1) or 10a of Directive 2001/83/EC, a homeopathic simplified registration or a traditional-use registration are not required to submit PSURs, unless there

are specific requirements in the MA for the product. PSURs shall also be submitted upon request of national competent authorities.

For more details on PSUR submissions for generics, products containing well-established substances, homeopathic or herbal medicinal products, please refer to the question *Do I have to submit a PSUR my medicinal product if it is a generic, a product containing a well-established substance, a homeopathic or herbal medicinal product?*

15.9. Do I have to submit a PSUR if the combination of active substances of my product is not on the EURD list but one or more individual components are listed? Rev. Mar 2013

If the specific fixed dose combination is not listed in the EURD list, PSURs should not be submitted according to the EURD list entry of one or more individual components. However PSURs should be submitted as specified in the conditions of the marketing authorisation for the combination product (if any), or otherwise according to the standard submission cycle (i.e. 6-monthly, yearly and thereafter 3-yearly) unless the combination medicinal product falls within the categories of medicinal products exempted from the obligation to submit PSURs.

MAHs or National Competent Authorities 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 requests to amend the EURD list can be found on the EURD list webpage.

15.10. Do I have to submit a PSUR for my medicinal product if it is a generic, a product containing a well-established substance, a homeopathic or herbal medicinal product? Rev. Sep 2014

Medicinal products authorised under Articles 10(1), 10a, 14 or 16a of Directive 2001/83/EC are exempted from routine submission of PSURs 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'). 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.

For medicinal product containing a known active substance, the requirement to submit a PSUR is only waived for those authorised under the legal basis mentioned above. Medicinal products containing a known substance authorised through another legal basis are required to submit PSURs.

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.

15.11. 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? Rev. Sep 2014

Medicinal products authorised under Articles 10(1), 10a, 14 or 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 by the MAH by submitting the appropriate variations taking account of the latest scientific knowledge or conclusions of assessments and recommendations made public by means of the EMA and National Competent Authority websites.

15.12. Do I have to submit a PSUR for my hybrid medicinal product? Rev. Sep 2014

Medicinal products authorised under Article 10(3) of Directive 2001/83/EC (hybrid application) are not exempted from the obligation to submit PSURs.

15.13. If the medicinal product is not marketed, is the MAH required to submit a PSUR? Rev. Mar 2013

MAHs are required to submit PSURs once a medicinal product is authorised in the EU, regardless of its marketing status.

15.14. Do PSURs need to contain case narratives and line listings? Rev. Sep 2014

The PSUR should focus on summary information, scientific assessment and integrated benefit-risk evaluation.

Marketing authorisation holders are not required to systematically include listings of individual cases, including case narratives, in the PSUR. However, they shall provide case narratives in the relevant risk evaluation section of the PSUR where integral to the scientific analysis of a signal or safety concern in the relevant risk evaluation section.

In this context “case narrative” refers to clinical evaluations of individual cases rather than the CIOMS narratives included in the individual case safety report (ICSR).

During the assessment of the PSUR, line listings for adverse reactions of special interest may be requested by the PRAC.

Reference

- Guideline on good pharmacovigilance practices (GVP) Module VII – Periodic safety update report

15.15. Can I submit a RMP update together with my PSUR? Rev. Sep 2014

A Risk Management Plan (RMP) update can be submitted with a PSUR for single centrally authorised medicinal product (CAP) or a mixture of CAPs belonging to the same Global Marketing Authorisation (GMA) when the changes to the RMP are a direct result of data presented in the PSUR. In this case no stand-alone RMP variation is necessary.

If the above does not apply, the updated RMP should be submitted as a stand-alone variation.

As an interim measure, submission of RMP updates cannot be accepted with PSURs subject to a PSUSA of:

- a mixture of CAPs pertaining to different GMAs;
- a mixture of centrally and nationally authorised medicinal products;
- a mixture of NAPs.

In these cases, MAHs should submit the updated RMPs as part of another procedure affecting the RMP, if one such procedure is foreseen. Alternatively, MAHs should submit a separate variation to update their RMP.

If an RMP is incorrectly submitted with a PSUR, this will be identified at the start of the procedure and both the MAH and PRAC Rapporteur will be made aware that the RMP will not be assessed and should be submitted through another appropriate procedure. If the RMP was submitted as an eCTD the MAH will have to delete that version of the RMP in the next sequence to maintain the correct lifecycle of the product.

The assessment of a PSUR may result in a recommendation to update the content of the RMP through a subsequent variation.

For nationally authorised medicinal products (i.e. authorised through MRP, DCP or National procedures), any RMP update should be submitted via a variation procedure to the National Competent Authority for assessment, even if PSURs are part of a PSUSA.

15.16. What are the timelines for the submission of PSURs? Rev. Sep 2014

Marketing authorisation holders should submit to the Agency PSURs as established in GVP Module VII 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); or
- 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 deadline for the submission of PSURs (Day 70 or Day 90 following the DLP) is published in the EURD list. This deadline is legally binding and must be adhered to.

The timetables for the PSUR assessments are published on the EMA website.

References

- Guideline on good pharmacovigilance practices (GVP) Module VII – Periodic safety update report, Rev 1 (EMA/816292/2011, 09 December 2013)
- Timetable: Periodic Safety Updated Reports (PSUR)

15.17. To whom should I submit my PSUR? Rev. Jul 2015

The use of the PSUR Repository will become mandatory for all PSUR submissions as of **13 June 2016** (EMA news item). From this date onwards, the MAHs will be required to submit PSURs to the EMA via the PSUR Repository only and there will no longer be any requirement to submit PSURs to National Competent Authorities. This will affect PSURs for both centrally and nationally authorised medicinal products.

There is a transition period until 13 June 2016 and the submission requirements for PSURs during that period are as follows:

For Centrally Authorised Products (CAPs):

- To the European Medicines Agency : PSUR submission (in eCTD format only) through eSubmission Gateway/ Web Client including XML delivery file created in the PSUR Repository user interface
- To the Rapporteur appointed for the procedure and all other Committee Members of the PRAC: follows CAP Dossier Requirements document for NCA submissions for countries not yet using the Common Repository

For Nationally Authorised Products (NAPs):

A) Mixed CAP/NAP PSUSA procedure:

- To all Member States in which the medicinal product has been authorised -(refer to Requirements for submissions for Periodic Safety Update Reports (PSUR) for MRP, DCP and National Products (NAPs))
- To the PRAC Rapporteur if different from one of the Member States where the product is authorised (refer to Requirements for submissions for Periodic Safety Update Reports (PSUR) for MRP, DCP and National Products (NAPs)
- To the European Medicines Agency – submission (in eCTD or Non eCTD electronic Submission (NeeS) format) through eSubmission Gateway/ Web Client including XML delivery file created in the PSUR Repository user interface.

B) NAPs only PSUSA procedure:

- To all Member States in which the medicinal product has been authorised -(refer to Requirements for submissions for Periodic Safety Update Reports (PSUR) for MRP, DCP and National Products (NAPs))

- Lead Member State appointed for the procedure (if different from where the product is authorised) (refer to Requirements for submissions for Periodic Safety Update Reports (PSUR) for MRP, DCP and National Products (NAPs))
- To the European Medicines Agency – submission (in eCTD or Non eCTD electronic Submission (NeeS) format) through eSubmission Gateway/ Web Client including XML delivery file created in the PSUR Repository user interface.

In order to determine the type of procedure (CAPs, CAP/NAP, NAPs only) please refer to the EURD list.

From 1 September 2015, the use of the XML delivery file for all PSUR submissions via the eSubmission Gateway and/or the Web Client will become mandatory. After this date, it will no longer be possible to submit PSUR submissions using the existing file naming convention. The mandatory use of the PSUR XML delivery file is introduced to harmonise the submission mechanism for all PSURs and it will apply to all types of PSUR and PSUR supplementary information submissions.

For technical queries, you can contact us using the following email address instead: eCTD@ema.europa.eu

For technical issues with the EMA gateway/webclient, you can contact us using the following email address instead: gatewaysupport@ema.europa.eu

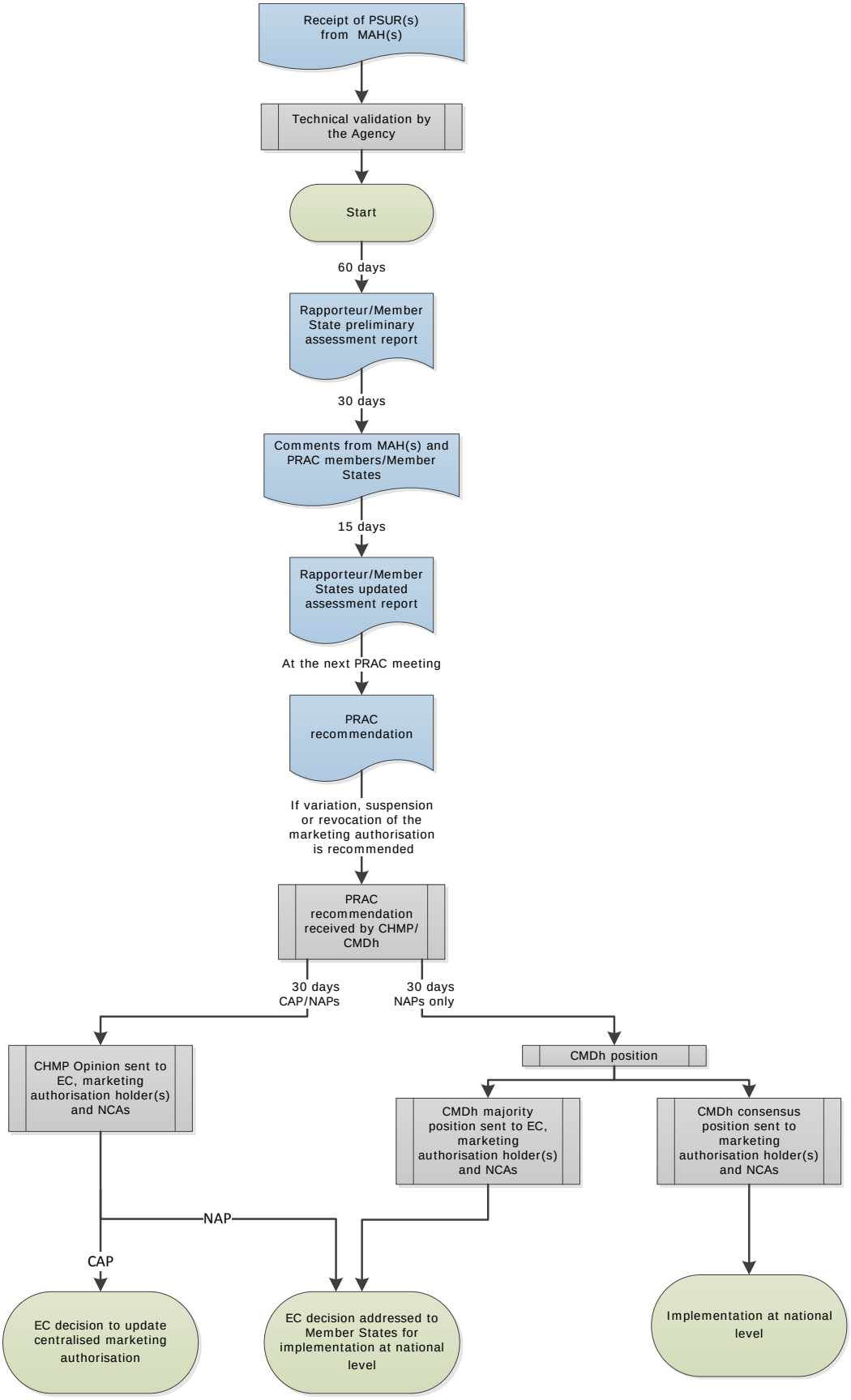
For issues with the PSUR Repository, you can contact us using the following email address instead: psurrepository@ema.europa.eu

References

- Dossier requirements for Centrally Authorised Products (CAPs)
- Requirements for submissions for Periodic Safety Update Reports (PSUR) for MRP, DCP and National Products (NAPs)
- CMDh PSUR submission guidance document
- eSubmission website
- eSubmission Gateway / Web Client website
- Common Repository website

15.18. How will my PSUR submission be handled? Rev. Dec 2014

The PSUR assessment under a PSUSA procedure is as follows, regardless whether it refers to one or more centrally authorised medicinal products, a mix of centrally authorised medicinal products and nationally authorised products or nationally authorised products only.


