EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

20 January 2010
EMA/40404/2010

Post-Authorisation Procedural Advice

Human Medicinal Products

New Variation Regulation (EC) No 1234/2008

7 Westferry Circus ● Canary Wharf ● London E14 4HB ● United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7523 7319
E-mail info@ema.europa.eu **Website** www.ema.europa.eu

An agency of the European Union

Post-authorisation procedural advice on variation regulation (EC) No 1234/2008

This version has been created to provide post-authorisation procedural advice specifically on the Variation Regulation (EC) No 1234/2008.

Taking into account that variations submitted according to Regulation (EC) No 1085/2003 are still being processed, the full integrated post-authorisation procedural advice will be maintained.

The full post-authorisation procedural advice will be updated to include this specific advice on Variation Regulation (EC) No 1234/2008 at a later stage.

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.

The Agency emphasises the usefulness of **pre-submission dialogue** between MAHs and the Agency/(Co-) Rapporteur. The Agency's Product Team is available to address any questions MAHs may have regarding a particular upcoming post-authorisation application. 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 speedily.

To obtain the information on a certain topic, simply **click** on the **highlighted key-word**. We trust that the information, linked to the key-word, answers most of your queries. However, in case of doubt and since applications may have their own particularities not addressed in this document, we strongly encourage MAHs in such cases to contact the Agency in advance of the planned submission.
Where necessary, a pre-submission meeting can be arranged.

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.

This Post-Authorisation procedural advice on Variation Regulation (EC) No 1234/2008 addresses the following topics:

- **Type IA Variations**
- **Type IB Variations**
- **Type II Variations**
- **Type II Variations vs Extension applications**
- **Extension Applications**
- **Grouping of Variations**
- **Worksharing**
- **Changing the (Invented) Name of a Centrally Authorised Medicinal Product**

Note:

It should be highlighted that this document has been produced for guidance only and should be read **in conjunction** with "The Rules governing Medicinal Products in the European Union, Volume 2, Notice to Applicants".

MAHs must in all cases comply with the requirements of Community Legislation. Provisions, which extend to Iceland, Liechtenstein and Norway by virtue of the EEA agreement, are outlined in the relevant sections of the text.

Type IA Variations

1. When shall I submit my Type IA/IA_{IN} variation?
2. Can I group the submission of Type IA/IA_{IN} variations? Can they be grouped with other types of variations?
3. Is the (Co-) Rapporteur involved in the review of Type IA/IA_{IN} variations?
4. How shall I present and submit my Type IA/IA_{IN} variation?
5. How shall my Type IA/IA_{IN} variation be handled (timetable)?
6. Can my type Type IA/IA_{IN} be part of worksharing?
7. What should I do in case of an unfavourable outcome for my type IA/IA_{IN} variation(s)?
8. What fee do I have to pay for a Type IA/IA_{IN} variation?
9. Do I have to submit mock-ups and specimens?
10. When do I have to submit revised product information? In all languages?
11. How and wenn will the updated product information Annexes become part of the Marketing Authorisation?
12. How to obtain new EU sub-numbers for a Type IA_{IN} variation concerning an additional presentation (e.g. new pack-size)?

Type IB Variations

1. What changes are considered Type IB Variations?
2. Is the (Co-) Rapporteur involved in Type IB Variations?
3. Can I group the submission of Type IB variations? Can they be grouped with other types of variations?
4. How shall I present and submit my Type IB Variation?
5. How shall my Type IB Variation be handled (timetable)?
6. What fee do I have to pay for a Type IB Variation?
7. Do I have to submit mock-ups and specimens?
8. When do I have to submit revised product information? In all languages?
9. How to obtain new EU sub-numbers before submitting a Type IB variation for an additional presentation (e.g. new pack-size)?
10. How and when will the updated Annexes become part of the Marketing Authorisation?