Receipt of PSUR(s) from MAH(s)
Technical validation by the Agency
Start
60 days
Rapporteur/Member State preliminary assessment report
30 days
Comments from MAH(s) and PRAC members/Member States
15 days
Rapporteur/Member States updated assessment report
At the next PRAC meeting
PRAC recommendation
If variation, suspension or revocation of the marketing authorisation is recommended
PRAC recommendation received by CHMP/ CMDh
30 days CAP/NAPs
30 days NAPs only
CHMP Opinion sent to EC, marketing authorisation holder(s) and NCAs
CMDh position
CMDh majority position sent to EC, marketing authorisation holder(s) and NCAs
CMDh consensus position sent to marketing authorisation holder(s) and NCAs
NAP
CAP
EC decision to update centralised marketing authorisation
EC decision addressed to Member States for implementation at national level
Implementation at national level

The assessment of a PSUR or several PSURs for the same active substance(s) is done by the PRAC or in case of nationally authorised products only by the appointed Member State, respectively. The timelines for assessment are for up to 134 days followed by 67 days of Commission decision making process (if applicable). Upon technical validation by the EMA of the submitted PSUR(s), the following timetable shall apply:

Day	Action
Day 0	Start of the procedure according to the published timetable
Day 60	PRAC Rapporteur's / Member State preliminary assessment report
Day 90	MAH and PRAC members' / Member States comments
Day 105	PRAC Rapporteur's / Member State updated assessment report (if necessary)
Day 120	PRAC recommendation adoption with the final PRAC assessment report
Day 134	CHMP opinion / CMDh position (in case PRAC recommends a variation, suspension or revocation of the MA)

The MAH is expected to provide, as applicable, by Day 90:

- responses to the "request for supplementary information" as outlined in the relevant section of the PRAC Rapporteur / Member State PSUR preliminary assessment report,
- comment on the proposed wording (in case the recommendation is a variation),
- propose a wording in case the recommendation is a variation but no exact wording is proposed by the PRAC Rapporteur / Member State,
- provide a justification in case the MAH does not agree with the PRAC Rapporteur / Member State recommendation to vary, suspend or revoke the MA; and/or
- include additional comments or clarification deemed necessary by the MAH.

The MAH's comments should be submitted as per the PSUR dossier submission requirements detailed in the question "*To whom should I submit my PSUR?".*

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 the PRAC recommends any regulatory action i.e. variation, suspension or revocation of the marketing authorisation, the PRAC recommendation 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, where the procedure includes at least one CAP, the Commission will adopt a decision to the MAHs for the centrally authorised products and, as applicable, to the competent authorities of the Member States for nationally authorised products. Where the procedure includes only

NAPs, the procedure ends with the CMDh position in case of consensus and in case of a majority vote, the CMDh position will be followed by a Commission decision to the Member States. For further details on the procedural aspects of the EU PSUSA for NAPs only, please refer to the relevant CMDh SOP.

The outcome of the PSUR assessment results in a legally binding decision or CMDh position and in case of any action to vary, suspend or revoke the marketing authorisations, this should be 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 are implemented without subsequent variation submission for centrally authorised products and through the appropriate variation at national level for nationally authorised products (including those authorised through the mutual recognition and decentralised procedures).

The Agency publishes the outcome of a PSUR procedure for the CAPs and will publish as well systematically the outcome for NAPs as of September 2014.

For further guidance on the variation to submit to implement the outcome of a single PSUR procedure, please refer to question "*How can I apply for the update of the product information after the outcome of a single PSUR procedure?".*

References

- Guideline on good pharmacovigilance practices (GVP) Module VII – Periodic safety update report
- CMDh SOP

15.19. How is the CHMP opinion/CMDh position structured and which annexes need to be translated? Rev. Sep 2015

This section presents the translation process of procedures of the below Annexes to the CHMP Opinion / CMDh position. The Annexes of both the CHMP opinion as well as the CMDh position will be translated into all EU languages following an agreed time table.

In addition, a linguistic review by Member States of these Annexes in all EU languages is performed after adoption of CHMP opinions and those CMDh positions, which will receive a Commission Decision.

Procedures that contain centrally authorised products (CAP(s))

- Annex B: Annexes I, II, IIIA, IIIB, IV[1] (Scientific conclusions and grounds for the variation of the marketing authorisation) and 127a (risk minimisation measures addressed to Member States)

Procedures that contain a mix of centrally authorised products (CAP(s)) and nationally authorised products (NAP(s))

For the CAP(s):

- Annex B: Annexes I, II, IIIA, IIIB, IV[7] (Scientific conclusions and grounds for the variation of the marketing authorisation) and 127a (risk minimisation measures addressed to Member States)

For the NAP(s):

[7] Annex IV are part of the next EPAR publication. However, they will not remain part of the EPAR and will become obsolete with the next following EPAR revision. They, however, remain part of the Commission Decision in the Community Registry on the Commission's webpage.

- Annex C:
  - Annex I (Scientific conclusions and grounds for variation to the terms of the marketing authorisations)
  - Annex II (Amendments to the product information of the nationally authorised medicinal products)
  - <Annex III (Conditions to the marketing authorisations)>

Procedures that contain nationally authorised products (NAP(s))

- Annex C:
  - Annex I (Scientific conclusions and grounds for variation to the terms of the marketing authorisations)
  - Annex II (Amendments to the product information of the nationally authorised medicinal products)

Where applicable:

- <Annex III (Conditions to the marketing authorisations)>
- <Annex III or IV (Timetable for implementation[8])>

The preparation of the translation process

In view of the short timeframe for finalisation of the translations and in order to optimise the quality of the translations, the MAHs are strongly advised to prepare for the translation process well in advance in the pre-opinion / position stage, i.e. just following adoption of the PRAC recommendation for variation.

In case of a PSUSA procedure where several MAHs are involved, the EMA will coordinate the translation process by approaching the MAHs individually. MAHs should translate all relevant Annexes for each procedure.

During the translation process

Depending on the type of outcome and whether a Commission Decision is required, the translation process will follow different timelines:

a) Should the outcome be a CHMP opinion or a CMDh position by majority i.e. followed a Commission Decision, the MAH has to provide the translations of the adopted Annexes in all EU languages (including Icelandic and Norwegian – if applicable) according to the following timelines:

Day 5 (5 days after opinion/ position)	Translations of the adopted Annexes in EN and in all other EU languages (Including Icelandic and Norwegian) are to be provided electronically (in one Eudralink package if applicable) to the Member States (MS) Contact Points for Translations and to the EMA's

[8] This time table is adopted in case a CMDh position reached by consensus and therefore not followed by a Commission Decision; in case of a majority position, the deadlines foreseen in the legislation for implementation after the Commission Decision apply

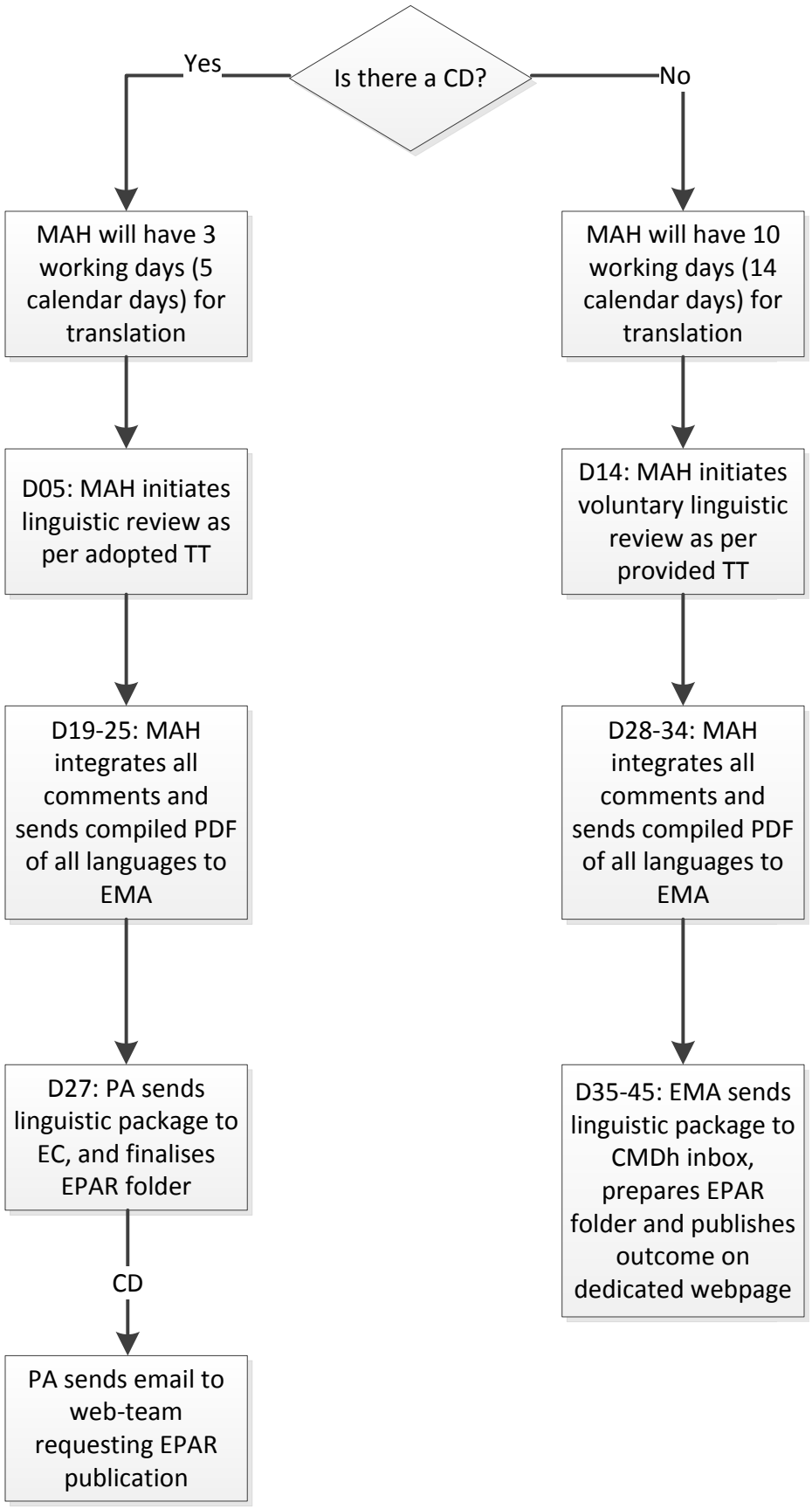
	procedure assistant and the PSUSA Mailbox.
Day 19 (19 days after opinion/ position)	Member States will send linguistic comments on the Annexes to the MAH by e-mail with a copy to the PSUSA Mailbox.
Day 25 (25 days after opinion / position)	The MAH(s) will implement the required changes, compile the translations and send it back to the EMA. In case of disagreement between a Member State and the MAH, the EMA will not interfere in the translation process at this stage. Disagreements should be solved directly with the concerned MS. In order to facilitate and accelerate the check of the implementation of the' comments, the MAH 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.

b) Should the outcome be a CMDh position by consensus, a linguistic review for the translations is not foreseen in the translation process, therefore the following timelines apply:

Day 1 – 14 (1 to 14 days after position):	MAH translates the adopted Annexes in **all** other EU languages based on the EN provided version. MAHs with marketing authorisations in Iceland and/or Norway will provide these languages as well.
Day 15 (15 days after the position):	Translations of the adopted Annexes in EN and all other EU languages (incl. Icelandic and Norwegian if applicable) are to be provided electronically (in one Eudralink package if applicable) to the Member States (MS) contact Points for Translations and to the EMA's procedure assistant and the PSUSA Mailbox for voluntary linguistic check.
Day 28-34 (28-34 days after position)	The MAH(s) will implement the required changes. Translation of the adopted Annexes in EN and in all other EU languages (Including Icelandic and Norwegian) are to be compiled and provided electronically (in one Eudralink Package if applicable) to the EMA's procedure assistant and the PSUSA Mailbox.

Day 35-45 (35-45 days after position)	The EMA will send the package to the CMDh and prepare the translations for publication.

The timelines for the translation process vary depending on the need for a linguistic review as illustrated below:


Is there a CD?
Yes
No
MAH will have 3 working days (5 calendar days) for translation
D05: MAH initiates linguistic review as per adopted TT
D19-25: MAH integrates all comments and sends compiled PDF of all languages to EMA
D27: PA sends linguistic package to EC, and finalises EPAR folder
CD
PA sends email to web-team requesting EPAR publication
MAH will have 10 working days (14 calendar days) for translation
D14: MAH initiates voluntary linguistic review as per provided TT
D28-34: MAH integrates all comments and sends compiled PDF of all languages to EMA
D35-45: EMA sends linguistic package to CMDh inbox, prepares EPAR folder and publishes outcome on dedicated webpage

After the translation process

Once the translations are received from the MAH, the Agency will check if all Member States' comments have been implemented.

a) In case of a CHMP opinion or a CMDh position (by majority) from the CMDh, the Agency will compile the Annexes in all languages and send the final copies to the Commission, members of the Standing Committee and the MAH(s) at Day 27 (27 days after opinion).
Following receipt of the final compiled translations, 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).

b) In case of a CMDh position (by consensus), the Agency will compile the Annexes in all languages, send the final copies to the Member States and, where applicable, the full set of Annexes will be published on the EMA website.

In order to facilitate and accelerate the check of the implementation of the Member States' comments, the MAHs 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.

Standards of translation of Annexes

- The structure of the English Annexes has to be strictly followed and should be exactly translated as per the adopted English version (i.e.: full product information or only amendments to the relevant sections of the product information).
- For translations of Annexes QRD templates for each language should be used
- Make sure that the title pages are adjusted and all brackets (i.e. <>) are taken out in the title.
- Do not leave sections out, do not update the Annex III, e.g. the sections [to be completed on a national level] simply to be translated as 'to be completed on a national level'.
- Good quality of the translations and compliance with the Member States' comments is required to facilitate the process.

If a translation is considered not to be of an acceptable quality, the Member State concerned will inform the MAH and the Agency within 3 days of receipt of the translation. The Agency will inform the MAH of the insufficient quality of the translations and the transmission to the Commission will be delayed until receipt of the amended translation (which would be expected within 1 week). A revised timetable will then be prepared.

The MAHs are also strongly advised to liaise directly with the Member States in case of disagreement with any of the comments made or in case further clarification on some comments is required, and to reflect the outcome in "QRD Form 2".

In addition, the MAHs are reminded that in case the complete product information is part of the Annex III, it should be presented in strict compliance with the QRD Convention (e.g. format, layout, margins).

The Agency will monitor the quality of the translations, the review by the Member States and industry's compliance with the Member States' comments as part of the Performance Indicators.

References

- QRD Convention
- Product Information Templates
- Product Information: Reference documents and guidelines
- User guide on the preparation of PDF versions of the product information
- List of Member States contact points for translations (with guidance on the sending of product information to Member States)
- EC Guideline on the operation of the procedures laid down in Chapters II, III and IV of Commission Regulation (EC) No 1234/2008 of 24 November 2008

15.20. What fee do I have to pay? NEW Sep 2014

The EMA will levy a fee for the assessment of PSUR(s) as of 26 August 2014.

For the PSUR assessment involving only one Marketing Authorisation Holder the total amount of the fee will be levied on that Marketing Authorisation Holder.

For the PSUR assessment under a PSUSA procedure involving more than one Marketing Authorisation Holder, the total amount of the fee will be divided among all the Marketing Authorisation Holders concerned proportionately to the number of chargeable units.

The Marketing Authorisation Holders concerned will be established on the basis of the obligation to submit the PSUR(s) and not on the basis of the actual PSUR submission(s) received by the EMA.

The total of chargeable units in the procedure will be identified from the Art. 57 database. The share payable by each marketing authorisation will be calculated by the EMA. In this respect, an advice note will be sent three months prior to the start date to the relevant QPPVs in order to ensure the accurate identification of the chargeable units for the products involved in the procedure. At start of the procedure, the invoice will be sent to each Marketing Authorisation holder with the relevant chargeable units calculation. The fee will be due to the EMA within 30 calendar days from the date of the invoice.

For Marketing Authorisation Holders already qualified as an SME (i.e. micro-, small- or medium-sized enterprise) by the EMA or for those that will send a SME declaration in advance of the start date or by the latest after 30 days of the invoice date, the fee will be reduced (small- or medium-sized enterprise) or waived (micro-sized enterprise).

The EMA will also publish further guidance on how the fees will be calculated and collected.

References

- Regulation (EU) No 658/2014
- Fees payable to the European Medicines Agency
- SME declaration
- Data submission for authorised medicines

15.21. How can I know about the outcome of a PSUSA procedure? Rev. Jul 2015

For products which were not part of the PSUSA procedure such as generics (under Art 10(1) and well established use (under Art 10a), MAHs should update the product information according to the outcome of the PSUSA procedure through a default type IB variation C.I.3.z, unless the MAH submitted data for assessment, in which case it would be a type II, C.I.3.b.

For nationally authorised products which are part of the PSUSA procedure, please refer to the CMDh website (Question & Answers, Pharmacovigilance legislation) for further guidance on the appropriate implementing variation to submit to the National Competent Authorities of the Member States where the concerned products are authorised.

Information on the outcome of centrally authorised medicinal products is made available in the European Public Assessment Report (EPAR) page of the relevant medicine. Information regarding the variation of NAPs that are part of a CAP/NAP procedure is available in the Community Register for nationally authorised products.

Information on the outcome of the EU single assessment of PSURs involving nationally authorised medicinal products only will be made available on the EMA web page under Home/Find medicine/Human medicines/PSUSA until the EU web portal if fully functional.

15.22. Can PSURs still be submitted with renewal application? Rev. Mar 2013

PSURs, PSUR addendums, summary bridging reports and line listings should no longer be submitted as part of a 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.

References

- Guideline on the processing of renewals in the centralised procedure
- Guideline on good pharmacovigilance practices (GVP) Module VII – Periodic safety update report

15.23. Who should I contact if I have a question when preparing my application? Rev. Jul 2015

If you cannot find the answer to your question in the Q&A when preparing your application, please contact us using the following email address: PSURquery@ema.europa.eu

The Agency aims to respond to your query within 5 working days. To help us deal with your enquiry, please provide as much information as possible including whether your query refers to a NAP or CAP, the name of the product and the name of the active substance/combination of active substances in your correspondence.

The above email address is only applicable when you have a pre-submission query. A dedicated Procedure Manager (PM) will be assigned to the procedure once your application has been received. You will be able to contact this PM throughout the procedure.

For queries on fees and QPPV advice notes (please refer to question "*What fee do I have to pay?*"), you can contact us using the following email address instead: PSUSAData@ema.europa.eu

For queries related to the content of the EURD list including requests to amend the EURD list, you can contact us using the following email address instead: EURDList@ema.europa.eu

For technical queries, you can contact us using the following email address instead: eCTD@ema.europa.eu

For technical issues with the EMA gateway/webclient, you can contact us using the following email address instead: gatewaysupport@ema.europa.eu

For issues with the PSUR Repository, you can contact us using the following email address instead: psurrepository@ema.europa.eu

For other general queries, you can use the following webpage: Send a question to the European Medicines Agency.

15.24. Who is my contact at the European Medicines Agency during post-authorisation procedures? NEW Apr 2015

Please refer to question 22.8 Other - Who is my contact at the European Medicines Agency during post-authorisation procedures?.

16. Article 46 paediatric study submission

16.1. What is the "Article 46 paediatric study submission"? Rev. Jul 2014

Article 46 of Regulation (EC) No 1901/2006 (The Paediatric Regulation) sets out the obligation for the Marketing Authorisation Holder to submit to the competent authority any MAH-sponsored studies involving the use in the paediatric population of an authorised medicinal product, whether or not they are part of a PIP. For centrally authorised medicinal products, the studies should be submitted to the European Medicines Agency.

This includes clinical studies that are:

- completed or discontinued;
- published or not;

Studies should be submitted regardless of the region where they were performed, the aim, outcome, population studied and indication.

Reference

- Article 46 of Regulation (EC) No 1901/2006

16.2. When shall I submit my article 46 paediatric study application? Rev. Dec 2014

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 standalone Marketing Authorisation Application.

Completion of a study is defined in the Commission guideline on the format and content of paediatric investigation plans. Clinical studies are deemed to have been completed on the date of the last visit of the last subject in the study or at a later point in time as defined in the protocol.

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

16.3. How shall I present my article 46 paediatric study application at submission? Rev. Feb 2014

A paediatric study is to be submitted pursuant to article 46 as a post-authorisation measure ('stand-alone' submission). However, if amendments to be introduced to Product Information are identified by the MAH, a variation (e.g. category C.1.4 or C.1.6) should be submitted directly containing the article 46 paediatric study.

The submission of an application under article 46 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. stand-alone study or study 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 of submission of a variation including study relevant to article 46, the application should be presented in EU-CTD format accordingly to the guidance for variation (see also in guidance on variations). The following box should be ticked in the variation application form: "*THIS APPLICATION RELATES TO PAEDIATRIC STUDIES SUBMITTED ACCORDING TO ARTICLE 45 OR 46 OF THE PAEDIATRIC REGULATION*".