Type II Variations

1. What changes are considered Type II Variations?
2. Is the (Co-) Rapporteur involved in Type II Variations?

3. Can I group the submission of Type II variations? Can they be grouped with other types of variations?
4. How shall I present my Type II Variation application?
5. How and to whom shall I submit my Type II Variation application?
6. When shall I submit my Type II variation application?
7. How shall my Type II application be handled (timetable)?
8. Which post-opinion steps apply to my Type II variation and when can I implement the approved changes?
9. What fee do I have to pay for a Type II Variation?
10. Do I have to submit mock-ups and specimens?
11. When do I have to submit revised product information? In all languages?
12. Will there be any publication on the outcome of my Type II variation?
13. What specific requirements apply to my Type II variation for a new orphan indication?
14. Do I need to address any paediatric requirements in my type II variation application?

Type II Variations *vs* Extension applications

1. When will my variation application be considered a Type II variation or an Extension application?

Extension Applications

1. Will my invented name change?
2. Is the (Co-) Rapporteur involved in Extension Applications?
3. How shall I present my Extension Application?
4. Can I group the submission of Extensions with other types of variations?
5. How, when and to whom shall I submit my Extension Application?
6. How shall my Extension application be handled (timetable)?
7. What fee do I have to pay for an Extension Application?
8. Do I have to submit mock-ups and specimens?
9. When do I have to submit revised product information? In all languages?
10. Will there be any publication on the outcome of my Extension application?
11. Do I need to address any paediatric requirements in my extension application?

Grouping of Variations

1. What type of variations can be grouped?
2. What groups of variations would be considered acceptable?
3. How shall I present a grouped variations application?
4. What procedure number will be given to grouped variation applications?
5. Can grouped variations be subject to a worksharing procedure?
6. How will grouped variation applications be handled (timetable)? What will be the outcome of the evaluation of a grouped variation application?
7. How and when will the marketing authorisation be updated for grouped variations; when can I implement the approved changes?
8. What fee do I have to pay for grouped variations?

Worksharing

1. What is worksharing and what type of variations can be subject to worksharing?
2. What variations would be considered acceptable for worksharing?
3. What pre-submission steps will apply to a worksharing procedure?
4. How shall I present a variation application under worksharing?
5. How and to whom shall I submit my variation application under worksharing?
6. What procedure number will be given to variation applications under worksharing?
7. How will variation applications under worksharing be handled (timetable)? What will be the outcome of the evaluation of a variation application under worksharing?
8. How and when will the marketing authorisations be updated following a worksharing procedure; when can I implement the approved changes?
9. What fee do I have to pay for variation applications under worksharing?
10. When do I have to submit revised product information? In all languages?

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

1. Can I change the (Invented) Name of my CAP?
2. Is the IN checking procedure mandatory for the new proposed IN?
3. How shall I present my IN change application?
4. Do I need to submit amended mock-ups/specimens?

Type IA variations

1. When shall I submit my Type IA/IA$_{IN}$ variation(s)?

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

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

- Type IA variations requiring immediate notification ('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.

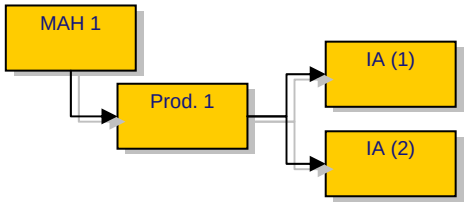
[1] For example the type IA_{IN} for addition, deletion or replacement of components in the flavouring or colouring system requires stability data on at least two pilot scale or industrial scale batches.

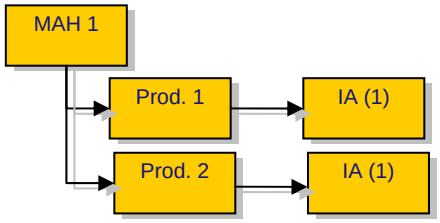
2. Can I group the submission of Type IA/IA$_{IN}$ variations? Can they be grouped with other types of variations?

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.