References

- ICH Topic E3, Note for Guidance on Structure and Content of Clinical Study Reports, CPMP/ICH/137/95

16.4. How and to whom shall I present my article 46 paediatric study application? Rev. Aug 2014

Please refer to question 22.5 Other – How and to whom shall I submit my application?

16.5. How shall the evaluation of my article 46 paediatric study application be handled (timetable), and what could be the outcome of the evaluation? NEW Feb 2014

The following 60-day timetable shall apply to the assessment of the paediatric study submitted by the MAH:

Day	Action
Day 1	Start of the procedure as per published timetable (see below)
Day 30	Receipt of Rapporteur's Assessment Report
Day 45	CHMP Members' comments
Day 50	Receipt of Rapporteur's updated Assessment Report (if necessary)
Day 60 (CHMP meeting) (up to Day 90 if a Request for Clarification is needed)	CHMP adoption of conclusion or Request for Clarifications

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 at D60:

- No amendment to the product information is required at this point of time.
- 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.
- 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.

At the time of finalising an opinion, it may be needed that the MAH generate additional data (see also guidance on post-authorisation measures).

16.6. Do I have to pay fees for the article 46 paediatric study submission? NEW Feb 2014

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.

16.7. Will there be any publication on the outcome of my article 46 paediatric study? Rev. Feb 2014

The assessment report of the procedure will be published on the European Medicines Agency website under the EPAR tab of the product after removal of commercially confidential information.

References

- EPARs

17. Transfer of Marketing Authorisation

17.1. What is a Transfer of Marketing Authorisation? Rev. Jul 2014

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 may result from the MAH's commercial decision to divest the MA or be needed in anticipation of the MAH ceasing to exist as a legal entity and MA being taken over by another legal entity.

In case a MA Transfer is sought for several medicinal products, an application must be submitted for each MA (i.e. 1 application per product).

A change of name and/or address of the MAH is not a MA Transfer if the holder remains the same person/legal entity. Such change should be notified through a Type IAIN, A.1 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. 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/legal entity 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 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

17.2. How shall I present my application for the Transfer of Marketing Authorisation? Rev. Jul 2014

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 and/or the Transferor, as appropriate, must be legible and preferably shall be printed on a headed paper. A template for each document is attached 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 on which the authorisation was granted. (Attachment 1) – see *"Authorisation details" of the product-specific webpage on the EMA website.*

2) The identification (name, address, contact person at address, telephone number and email addresses) 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 issued in accordance with national provisions. The Proof of Establishment is commonly issued by appropriate Chamber of Commerce. (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), the Member State(s) in which he/she resides and carries out his/her tasks, email address, telephone and fax numbers. It must be stated that the Transferee has permanently and continuously at its disposal the services of a QPPV, that it has the necessary means to fulfill the tasks and responsibilities listed in Title IX of Directive 2001/83/EC and that the QPPV resides and operates within the European Economic Area. In case a summary of the pharmacovigilance system was introduced as part of the MA prior to the transfer, please also mention the location where the pharmacovigilance master file is kept together with its reference number. 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. (Attachment 6.1)

   - 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, 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, 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 EEA in any of its presentations, this should be specified in a signed statement. Attachment 7)

8) If appropriate, a letter of recommendation or a letter of undertaking signed by the Transferee listing any remaining recommendations or follow-up measures. (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. When the name of a product is composed of INN + company name see - (See also Transfer of Marketing Authorisation - "Can I change the name of a medicinal product as part of a transfer application?).

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 SmPC, Annex II, Labelling and Package Leaflet

The revised product information (SmPC, Annex II, labelling, and package leaflet) in all EU languages including Iceland and Norway must be provided electronically in Word format (highlighted using track changes) and in PDF format (clean)

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?).

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
- 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)
- Guideline on Pharmacovigilance for Medicinal Products for Human Use, Volume 9A of the Rules governing Medicinal Products in the European Union

17.3. How and to whom shall I submit my Transfer of Marketing Authorisation application? Rev. Aug 2014

Please refer to question 22.5 Other – How and to whom shall I submit my application?

17.4. How shall my Transfer of Marketing Authorisation application be handled (timetable)? Rev. Jul 2014

A Transfer application follows a 30-day procedure following receipt of the application. There are no set 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 Pre-submission Queries Services (MATransferquery@ema.europa.eu) at least 1 month before submission of the application.

Within 7 days upon receipt of the Transfer application, the EMA will check whether the Transfer application is correct and complete. In case the application is correct and complete the Agency aims to finalise the procedure by Day 10.

In case of an incorrect or incomplete application the applicant will be notified and required to provide the amended and/or additional documentation via eCTD submission within 10 calendar days from the date of the EMA notification. The EMA will not be able to issue a favourable opinion on the Transfer in case the documentation is incomplete. Upon receipt of the applicants' responses the Agency aims to finalise the procedure by Day 20.

In any case finalisation of the opinion should be within 30 days upon receipt of the Transfer 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 is 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?").

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

17.5. How to choose the implementation date? Rev. Jul 2014

The implementation date is the date on which the Transferee takes over ALL responsibilities as the Holder of the MA.

This date is proposed by the Transferor and Transferee in the Transfer application and will be subject to agreement by the EMA.

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.

For the Transfer of a Marketing Authorisation covering medicinal products not yet marketed in the EEA by the Transferor, the proposed date should always refer to the day on which the Commission Decision on the Transfer will be issued.

17.6. What fee do I have to pay for my Transfer of Marketing Authorisation application? Rev. June 2013

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 fee will become due on the date of receipt of Transfer application 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 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.

The Agency will charge the fee for Transfer application notification at the start of the procedure, irrespective of its outcome (positive, negative or partial/full withdrawal).

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

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

17.7. How to handle planned/ongoing variations procedures during the Transfer of Marketing Authorisation? Rev. Jul 2014

MAHs should avoid submitting variation procedures in parallel to a Transfer of MA application.

MAHs are strongly advised to contact the Pre-submission Queries Service (MATransferquery@ema.europa.eu) in advance of the submission of the Transfer of application, in order to discuss how to handle any planned/ongoing procedures (especially in case the product information is affected) or in case there are variations linked to the Transfer procedure.

17.8. How to handle remaining Post-authorisation measures and recommendations when transferring a Marketing Authorisation? Rev. Dec 2013

Enforceable post-authorisation measures (PAMs) may have been agreed for the medicinal product at the time of the granting of the marketing authorisation or subsequent modifications. If such PAMs are still remaining for the medicinal product concerned, it is the responsibility of the Transferee to fulfil them within the timeframe previously agreed.

In case of remaining recommendations or follow-up measures, a letter of recommendation or a letter of undertaking signed by the Transferee listing them must be submitted (Attachment 8 to the cover letter).

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

17.9. Do I have to submit mock-ups and specimens? Rev. Dec 2013

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. Ideally, applicants must provide at submission 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. If not available, relevant example mock-ups of the marketed presentation may be submitted instead.

If the transfer only affects the MAH details on the packaging and package leaflet without any impact on the overall design, a declaration 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 module 1.3.2 of the application dossier.

In case of comments on the mock-ups, the MAH should submit responses and/or updated mock-ups, as applicable, to the EMA (muspecimens@ema.europa.eu) prior to the specimen printing. EMA will discuss the best and feasible corrective action with the MAH, taking into account the nature and amount of issues identified. EMA will endeavour to provide such feedback as soon as possible and taking into consideration the production plan of the medicinal product, as applicable.

Specimens:

Only in case the transfer has an impact on the overall design, relevant revised example specimens should be provided to the EMA by the new MAH, in line with the requirements for new applications and extensions.

If the transfer only affects the MAH details on the packaging and package leaflet without any impact on overall design, specimens are not required.

The EMA will perform a general check 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.

In case of comments on the specimens, the MAH should submit responses and/or updated mock-ups, as applicable, to the EMA (muspecimens@ema.europa.eu) prior to the launch of the medicinal product. EMA will discuss the best and feasible corrective action with the MAH, taking into account the nature and amount of issues identified. EMA will endeavour to provide such feedback as soon as possible and taking into consideration the launch plan of the medicinal product, as applicable.

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 (EMA/305821/2006/Rev.1)

17.10. Do I also have to transfer the orphan designation when my medicinal product has been granted such a designation? Rev. Dec 2007

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 Agency.

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 the format and content of applications for designation as orphan medicinal products and on the transfer of designation from one sponsor to another" and in the "Checklist for sponsors applying for the transfer of orphan medicinal product designation".

References

- Article 5(11) of Regulation (EC) No 141/2000 of 16 December 1999 on orphan medicinal products
- 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)

17.11. Can I include changes to manufacturing sites in my Transfer of Marketing Authorisation application? Rev. Jul 2004

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 Pre-submission Queries Service (MATransferquery@ema.europa.eu) prior to submitting a transfer application in order to discuss the appropriate timeframe of such variations.

In addition, when the need for good-manufacturing practice inspections is anticipated by the MAH, it is advisable to contact the Agency in advance of the variation and transfer submission.

17.12. Can I change the Qualified Person for Pharmacovigilance information as part of my Transfer of Marketing Authorisation application? Rev. Jul 2014

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 that have introduced the Summary of the Pharmacovigilance System master file (PSMF) in their marketing authorisation dossier and to MAs with or without a Detailed Description of the Pharmacovigilance System (DDPS).

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)

17.13. Can I change the name of a medicinal product as part of a transfer application? New June 2013

In order to change the name of a medicinal product, a variation is required and should be submitted separately to the transfer procedure.

In the case the transfer procedure concerns a medicinal product whose name is constructed as [INN / common name + name of the MAH], the name of the medicinal product needs to be changed to reflect the name of the transferee.

As a result, the variation to change the name of the medicinal product constructed as [INN / common name + name of the transferee] should be submitted in parallel of the transfer procedure.

For more information on the procedure to change the name of a medicinal product, please refer to the post-authorisation guidance “Changing the (invented) name of a centrally authorised medicine:

questions and answers" and the generics guidance "How will I know if the proposed (invented) name of my generic/hybrid medicinal product is acceptable from a public health point of view?"

The acceptance by the Name Review Group (NRG) of the new name has to be finalised prior to the submission of the variation for changing the name of the medicinal product, including where the transferee wishes to use the common or scientific name, together with a trademark or the name of the Marketing Authorisation Holder.

17.14. Will there be any publication on the Transfer of Marketing Authorisation?

The European public assessment report (EPAR) will be revised to implement the change in MAH.

Reference

- EPARs

17.15. Who should I contact if I have a question when preparing my application? NEW Apr 2014

If you cannot find the answer to your question in the Q&A when preparing your application, please contact us using the following email address: MATransferquery@ema.europa.eu

The Agency aims to respond to your query within 5 working days. To help us deal with your enquiry, please provide as much information as possible including the name of the product in your correspondence.

The above email address is only applicable when you have a pre-submission query. A dedicated Procedure Manager (PM) will be assigned to the procedure once your application has been validated. You will be able to contact this PM throughout the procedure.

17.16. Who is my contact at the European Medicines Agency during post-authorisation procedures? NEW Apr 2015

Please refer to question 22.8 Other - Who is my contact at the European Medicines Agency during post-authorisation procedures?.

18. Transparency

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.

18.1. Which transparency measures apply with regards to the PRAC meeting? NEW Mar 2013

- 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.

18.2. Which transparency measures apply with regards to the CHMP meeting? NEW Mar 2013

- 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 meting 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 is 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.

18.3. Which EMA transparency measures apply for on-going procedures? NEW Mar 2013

- 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.

18.4. Which transparency measure applies for the publication of assessment reports? Rev. July 2013

- 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.

18.5. Which specialised databases are publicly available? NEW Mar 2013

- 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.

18.6. Does the EMA provide monthly figures on centralised procedures for human medicines? NEW Mar 2013

- 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 mediciens-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)
- Procedural advice on publication of information of negative opinions and refusals of applications EMA/599941/2012
- Procedural advice on publication of information on withdrawals of applications EMA/599977/2012
- 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)

19. Pharmacovigilance system summary

19.1. Requirements regarding the summary of the pharmacovigilance system Rev. Feb 2015

Applicants for marketing authorisation are required to provide a summary of their pharmacovigilance system, in accordance with Article 8(3)(ia) of Directive 2001/83/EC, which they will introduce once the authorisation is granted.

The requirement for the summary of the pharmacovigilance system was introduced by the new pharmacovigilance legislation (Directive 2010/84/EU amending, as regards pharmacovigilance, Directive 2001/83/EC) and replaced the previous requirement for the submission of a detailed description of pharmacovigilance system (DDPS) as part of the marketing authorisation application.

The summary of the pharmacovigilance system should be provided in Module 1.8.1 of the application for marketing authorisaton 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) of Directive 2001/83/EC regarding the obligation to have the necessary means to fulfil the tasks and responsibilities listed in Title IX. Such statement should be signed by an individual who can act on behalf of the legal entity of the applicant/MAH and by the qualified person for pharmacovigilance (QPPV). The title, role and responsibility of each individual signing the statement should be clearly specified in the document.

The summary of pharmacovigilance system is specific to each application/marketing authorisation as per legislation and therefore should be signed by the relevant applicant/MAH.

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.

References

- Directive 2001/83/EC
- Directive 2010/84/EU
- Commission implementing Regulation No 520/2012 of 19 June 2012 on the performance of pharmacovigilance activities provided for in Regulation (EC) No 726/2004 of the European

Parliament and of the Council and Directive 2001/83/EC of the European Parliament and of the Council

- European Commission Question on transitional arrangements concerning the entering into force of the new pharmacovigilance rules provided by Directive 2010/84/EU amending Directive 2001/83/EC and Regulation (EU) No 1235/2010 amending Regulation (EC) No 726/2004 (SANCO/D5/FS/(2012)1014848)
- HMA-EMA Questions and answers on practical transitional measures for the implementation of the pharmacovigilance legislation (EMA/228816/2012 – v.3)
- 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)

19.2. Requirements regarding the pharmacovigilance system and pharmacovigilance system master file ***NEW Mar 2013***

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 MA 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 MA and placing of the product on the market. During the evaluation of a MA the applicant may be requested to provide a copy of the PSMF for review.

The PSMF 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 MA and placing of the product on the market.

References

- Directive 2001/83/EC
- Guideline on good pharmacovigilance practices - Module II – Pharmacovigilance system master file (EMA/816573/2011)

19.3. Subcontracting pharmacovigilance activities NEW Mar 2013

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 (PSMF).

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 PSMF location, maintenance of the PSMF and its provision to competent authorities upon request. Detailed written agreements describing the roles and responsibilities for PSMF 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.

References

- 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)

19.4. When to submit a summary of the pharmacovigilance system? NEW Mar 2013

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.

References

- Directive 2001/83/EC

- European Commission Question on transitional arrangements concerning the entering into force of the new pharmacovigilance rules provided by Directive 2010/84/EU amending Directive 2001/83/EC and Regulation (EU) No 1235/2010 amending Regulation (EC) No 726/2004 (SANCO/D5/FS/(2012)1014848)
- HMA-EMA Questions and answers on practical transitional measures for the implementation of the pharmacovigilance legislation (EMA/228816/2012 – v.3)

19.5. Which type of variation is required to introduce or change the summary of the pharmacovigilance system? Rev. Feb 2015

The introduction of the summary of pharmacovigilance system requires a type IA^{IN} variation (the 'implementation' is when the marketing authorisation holder (MAH) introduces the PSMF, i.e. when it internally approves the use of the PSMF), please see the "Guideline on the details of the various categories of variations". 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^{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 4 applies per each marketing authorisation (MA), 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^{IN} should be submitted to update the MA for this product and reflect the use of the PSMF accordingly.

One grouped type IA^{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^{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^{IN} variation, please see the"Guidelines on the details of the various categories of variations".

As per Rules for the implementation of Council Regulation (EC) No 297/95 on fees payable to the European Medicines Agency and other measures, a total exemption from the payment of the fees laid down in the fee regulation is granted for the type IA variation relating to scope C.I.8, i.e. an introduction of/or changes to a summary of pharmacovigilance system for medicinal products for human use.

References

- 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 - Guidelines on the details of the various categories of variations, on the operation of the procedures laid down in Chapters II, IIa, III and IV of 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 and on the documentation to be submitted pursuant to those procedures
- EMA post-authorisation procedural advice – Grouping of variations
- Rules for the implementation of Council Regulation (EC) No 297/95 on fees payable to the European Medicines Agency and other measures - Revised implementing rules to the Fee Regulation as of 1 April 2014.

19.6. Pharmacovigilance system master file (PSMF) number NEW Mar 2013

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.

References

- Detailed Guidance on electronic submission of information on medicines

19.7. Is the information on the Deputy QPPV required as part of the summary of the pharmacovigilance system? NEW Feb 2015

No, the information on the deputy QPPV is not within the required information to be included in the summary of the applicant's pharmacovigilance system, as per Article 8(3)(ia) of Directive 2001/83/EC, and therefore no variation is foreseen for the purpose of changing this information.

According to the legislation and guidance in GVP Module I, as part of the pharmacovigilance system, the marketing authorisation holder shall have permanently and continuously at its disposal an appropriately qualified person responsible for pharmacovigilance in the EU (QPPV). Therefore back-up procedures in case of absence of the QPPV shall be in place. The QPPV should ensure that the back-up person has all necessary information to fulfil the role. The information relating to the QPPV provided in the PSMF shall include details of back-up arrangements to apply in the absence of the QPPV.

References

- Directive 2001/83/EC
- Guideline on good pharmacovigilance practices - Module I – Pharmacovigilance systems and their quality systems (EMA/541760/2011)

20. Article 61(3) Notifications

20.1. What are Article 61(3) Notifications? Rev. Aug 2014

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 only the Annexes IIIA (labelling) and/or IIIB (PL), with no changes to the SmpC and/or the Annex II.
- In addition, the changes must affect the English labelling and/or PL text, with consequential amendments to all other language versions.

Examples of changes falling within the scope of 61(3) Notification:

- Changes in the local representatives
- Minor changes to the labelling and/or PL
  - Labelling: e.g. changes of abbreviation for the batch number
  - PL: Harmonisation of wording used in the PL
- Updated PL after User Testing when the User Testing report and amended leaflet cannot be included in an upcoming regulatory procedure which affects the Annexes (e.g. Type II variation)
- Introduction of combined PL (after prior consultation with QRD)
- Change in Braille (inclusion/deletion/change)
- Change in instruction for use in the PL

The following examples **do not** fall within the scope of 61(3) Notification:

- Changes to SmPC or Annex II,
- Changes that only affect some languages but not all,
- Changes in overall lay-out, design, readability of labelling,and/or PL with no changes to the text. 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.

It is possible to introduce within a single 61(3) Notification, several changes to the labelling and/or the package leaflet, which do not affect the SmPC or the Annex II (e.g. submission of a change in the local representative and harmonisation of the wording used in the PL).

The Agency strongly recommends, that whenever possible, the marketing authorisation holder (MAH) includes minor changes to the labelling and/or PL as part of another on-going or upcoming regulatory procedure amending the Product Information (e.g. Type IB or II variation affecting the product information, renewal, etc.). Should the MAH have a query on changes that may fall under the scope of 61(3) Notification, they should contact the EMA query service (61.3.query@ema.europa.eu).

However, if submitted stand-alone, changes only affecting Annex III have to be submitted as a 61(3) Notification (i.e. not possible to submit as a variation).

Upon submission, the Agency will inform the marketing authorisation holder (MAH) within 90 days whether the proposed changes are accepted or not. The Agency will inform concomitantly the Commission in cases where the changes have been accepted (for information on the update of the Commission Decision see: How and when will the updated Annexes become part of the Marketing Authorisation?).

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)

20.2. 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).

20.3. When can I submit my 61(3) Notification? Rev. Aug 2014

There are no recommended submission dates for 61(3) Notifications. Hence the MAH can submit a 61(3) Notification at any time.

The Agency strongly recommends that whenever possible the marketing authorisation holder (MAH) includes these minor changes to the labelling and/or PL as part of another on-going or upcoming regulatory procedure amending the Product Information (e.g. Type IB or II variation affecting the product information, renewal, etc.). Should the MAH have a query on changes that may fall under the scope of 61(3) Notification, they should contact the EMA query service (61.3.query@ema.europa.eu).

20.4. How shall I present my 61(3) Notification? Rev. Aug 2014

The submission of a 61(3) Notification should include:

20.4.1. Cover Letter indicating the product name:

- dated, signed by the official contact person,
- including a summary and / or explanation of the proposed changes
- including a list of on-going/upcoming regulatory procedures affecting the Annexes and including a confirmation that the proposed changes only affect Annex III.including a confirmation from the MAH that there are no other changes than those identified in the cover letter (except for those addressed in other variations submitted in parallel),

- present/proposed table of the changes (this can be a separate annex).

20.4.2. Product information:

- The revised product information ('complete set of Annexes' includes Annex I, II, IIIA and IIIB i.e. all SmPC, labelling and PL texts for all approved strengths and pharmaceutical forms of the product concerned) in all EU languages (incl. IS+NO)
  - in Word format (highlighted) indicated via 'Tools – Track changes'
  - in PDF format (clean) with all changes 'accepted'

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, and MAHs should follow/pay attention to the guidance on how to correctly prepare the PDF versions.

The Annexes should be presented on the latest CHMP approved version.

The Annexes provided should only reflect the changes introduced by the 61(3) Notification. However, it is possible for the MAHs to take the opportunity to introduce minor linguistic amendments in the labelling and/or the PL for all or some EU languages. These changes should be clearly mentioned in the cover letter. Any changes not listed in the Notification cover letter will not be considered as part of the 61(3) Notification. In addition, it is not possible for the MAHs to introduce minor linguistic amendments in the SmPC and/or the Annex II.

20.4.3. If applicable:

- Any supportive relevant documentation (e.g. User Testing reports 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) to the 61(3) Notification, presented under the appropriate headings and numbering of the EU-CTD format.

20.5. How and to whom shall I submit my 61(3) Notification? Rev. Aug 2014

Please refer to question 22.5 Other – How and to whom shall I submit my application?