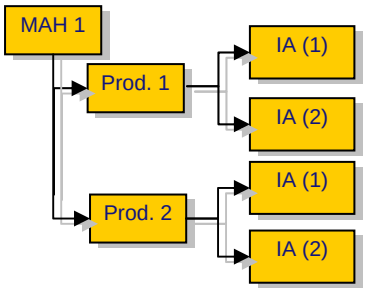
Possible grouping of Type IA/IA$_{IN}$ changes only:

- **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:

- Type IA/IA$_{IN}$ can also be grouped with other variations (e.g. Type IB, Type II, Extension).
- 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.

3. Is the (Co-) Rapporteur involved in the review of Type IA/IA$_{IN}$ Variations?

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 (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 (IB, II, extension), the Rapporteur will be involved.

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

A Type IA/IA$_{IN}$ variation notification should contain the elements listed in Annex IV of the Variations Regulation and should be presented in accordance with the appropriate headings and numbering of the EU-CTD format.

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

- Cover letter (for groupings, include a short overview of the nature of the changes).
- The completed EU variation application form (as published on the Commission's website in Volume 2C of the Notice to applicants), including the details of the marketing authorisation(s) concerned, as well as a description of all variations submitted together with their date of implementation. Where a variation leads to or is the consequence of other variations, a description of the relation between these variations should be provided in the appropriate section of the application form. MAHs are reminded that the variation application form should be signed by the official contact person as specified in section 2.4.3 of Part IA/Module 1. Should the official contact person not be available, an official letter of authorisation confirming the delegation of signature to a different person should be enclosed. For a grouping affecting several medicinal products, MAHs are reminded to confirm in the application form under "Declaration of the applicant" that the MAs concerned belong to the same MAH and that the main signatory confirms authorisation to sign on behalf of the designated contacts.
- Reference to the part of the Classification guideline, indicating that all conditions and documentation requirements are met, or reference to the published Article 5 Recommendation, if applicable, used for the relevant application.
- All documentation as specified in the Commission Classification Guideline.
- If applicable, the revised summary of product characteristics, labelling and/or package leaflet as a full set of annexes. (See also 10. When do I have to submit revised product information? In all languages?)
- Where the overall design and readability of the outer and immediate packaging and/or package leaflet is affected, the need for the provision of mock-ups or specimens should be discussed with the Agency Medical Information Sector on a case-by-case basis.

Grouped Type IA/IA$_{IN}$ 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?".

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

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 rapid procedures. Similarly, deficient and missing

documentation can lead to rejection of the variation. The MAH can be requested to provide missing documentation during the validation of the application. Not providing the requested information immediately on request of the Agency can lead to rejection of the variation.

For more detailed queries on technical and procedural matters related to a Type IA/IA_{IN} Variation for a specific product and in order to avoid rejection, please contact the relevant Product Team Member for your product in the Quality Sector or Safety and Efficacy, Sector for quality or safety/efficacy related variations respectively.

Submission of Type IA/IA_{IN} Variation Notifications

Type IA/IA_{IN} variation notifications should be addressed and sent to the attention of the Product and Application Business Support (V-PD-BUS) at the following address:

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

Two electronic copies (CD-ROM or DVD) of the Variation Notification presented in eCTD format should be submitted to the Agency, together with an original, signed paper cover letter. The Product Team Leader and Product Team Member in the Quality Sector should be indicated in copy ("cc") on the cover letter.

Where applicable, revised product information Annexes should be included in electronic (Word and PDF) format (see also "When do I have to submit revised product information? In all languages?").

Two electronic copies should also be sent to the Rapporteur at the time of submission (for information). For maintaining the life cycle of the eCTD dossier, the MAH should also submit one electronic copy of the Variation Notification in eCTD format to the Co-Rapporteur and CHMP members. Where applications are amended during the agency's review, such as a withdrawal, a closing 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.