20.6. How shall my 61(3) Notification be handled (timetable), and what could be the outcome? Rev. Aug 2014

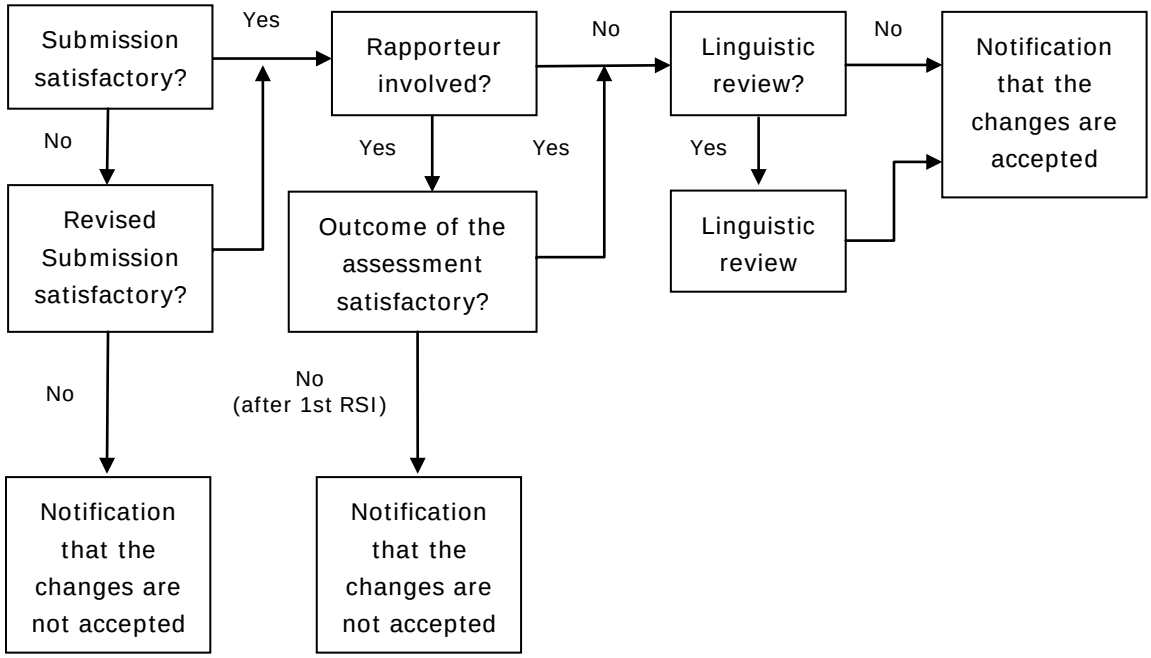
A dedicated Procedure Manager (PM) will be assigned to the procedure once your notification has been submitted.

20.6.1. Timelines

When the documentation submitted by the MAH meets the requirements and the Rapporteur's involvement is not needed and no linguistic review is needed, the EMA will aim to finalise the procedure within 8 working days.

For other cases, the length of the procedure will vary depending on the need for Rapporteur's involvement, linguistic review and the submission of revised information by the MAH when required. Additionally if the EMA Notification is not issued within 90 days following the introduction of the request, the applicant may put the change into effect.

20.6.2. Process



- Upon submission of your notification, the PM will review the content of the notification.
- When the documentation submitted by the MAH meets the requirements and the Rapporteur's involvement is not needed and no linguistic review is needed, the PM will aim to finalise the procedure within 8 working days.
- When the documentation submitted by the MAH does not meet the requirements, the PM will aim to contact the MAH within 5 working days. The MAH should then provide revised documentation within 5 days. Upon receipt of the revised documentation, the PM will aim to review the information within 3 working days. Should the information provided by the MAH be incomplete or does not fall under the scope of 61(3) notification, the PM will inform the MAH that the proposed change cannot be implemented.
- Upon receipt of satisfactory documentation and in cases where the Rapporteur's input is needed (e.g. submission of user testing results), the Rapporteur will assess the MAH's proposal within 15 working days. Should the outcome of the Rapporteur's assessment be not satisfactory, the MAH will be requested to provide revised documentation within 5 days. Upon assessment of the MAH's

responses, should the outcome of the Rapporteur's assessment remain unsatisfactory, the PM will inform the MAH that the proposed change cannot be implemented.

- Once the proposed changes have been agreed and the linguistic review is complete (when applicable), the MAH will receive a Notification via email that the changes have been accepted.

20.6.3. Possible outcomes

In summary, the following outcomes may be envisaged for 61(3) notification:

- Changes are acceptable and an EMA Notification is issued within a maximum of 90 days.
- Changes are not acceptable (even after receipt of additional/revised information if required). The PM will inform the MAH that the proposed change cannot be implemented.
- The proposed changes do not fall under the scope of a 61(3) Notification (even after receipt of additional/revised information if required). The PM will inform the MAH that the notification does not fall under the scope of Article 61(3) and cannot be processed. The proposed change cannot be implemented.

20.7. What fee do I have to pay for a 61(3) Notification?

There is no fee payable for 61(3) Notifications.

20.8. Do I have to submit mock-ups and specimens? Rev. Aug 2014

Mock-ups

In principle, no mock-ups are to be provided with 61(3) notifications, however, 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 mock-ups should be discussed with the EMA (muspecimens@ema.europa.eu) on a case-by-case basis (e.g. mock-ups would be required when proposing a new corporate design of packs, use of different colours, major changes in layout, introduction of new text in the labelling in line with the SmPC).

In case the submission of mock-ups is required, the relevant example mock-ups would need to be included in the module 1.3.2 of the application dossier.

In case of comments on the mock-ups, the MAH should submit responses and/or updated mock-ups, as applicable, to the EMA (muspecimens@ema.europa.eu) prior to the specimens printing. EMA will discuss the best and feasible corrective action with the MAH, taking into account the nature and amount of issues identified. EMA will endeavour to provide such feedback as soon as possible and taking into consideration the production plan of the medicinal product, as applicable.

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)

20.9. How and when will the updated Annexes become part of the Marketing Authorisation? Rev. Aug 2014

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

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. Additionally if the EMA Notification is not issued within 90 days following the introduction of the request, the applicant may put the change into effect.

20.10. Will there be any publication on the outcome of my 61(3) Notification? Rev. Apr 2012

The EPAR will be revised to implement the outcome of the 61(3) Notification, after issuance of the EMA Notification.

References

- EPARs

20.11. Who is my contact at the European Medicines Agency during post-authorisation procedures? NEW Apr 2015

Please refer to question 22.8 Other - Who is my contact at the European Medicines Agency during post-authorisation procedures?.

21. Withdrawn products notification

Obligations of marketing authorisation holders to notify withdrawals and cessations of human medicinal products authorised nationally and centrally – 2012 amendments to the pharmacovigilance legislation

This Question & Answer document addresses a number of questions relating to marketing cessation, marketing suspension and withdrawals of medicinal products from the market and of marketing authorisations in the context of the implementation of Directive 2012/26/EU and Regulation (EU) No 1027/2012 amending the pharmaceutical legislation with respect to pharmacovigilance.

The aim of these amendments is to strengthen the European system for the monitoring of safe and effective use of medicinal products including communication and transparency on potential safety issues and to allow consideration of the need for action in different Member States or at EU level.

21.1. Do I have to notify market cessation, withdrawal, suspension of my medicinal product / marketing authorisation? Rev. Aug 2014

Marketing Authorisation Holders (MAHs) have to notify to the competent authorities any of the following actions they intend to take:

- Temporary or permanent cessation of marketing of a medicinal product;
- Suspension of marketing of a medicinal product;
- Withdrawal of a medicinal product from the market;
- Request for the withdrawal of a marketing authorisation;
- Non-application for the renewal of a marketing authorisation.

Hereafter the medicinal products affected by any of these actions will be referred to as “withdrawn products”.

Such notification on “withdrawn products” should be provided by MAHs when the action affects either a pharmaceutical form or strength of a medicinal product in at least one Member State.

When the action affects a presentation in at least one Member State, the MAH should report such action via other means in the context of the “sunset clause monitoring”:

- For centrally authorised products, this should be done through the marketing status overview. (See section 20 “Marketing and cessation notification” of the Post-authorisation Guidance)
- For nationally authorised product, this should be done according to national requirements of competent authorities of Member State(s).

However, when the action affects a presentation that may raise a public health concern, a notification should also be made to the Agency through the dedicated mailbox withdrawnproducts@ema.europa.eu using the template cover letter and notification report table “Notification of withdrawn products” and to the Member State(s) concerned as applicable. The MAH has to exercise his best judgement to determine when it is appropriate to notify such cessation.

Regarding the definition of "cessation of placing on the market", please refer to section 20 "Marketing and cessation notification" of the Post-authorisation Guidance, Question 1.2 "*What is the meaning of "cessation of placing on the market"?.*

References

- Article 23a of Directive 2001/83/EC, as amended
- Article 123(2) of Directive 2001/83/EC[9], as amended
- Article 13(4) of Regulation (EC) No 726/2004, as amended
- Article 14b of Regulation (EC) No 726/2004[10], as amended

21.2. Which medicinal products are concerned? Rev. Aug 2014

The obligation for the notification of cessation of placing a medicinal product on the market, suspension of the marketing of a medicinal product, withdrawal of a medicinal product from the market, request for the withdrawal of a marketing authorisation and the non-application for the renewal of a marketing authorisation to both centrally and nationally authorised medicinal products (including those authorised through the mutual recognition and decentralised procedures).

For nationally authorised products, notification to the EMA should only take place if the reason for the aforementioned actions is related to efficacy, safety, quality or compliance issues as listed in question " "What information should be included in my notification and to whom should I notify?".

21.3. What information should be included in my notification and to whom should I notify? Rev. Aug 2014

The notification should clearly state the action intended to be taken by the MAH (see Question 1 "*Do I have to notify market cessation, withdrawal, suspension of my medicinal product / marketing authorisation?*") and the reason for such action, in particular when these are based on any of the following grounds:

- the medicine is harmful;
- the medicine lacks therapeutic efficacy;
- the risk-benefit balance of the medicine is not favourable;
- the qualitative and quantitative composition of the medicine are not as declared;
- the controls on the medicinal product and/or on the ingredients and the controls at an intermediate stage of the manufacturing process have not been carried out or if some other requirement or obligation relating to the grant of the manufacturing authorisation has not been fulfilled.

[9] DIRECTIVE 2012/26/EU OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 25 October 2012 amending Directive 2001/83/EC as regards pharmacovigilance
[10] REGULATION (EU) No 1027/2012 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 25 October 2012 amending Regulation (EC) No 726/2004 as regards pharmacovigilance

For centrally authorised medicinal products, MAHs have to notify the Agency.

For nationally authorised medicinal products, MAHs have to notify the competent authorities of the Member State(s) concerned. They also have to notify the Agency when the action is based on one of the grounds listed above. Otherwise, the Agency should not be notified of such action.

MAHs are advised that where the action is due to efficacy, safety and/or quality related issues for which particular procedures are already established, the notification according to the present provisions is without prejudice to any other reporting obligations related to medicinal products (e.g. quality/compliance issues, pharmacovigilance issues, etc.), as appropriate (see Questions 5 and 6 "How should I proceed for my notification for a centrally / nationally authorised medicinal products").

Such notification is also without prejudice to reporting the marketing status overview for the centrally authorised medicinal products at presentation level and per Member State, as detailed in the section 20 "Marketing and cessation notification" of the Post-authorisation Guidance.