For a full overview of dossier requirements for (Co-)Rapporteur and CHMP members, including delivery addresses, please refer to the following document: PAG dossier requirements.

For general guidance regarding the format of submissions to the Agency, please refer to: "Can or must I submit my post-authorisation application in eCTD format", as well as to the "EMA Q&A relating to Practical and Technical aspects of eCTD implementation" published on the Agency e-submission website (http://esubmission.ema.europa.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.

References

- Commission Regulation (EC) No 1234/2008 (OJ L334 of 12 December 2008)
- "Variation application form, The Rules governing Medicinal Products in the European Union, Notice to Applicants, Volume 2C
- Dossier requirements for post-authorisation submissions in the centralised procedure
- "General Information", The Rules governing Medicinal Products in the European Union, Notice to Applicants, Volume 2A, Chapter 7

5. How shall my Type IA/IA$_{IN}$ variation be handled (timetable)?

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 the MAH by fax or Eudralink and paper copy by post about the outcome of the review.

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.

6. Can my Type IA/IA$_{IN}$ be part of worksharing?

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?"

In addition, it is also possible to include 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 review of the Type IA/IA$_{IN}$ variation will be performed as part of the worksharing procedure.

7. What should I do in case of an unfavourable outcome for my type IA/IA$_{IN}$ variation(s)?

A Type IA/IA$_{IN}$ variation will be rejected when not all of the conditions for the Type IA/IA$_{IN}$ variation are met, or when the submitted documentation as required by the Classification Guideline is deficient. 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 Product Defects (http://www.ema.europa.eu/Inspections/Defectinstruction.html).

8. What fee do I have to pay for a Type IA/IA$_{IN}$ variation?

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/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 IA/IA$_{IN}$ variations, whether consequential or not, will each attract a separate Type IA fee.

The Agency will issue an invoice on the date of the notification of the review outcome to the applicant and fees will be payable within 45 calendar days of the date of the said notification. The invoice will be sent to the billing address indicated by the applicant and will contain clear details of the product(s) and procedures involved, the type of fee, the amount of the fee, the bank account to where the fee should be paid and the due date for payment. Where more than one procedure is processed in a given month a summary invoice or statement will be issued at the end of each month for payment within 30 days of the end of the month.

To facilitate this operation, applicants/MAHs who are demanding a Purchase Order Number on the Agency invoice must quote this Number clearly on the cover letter of a given application. The Agency will no longer accept separate notifications of Purchase Order Numbers not associated with the dossier. The applicants/MAHs must state the following sentence on the cover letter of each application:

Please quote Purchase Order Number …….. on the invoice.

If the applicants/MAHs do not require a Purchase Order Number on the Agency invoice, this must also be clearly stated in the cover letter.

Where a Type IA/IA$_{IN}$ application is considered 'invalid', an administrative fee may be charged by the Agency.

If the MAH withdraws the Type IA variation application before the review outcome fax has been sent out to the MAH, no fee will be retained.

For more information about fees and fee payment in the Centralised Procedure, please consult: http://www.ema.europa.eu/htms/general/admin/fees/feesfaq.htm.

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" (EMA Website / General / Admin)

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

Mock-ups

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

Specimens

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

Note:

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

The above principles also apply to mock-ups and specimens for Iceland, which have to be sent directly to the Icelandic authorities:

Ms Thorbjorg Kjartansdottir / Ms Gudrun Einarsdottir
ICELANDIC MEDICINES CONTROL AGENCY
Eiðistorg 13-15,
IS - 170 Seltjarnarnes
Tel.: + 354 520 2100, Fax: + 354 561 2170
E-mail: thorbjorg.kjartansdottir@lyfjastofnun.is / gudrun.einarsdottir@lyfjastofnun.is

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)

10. When do I have to submit revised product information? In all languages?

In case the Type IA/IA$_{IN}$ notification affects SPC, 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)

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

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

Icelandic and Norwegian language versions must always be included.

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

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

MAHs are reminded that any type of change to the list of Local Representatives cannot be included in a Type IA/IA$_{IN}$ application, but need to be submitted as a 61(3) Notification procedure or as part of an ongoing/upcoming Type II variation affecting Annex IIIB.

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 clean Word and PDF format, together with the variation application. Where the variation introduces a new EU sub-number, the new 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 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.

11. How and when will the updated product information Annexes become part of the Marketing Authorisation?

For Type IA/IA$_{IN}$ variations affecting the product information Annexes to the Commission Decision, the Commission Decision will be updated within

2 months for a Type IA variation

6 months for a Type IA$_{IN}$ variation.

By the end of these periods, 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 2 or 6 months 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.

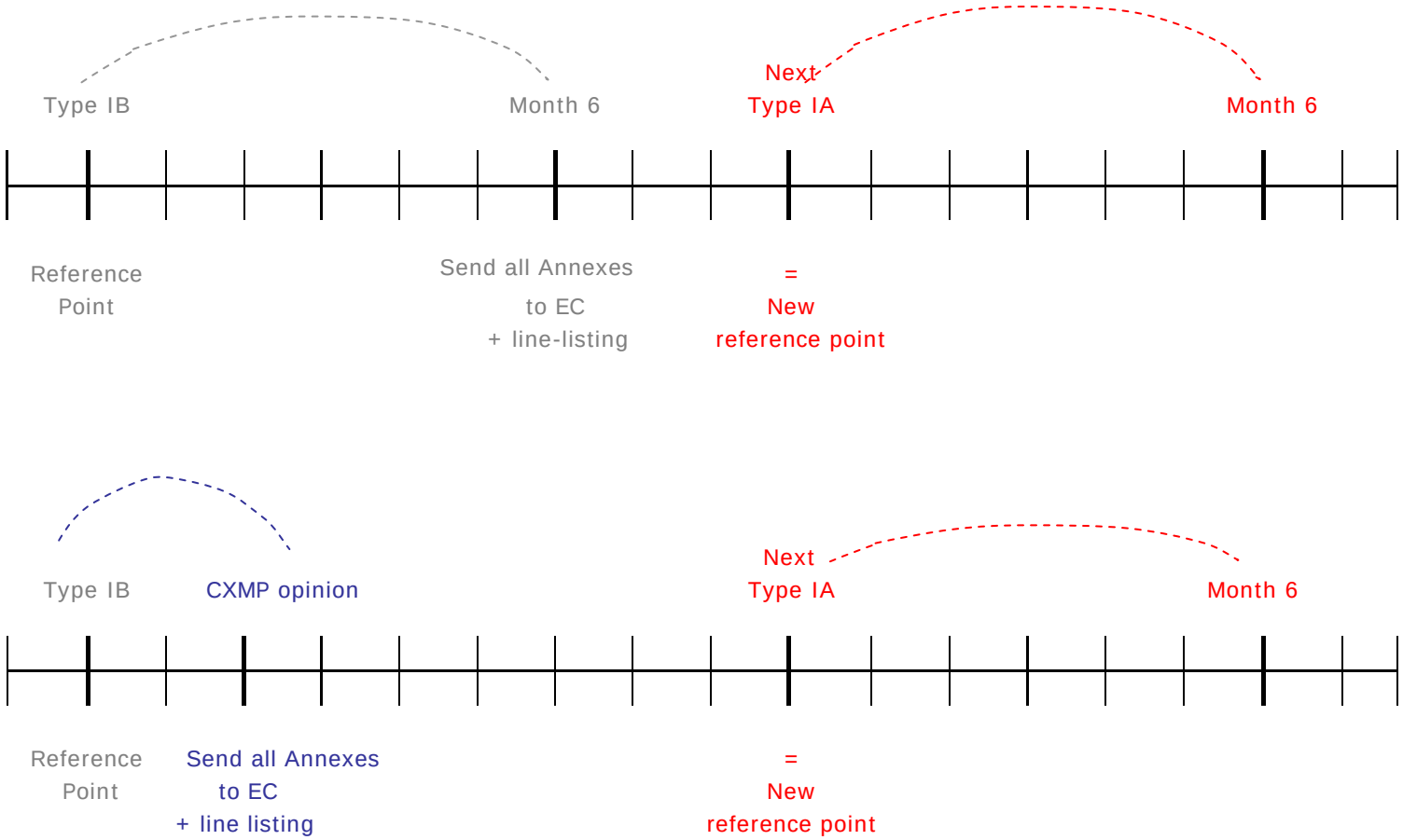
However, where any Opinion affecting the Annexes is transmitted to the Commission within these 2 or 6 months, respectively, the changes of the Type IA/IA$_{IN}$ notification(s) concerned will already be included in the Annexes to that Opinion and will consequently be reflected in the resulting Commission Decision. This Commission Decision will therefore replace the 2 or 6-monthly updating of the MA for the Type IA/IA$_{IN}$ notification(s) concerned.