References

- Article 116 and Article 117(1) of Directive 2001/83/EC, as amended
- Article 23a of Directive 2001/83/EC, as amended
- Article 123 of Directive 2001/83/EC, as amended
- Article 13(4) of Regulation (EC) No 726/2004, as amended
- Article 14b of Regulation (EC) No 726/2004, as amended

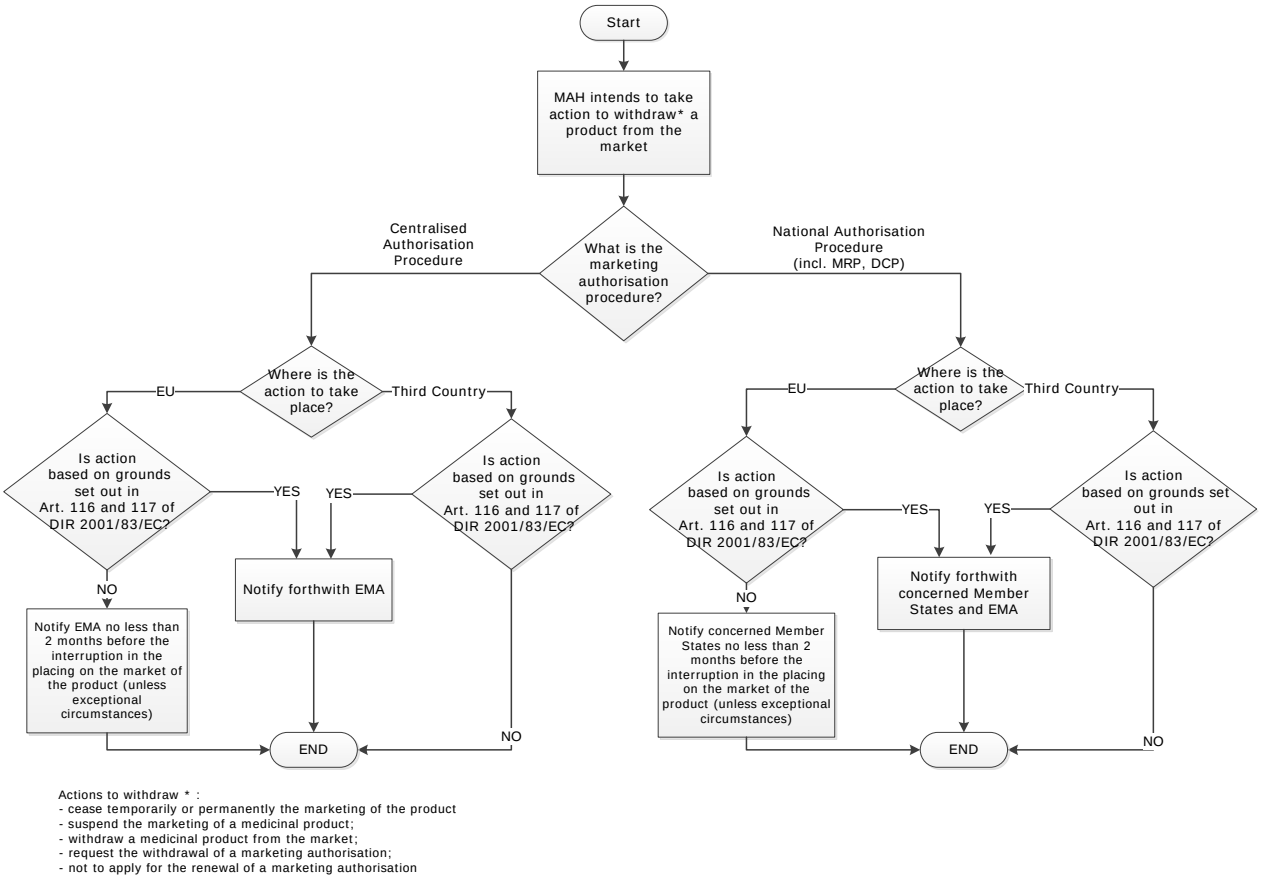
21.4. When shall the notification be made? Rev. Aug 2014

The MAH shall notify the competent authorities, other than in exceptional circumstances, no less than two months before the interruption in the placing on the market of the product. This applies to both temporary interruptions and permanent interruptions.

Besides, the MAH shall notify the competent authorities forthwith of any action taken either in the EEA or in a third country to:

- suspend the marketing of a medicinal product;
- withdraw a medicinal product from the market;
- request the withdrawal of a marketing authorisation;
- not to apply for the renewal of a marketing authorisation.

The grounds for any of the (intended) actions above should be declared as indicated in this Q&A (see Question 5 "*How should I proceed for my notification for a centrally authorised medicinal product?"* and Question 6 "*How should I proceed for my notification for a nationally authorised medicinal product?")*



References

- Article 23a of Directive 2001/83/EC, as amended
- Article 123 of Directive 2001/83/EC, as amended
- Article 13(4) of Regulation (EC) No 726/2004, as amended
- Article 14b of Regulation (EC) No 726/2004, as amended

21.5. How should I proceed with my notification for a centrally authorised medicinal product? Rev. Aug 2014

The MAH of a centrally authorised medicinal product should inform the Agency of the (intended) action together with the reasons:

- the action considered is taken in the EEA;
- the action considered is taken in a third country and is related to efficacy, safety, quality and/or compliance issues as listed in question “What information should be included in my notification and to whom should I notify?”.

The notification should be made to the Agency via the dedicated mailbox withdrawnproducts@ema.europa.eu by using the template cover letter and notification report table “Notification of withdrawn products”.

The EMA Product Lead and the Rapporteur of the product should always be kept informed.

Particular cases:

- In case of an emerging safety issue11 (ESI), should the MAH decide to take any action with regards to the marketing of the medicinal product or to the marketing authorisation of this medicinal product, the notification of such action to the Agency according to the present provisions should be done in parallel to the notification to the ESI mailbox (P-PV-emerging-safety-issue@ema.europa.eu).
- In case of a quality defect, should the MAH decide to take any action with regards to the marketing of the medicinal products or to the marketing authorisation of this medicinal products, the MAH should complete the published Defective Product Report Form, specifying in which countrie(s) the action(s) is/are taken and the anticipated date(s) as to when the medicinal product is no longer available on the market of the concerned countrie(s). The form should be sent to qdefect@ema.europa.eu as detailed in Notifying quality defects or products recalls. Please note that no separate notification to the EMA via the mailbox withdrawnproducts@ema.europa.eu is required.

In case of a voluntarily request from the MAH to withdraw a marketing authorisation, the MAH should send a letter to the European Commission to request a withdrawal of the marketing authorisation. The MAH should notify the Agency of such request to the Commission via the dedicated mailbox withdrawnproducts@ema.europa.eu by using the template cover letter and notification report table "Notification of withdrawn products", and should copy the EMA EPL and the CHMP Chair. The MAH should attach to its notification a scanned copy of the letter addressed to the European Commission.

References

- Article 13(4) of Regulation (EC) No 726/2004, as amended
- Article 14b of Regulation (EC) No 726/2004, as amended
- Article 16(2) of Regulation (EC) No 726/2004, as amended

21.6. How should I proceed with my notification for a nationally authorised medicinal product? Rev. Dec 2014

The MAH of a nationally authorised medicinal product (including those authorised through the mutual recognition and decentralised procedures) should inform the competent authorities of the Member states concerned of the (intended) action together with the reasons for such action if:

- the action considered is taken in the EEA;
- the action considered is taken in a third country and is related to efficacy, safety, quality and/or compliance issues as listed in question "What information should be included in my notification and to whom should I notify?".

[11] An emerging safety issue (ESI) is defined as a new information on the safety or efficacy of the medicinal product in the post-authorisation phase used inside or outside the terms of its marketing authorisation which might influence the evaluation of its benefit-risk profile or have an impact on the public. An ESI may arise from any source including (but not limited to) a study (interventional or non-interventional), scientific or medical literature, signal detection activities, any routine activities performed by the MAH, or regulatory actions taken outside the EU.

Notification to the competent authorities of the Member State(s) concerned should be submitted in accordance with the practices established at national level if applicable. Where national competent authorities have not provided particular instructions the template cover letter and notification report table “Notification of withdrawn products” should be used.

In addition, if the action is related to efficacy, safety, quality and/or compliance issues as listed in question “What information should be included in my notification and to whom should I notify?”, the MAH of a nationally authorised medicinal product should also notify the Agency together with the reasons for such action, regardless of whether the action is going to be taken in the EEA or in a third country.

In case of an emerging safety issue (ESI), should the MAH decide to take any action with regards to the marketing of the medicinal product or to the marketing authorisation of this medicinal product, the notification of such action to the Agency according to the present provisions should be done in parallel to the notification to the ESI mailbox (P-PV-emerging-safety-issue@ema.europa.eu).

References

- Article 23a of Directive 2001/83/EC, as amended
- Article 123 of Directive 2001/83/EC, as amended

21.7. How will the Agency inform the Member States? Rev. Aug 2014

Once the Agency receives a notification of a “withdrawn product” from a MAH whether for a centrally or nationally authorised medicinal product, the Agency forwards such notification to all Competent Authorities in the EEA without undue delay.

References

- Article 14b of Regulation (EC) No 726/2004, as amended
- Article 123 of Directive 2001/83/EC, as amended

21.8. What will be the follow-up of my notification?

As part of the follow-up of the notified action, Member States and/or the Agency may request additional information from the MAH. Depending on the action taken and the grounds for such action, the appropriate regulatory procedure will be initiated where applicable.

21.9. Will the Agency publish the list of “withdrawn medicinal products”? Rev. Aug 2014

The Agency should annually make public a list of human medicinal products which have been withdrawn from the EU market. This includes both centrally and nationally authorised products for

which marketing authorisations have been refused, revoked or suspended and products, whose supply has been prohibited or which have been withdrawn from the market.

The list specifies whether the action has been initiated by the Marketing Authorisation Holder or whether it was imposed by the Competent Authorities (e.g. following a review procedure at European level).

The EMA aims at publishing an updated list twice a year.

Link to the list of "withdrawn medicinal products": *<List of withdrawn medicinal products in accordance with Art. 123(4) of the Directive>*

References

- Article 123(4) of Directive 2001/83/EC, as amended
- List of withdrawn medicinal products in accordance with Art. 123(4) of the Directive

22. Marketing and cessation notification

The following guidance should be read in conjunction with “Questions and answers on the application of the so-called ‘sunset clause’ to centrally authorised medicinal products (EMEA/180079/2005)” and questions and answers on “Withdrawn products notification (EMA/660402/2013)”.

22.1. What is the meaning of “actual marketing” / “placing on the market”? Rev. Oct 2013

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) of Regulation (EC) No 726/2004
- Article 23a 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

22.2. What is the meaning of “cessation of placing on the market”? Rev. Oct 2013

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 may no longer be 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) of Regulation (EC) No 726/2004
- Article 23a 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

22.3. When to report / notify cessation to the Agency? Rev. Aug 2014

When the cessation affects a presentation of a centrally authorised product in at least one Member State, the MAH should report such action through the marketing status overview in the context of the "sunset clause monitoring" (see questions 1.4 "*When and how to report the Agency with the marketing status overview*?" and 1.6 "*What information should be reported to the Agency on the medicinal product marketing status*?").