At the occasion of a 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 6-monthly updating process. A similar process will be followed in case of 2-monthly MA updating)

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 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.


Type IB
Month 6
Next
Type IA
Month 6
Reference
Point
Send all Annexes
to EC
+ line-listing
=
New
reference point

Type IB
CXMP opinion
Next
Type IA
Month 6
Reference
Point
Send all Annexes
to EC
+ line listing
=
New
reference point

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

In the specific case of a Type IA_{IN} Variation for an additional presentation, the MAH should obtain the new EU marketing authorisation sub-number in advance of implementation, in order to be able to include the new sub-number on the packaging of the presentation concerned. The new sub-number should therefore be requested from and 'reserved' (for future formal variation notification submission) with the European Commission's Decision-Making contact point in advance of the planned implementation of the Type IA_{IN} Variation.

When submitting the corresponding Type IA_{IN} Variation notification to the Agency, the MAH should confirm in the application form and/or cover letter that the new EU sub-number(s) had been 'reserved' with the European Commission.

Type IB variations

1. What changes are considered Type IB Variations?

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. However, the MAH must wait a period of 30 days to ensure that the notification is deemed acceptable by the National Competent Authority/the Agency before implementing the change ("Tell, Wait and Do" procedure).

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

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

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

References

- Commission Regulation (EC) No 1234/2008 (OJ L334 of 12 December 2008)
- Classification guideline
- Procedural guideline

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 I notification be handled (timetable”?

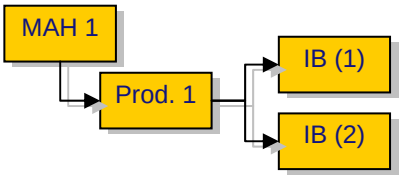
The Co-Rapporteur is not involved in Type IB variations. However, a copy of the complete Type IB notification must also be submitted to the Co-Rapporteur.

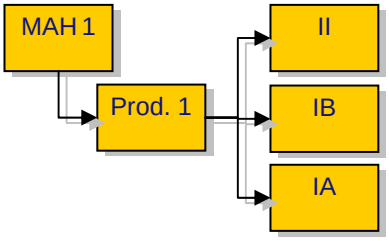
3. Can I group the submission of Type IB variations? Can they be grouped with other types of variations?

MAHs may choose to group the submission of several Type IB variations for the same product into one notification. It is also possible for a MAH to group a Type IB variation with other variation(s) for the same product (e.g. Type IA, Type II, Extension), where applicable.

Allowed groupings are listed in Annex III of the Variations Regulation. Other groupings have to be agreed in advance with the Agency. Any proposal to group clinical and quality variations should be adequately justified.

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





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

References

- Commission Regulation (EC) No 1234/2008 (OJ L334 of 12 December 2008)
- Procedural guideline

4. How shall I present and submit my Type IB Variation?

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

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

- Cover letter (for groupings, include a short overview of the nature of the changes and indicate whether it is an allowed grouping in Annex III of the variations regulation or the grouping has been agreed with the Agency).
- The completed EU variation application form (as published on the Commission's website in Volume 2C of the Notice to applicants), including the details of the marketing authorisation concerned. Where a variation is considered a Type IB by default, a detailed justification for its submission as a Type IB notification must be included. MAHs are reminded that the variation application form should be signed by the official contact person as specified in section 2.4.3 of Part IA/Module 1. Should the official contact person not be available, an official letter of authorisation confirming the delegation of signature to a different person should be enclosed.
- Reference to the part of the Classification guideline, or reference to the published Article 5 Recommendation, if applicable, used for the relevant application.
- Relevant documentation in support of the proposed variation including all documentation as specified in the Commission Classification Guideline.
- For variations submitted to implement changes requested by the Agency or for generic/hybrid/biosimilar medicinal products, where no new additional data are submitted by the MAH, a copy of the request should be annexed to the cover letter.
- If applicable, the revised summary of product characteristics, labelling and/or package leaflet as a full set of annexes. (See also 8. When do I have to submit revised product information? In all languages?).
- 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 variation complies fully with the data and documentation requirements as specified in the Classification Guideline and in the Procedural Guideline. The MAH should pay particular attention to grouping of variations, for which each change should be clearly identified as well as the related supportive documentation. A confusing dossier presentation will not facilitate rapid procedures.

For more detailed queries on technical and procedural matters related to a Type IB notification for a specific product and in order to avoid rejection, please contact the relevant Product Team Member for your product in the Quality Sector or Safety and Efficacy, Sector for quality or safety/efficacy related variations respectively.

Submission of Type IB Notifications

Type IA/IA_{IN} variation notifications should be addressed and sent to the attention of the Product and Application Business Support (V-PD-BUS) at the following address:

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

Two electronic copies (CD-ROM or DVD) of the Variation application form and supportive documentation should be submitted to the Agency, together with an original, signed cover letter. The Product Team Leader and Product Team Member in the Quality Sector should be indicated in copy ("cc") on the cover letter.
Where applicable, revised product information Annexes should be provided in electronic (Word and PDF) format (see also Type IB variations - "When do I have to submit revised product information? In all languages?").

Two electronic copies should also be sent to the Rapporteur at the time of submission for evaluation. For maintaining the life cycle of the eCTD dossier, the MAH should also submit one electronic copy of the Variation Notification in eCTD format to the Co-Rapporteur and CHMP members. Where applications are amended during the agency's review, such as a withdrawal, a closing 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.

For a full overview of dossier requirements for (Co-)Rapporteur and CHMP members, including delivery addresses, please refer to the following document: PAG dossier requirements.

For general guidance regarding the format of submissions to the Agency, please refer to: "Can or must I submit my post-authorisation application in eCTD format", as well as to the "EMA Q&A relating to Practical and Technical aspects of eCTD implementation" published on the Agency e-submission website (http://esubmission.ema.europa.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.

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

Where the CHMP requests a Type IB variation following the assessment of a PSUR, FUM or SO, data submitted under Article 45/46 of Regulation (EC) No 1901/2006, following adoption of class-labelling or amendments to a Core SPC or requests a Type IB 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)
- "Variation application form", The Rules governing Medicinal Products in the European Union, Notice to Applicants, Volume 2C
- Dossier requirements for post-authorisation submissions in the centralised procedure

- "General Information", The Rules governing Medicinal Products in the European Union, Notice to Applicants, Volume 2A, Chapter 7

5. How shall my Type IB variation be handled (timetable)?

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

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

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

Receipt of Type IB variation	Day x
Start of Agency validation	Day x+1
Agency validation *(in case of missing information, this period will be extended)*	Day x+5

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

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

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

Within 30 days following the acknowledgement of receipt of a valid notification, the Agency will notify the MAH and the Commission of the outcome of the procedure. If the Agency has not sent the holder its opinion on the notification within 30 days, the notification shall be deemed acceptable.