In addition when the cessation affects either a pharmaceutical form or strength of a medicinal product in at least one Member State, a notification should be made to the Agency according to the provisions laid down in article 23a and 123 (2) of Directive 2001/83/EC and article 13 and 14b of Regulation (EU) No 726/2004 via the dedicated mailbox "withdrawnproducts@ema.europa.eu" using the template cover letter and notification report table "Notification of withdrawn products" (see Questions and answers on the application of the so-called 'sunset clause' to centrally authorised medicinal products).

Please note that when the cessation concerns a presentation that may raise a public health concern. The MAH has to exercise his best judgement to determine when it is appropriate to notify such cessation.

References

- Article 13(4) of Regulation (EC) No 726/2004
- Article 23a of Directive 2001/83/EC, as amended

22.4. When and how to report the marketing status overview to the Agency? Rev. Aug 2014

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 Agency of the marketing status of their medicinal product(s) considering 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 Union. 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 the anniversary of the Commission Decision date. The reporting table should be attached to the cover letter (see also question 1.7 "*What is the reporting format to the Agency and to whom to report*?").

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.

References

- Article 13(4) of Regulation (EC) No 726/2004
- Article 20 of the Regulation (EC) No 726/2004

22.5. What is the intended use of the marketing status reporting for the purpose of the sunset clause monitoring? Rev. Oct 2013

The marketing status overview/reporting provides data that are the basis for the monitoring of the sunset clause (See also Sunset clause monitoring).

22.6. What information should be reported to the Agency on the medicinal product marketing status? Rev. Aug 2014

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.

MAHs shall also report to the Agency any cessation (temporary/permanent) of marketing of their medicinal product per presentation and per Member State.

MAHs are advised that when 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) 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.

22.7. What is the reporting format to the Agency and to whom to report? Rev. Aug 2014

MAHs should inform the Agency of the marketing status of their medicinal product(s) using the electronic template provided in question 1.4 "*When and how to report the Agency with the marketing status overview?*"

Marketing status reports relating either to the first marketing or updates should be sent by the MAH to the mailbox marketingstatus@ema.europa.eu and copy the EMA Product Lead and the medicinal product mailbox. See questions "*When to report / notify a cessation to the Agency?*" and "*When and how to notify the Agency with the marketing overview?").*

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

22.8. Is there a database to collect the marketing status information? Rev. Aug 2014

To make the reporting for the MAH easier and to facilitate the tracking of this information by the Agency 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 Agency will make a public announcement prior to the entry into force of this extension of the database.

22.9. Does the Agency intend to publish information about the marketing status of the medicinal products? Rev. Aug 2014

Currently the marketing status is not published. However, MAHs should be aware that when the particular reporting functionality within EVMPD is set up, the information on availability of the medicinal product and its various presentations per Member State will be made public by the Agency as “marketed”/ “not marketed” based on the data entered in EVMPD by the MAH.

23. Sunset clause monitoring

23.1. 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

23.2. 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

- Document published by the Commission on 10 October 2005 - Application of the “Sunset Clause” in the Review of the Pharmaceutical Legislation to Medicinal Products Authorised before Directives 2004/27/EC and 2004/28/EC and Regulation (EC) No 726/2004 start to apply
- Chapter 1 (section 2.4.2), The Rules governing Medicinal Products in the European Union, Notice to Applicants, Volume 2A

23.3. 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

23.4. 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

23.5. 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

23.6. 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.

23.7. 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

24. Other

24.1. 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

24.2. Can I request Scientific advice / Protocol assistance during the post-authorisation phase? Rev. Mar 2009

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)

24.3. Could my medicinal product be subject of Parallel distribution? Rev. May 2013

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 Competent Authorities may have on the parallel distribution notification procedure.

Reference

- Title IV of Regulation 726/2004 (EC)
- FAQ (frequently asked questions) on Parallel Distribution

24.4. 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 IA_{IN} 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

24.5. How and to whom shall I submit my application? Rev. Jul 2015

24.5.1. Submission to the EMA

From 1 March 2014, the use of the eSubmission Gateway or web client is mandatory for all electronic Common Technical Document (eCTD) submissions through the centralised procedure. The European Medicines Agency (EMA) no longer accepts submissions on CD or DVD. This applies to all applications for human medicines.

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 European Medicines Agency eSubmission Gateway: Questions and answers relating to practical and technical aspects of the implementation and the eSubmission Gateway web client: Guidance for applicants . Applicants must not send duplicate submissions electronically or via CD-ROM or DVD as this might lead to delays in the handling of applications.

An automated acknowledgement email is sent from the system confirming whether the submission has passed the relevant technical validation criteria and whether it has been uploaded to the Agency's review tool and made available via the Common Repository. There is no need to send any accompanying hard media or separate paper cover letter as the cover letter will be in the relevant part of eCTD module 1 in PDF format.

Where applicable, revised product information Annexes (including Annex A, if applicable) should be included in electronic (Word and PDF) format in the same eSubmission Gateway and eSubmission Web Client package within a folder called 'working documents'. Where applicable changes in Word

documents should be indicated using 'Tools-Track Changes'. Clean PDF versions should have all changes 'accepted'.

24.5.2. Submission to the (Co-) Rapporteurs and other Committee Members

- **Type IAs, IBs, PAMs, Art 46, Transfers, 61(3) Notifications**

  An electronic copy should also be sent to the (Co-) Rapporteurs and other Committee members after the e-submission Gateway/ Web Client confirmation of a technically valid submission to the EMA if the relevant NCA is not using the Common Repository.

  For the dossier requirements of the (Co-) Rapporteurs and other Committee members, including delivery addresses where applicable, please refer to the following document: Dossier requirements for Centrally Authorised Products (CAPs).

- **Type II variations, Extensions of indications, Renewals, Annual Renewals, Annual reassessment, PASS**

  One electronic copy should be submitted to the (Co-) Rapporteurs after the e-submission Gateway/ Web Client confirmation of a technically valid submission to the EMA if the relevant NCA is not using the Common Repository.

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

  Upon validation by the agency the MAH should forthwith send one electronic copy of the type application to other Committee members who are not yet using the Common Repository, including any additional data or information supplied during the validation phase.

  For the dossier requirements of the (Co-) Rapporteurs and other Committee members, including delivery addresses where applicable, please refer to the following document: Dossier requirements for Centrally Authorised Products (CAPs).

  For the particularities concerning applications under Worksharing and PSUR which may include nationally authorised products please check the information in the respective sections of the Post-authorisation Guidance.

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

  Please also refer to the TIGes Harmonised Guidance for specific advice on eCTD Submissions in the EU.

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.

The use of the electronic Application Forms (eAFs) in the Centralised Procedure is mandatory as of 1 July 2015. Information on the electronic Application Form can be found in the eSubmissions eAF webpage.4

When submitting applications the MAH should observe the recommended submission dates published on the agency website (see 'submission deadlines and full procedural timetables')

References

- 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)
- TIGes Harmonised Guidance for eCTD Submissions in the EU
- eSubmission website
- eSubmission Gateway Q&A
- eSubmission Gateway Web Client Q&A

24.6. Must I submit my post-authorisation application in eCTD format? ***Rev. Aug 2014***

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)for centrally authorised products, Notifications etc).

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 the same eSubmission Gateway and eSubmission Web Client package within a folder called "xxxx_working documents", where the number (xxxx) equals the sequence number..

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.

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 Committee members only in accordance with the Dossier requirements for Centrally Authorised Products (CAPs).

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

24.7. What happens to my orphan designation at the end of the market exclusivity period? New Feb 2013

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

24.8. Who is my contact at the European Medicines Agency during post-authorisation procedures? NEW Apr 2015

During the post-authorisation phase of a medicinal product a Procedure Manager (PM) will be allocated for each post-authorisation procedure submitted. This concerns all types of variations, extension applications, renewals, annual-reassessments, PSURs/PSUSAs, PASS protocols, referrals, post-authorisation measures as well as administrative procedures (marketing authorisation transfers, Article 61(3) notifications).

The allocated PM is the marketing authorisation holder's (MAH) primary contact point for a particular procedure. The PM is nominated upon receipt of the application and will validate the application where applicable. The MAH will be notified of her/his name and contact details in the context of the validation or by notification of the start of the procedure. Subsequent to the validation the allocated PM will remain the contact point throughout the procedure until Commission Decision where applicable.

The PM oversees all aspects of the management of the specific procedure. The MAH should contact the PM for any questions regarding the evaluation procedure.

Depending on the scope and the complexity of the particular application other members of the product team may be involved during the evaluation, as needed. In such cases the EMA product lead (EPL) or other members of the product team may contact the MAH directly to facilitate the discussion on the scientific aspects of the evaluation. Where the applicant is in direct contact with the EPL (or another member of the EMA product team) the PM should always be copied on the correspondence.

Regarding the handling of procedures for extension of indication, please refer to the specific Q&A.

Where an MAH requires regulatory procedural guidance or has questions prior to submission of the application, the **Pre-submission Queries Service (PQS)** can be contacted. The PQS aims at addressing the queries within 5 working days. To help the EMA deal with the enquiry, the product name should be provided together with detailed background information relating to the query. With the response to the query, the MAH will be notified of the contact who dealt with the request in case follow-up or clarification is required. Any PQS advice received should be attached to the cover letter at time of submission of the application to facilitate the validation process when applicable. For more information on how to contact the PQS please refer to the post-authorisation guidance Q&A's for each procedure under the query: "Who should I contact if I have a question when preparing my application?"

For products with a high number of upcoming post-authorisation procedures, which may require a detailed planning discussion, the PQS should be the first point of contact. The PQS team will liaise with the relevant members of the product team to provide a comprehensive response, and a follow-up discussion will be arranged where necessary.

Please see other relevant questions and answers in the EMA pre-authorisation guidance "What is the role of the EMA product team? and Who is my contact at the European Medicines Agency during a marketing authorisation application (MAA) evaluation procedure?" and in the EMA post-authorisation guidance "Who is my contact at the European Medicines Agency during an application procedure for extension of indication?" and "Who is my contact at the European Medicines Agency during the post-authorisation phase outside any evaluation procedures?".

24.9. Who is my contact at the European Medicines Agency during the post-authorisation phase outside any evaluation procedures? NEW Apr 2015

Where any issue in relation to the product arises during the post-authorisation phase, which is not covered by a specific evaluation procedure (i.e. not related to a variation, extension application, renewal, annual-reassessment, PSURs/PSUSA, PASS protocol, referral, post-authorisation measure as well as an administrative procedures), the assigned EMA product lead (EPL) is the contact for the marketing authorisation holder (MAH).

Such situations refer to a variety of topics and do include, where applicable, upcoming shortages in supply of the medicinal product, information about emerging safety issues, provision of important late-breaking information that potentially impacts the product profile or the marketing authorisation, as well as withdrawal of the marketing authorisation.

Communication through the EPL is supplementary to, not replacing, the formal reporting requirements and established reporting channels where they exist, e.g. for pharmacovigilance reporting.

Please see other relevant questions and answers in the EMA pre-authorisation guidance “What is the role of the EMA product team? and Who is my contact at the European Medicines Agency during a marketing authorisation application (MAA) evaluation procedure?” and in the EMA post-authorisation guidance “Who is my contact at the European Medicines Agency during an application procedure for extension of indication?” and “Who is my contact at the European Medicines Agency during the post-authorisation procedures?”.