In case of an unfavourable outcome the MAH may, within 30 days, amend the notification to take due account of the grounds for the non-acceptance of the variation. If the MAH does not amend the notification as requested, the notification shall be rejected.
Within 30 days of receipt of the amended notification, the Agency will inform the MAH and the Commission of its final (non-)acceptance of the variation and whether the Commission Decision granting the Marketing Authorisation requires any amendments.

Where Type IB Variations affect the Annexes to the Marketing Authorisation, such changes can be implemented without awaiting the 6-monthly update of the Commission Decision and the agreed change(s) should be included in the Annexes of any subsequent Regulatory Procedure.

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

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

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

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

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

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

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

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

6. What fee do I have to pay for a Type IB Variation?

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

The Agency will issue an invoice 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. The invoice will be sent to the billing address indicated by the MAH and will contain clear details of the product and procedures involved, the type of fee, the amount of the fee, the bank account to where the fee should be paid and the due date for payment. Where more than one procedure is processed in a given month a summary invoice or statement will be issued at the end of each month for payment within 30 days of the end of the month.

To facilitate this operation, applicants/MAHs who are demanding a Purchase Order Number on the Agency invoice must quote this Number clearly on the cover letter of a given application. The Agency will no longer accept separate notifications of Purchase Order Numbers not associated with the dossier. The MAH must state the following sentence on the cover letter of each application:

Please quote Purchase Order Number …….. on the invoice.

If the MAH does not require a Purchase Order Number on the Agency invoice, this must also be clearly stated in the cover letter.

For more information about fees and fee payment in the Centralised Procedure, please consult: http://www.ema.europa.eu/htms/general/admin/fees/feesfaq.htm.

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

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" (EMA Website / General / Admin)

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

Mock-ups

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

Specimens

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

Note:

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

The above principles also apply to mock-ups and specimens for Iceland, which have to be sent directly to the Icelandic authorities:

Ms Thorbjorg Kjartansdottir / Ms Gudrun Einarsdottir
ICELANDIC MEDICINES CONTROL AGENCY
Eiðistorg 13-15,
IS - 170 Seltjarnarnes
Tel.: + 354 520 2100, Fax: + 354 561 2170
E-mail: thorbjorg.kjartansdottir@lyfjastofnun.is / gudrun.einarsdottir@lyfjastofnun.is

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)

8. When do I have to submit revised product information? In all languages?

In case the Type IB notification affects SPC, 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)

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 website should be followed. When submitting the full set of Annexes in PDF format, this should be accompanied by the completed formatting checklist which provides guidance on how to correctly prepare the PDF versions.

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

Icelandic and Norwegian language versions must always be included.

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

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

For those **variations which affect the 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 Word format (clean) and PDF, together with the variation notification. Where the variation introduces a new EU sub-number, the sub-number should be requested from the Agency before submission and should subsequently be included in the SPC, labelling and PL texts as part of the variation notification (see also "How to obtain new EU sub-numbers before submitting a Type IB variation for an additional presentation?").

In case of a deletion of a pharmaceutical form/strength(s), such prior liaison with Agency is not required, and the amended Annex A and product information Annexes should be provided as part of the Variation notification.

9. How to obtain new EU sub-numbers before submitting a Type IB variation for an additional presentation (e.g. new pack-size)?

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

The request should be sent together with a draft Annex A (in English only) to the Product Team Member 'Quality' in charge of the product, 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.

10. How and when will the updated Annexes become part of the Marketing Authorisation?

Upon finalisation of a valid Type IB notification affecting the Annexes to the Commission Decision, the Commission Decision will be updated within 6 months. However, Type IB Variations affecting the Annexes can be implemented without awaiting the 6-monthly update of the marketing authorisation and the agreed Type IB changes should be included in the Annexes of any subsequent Regulatory Procedure.

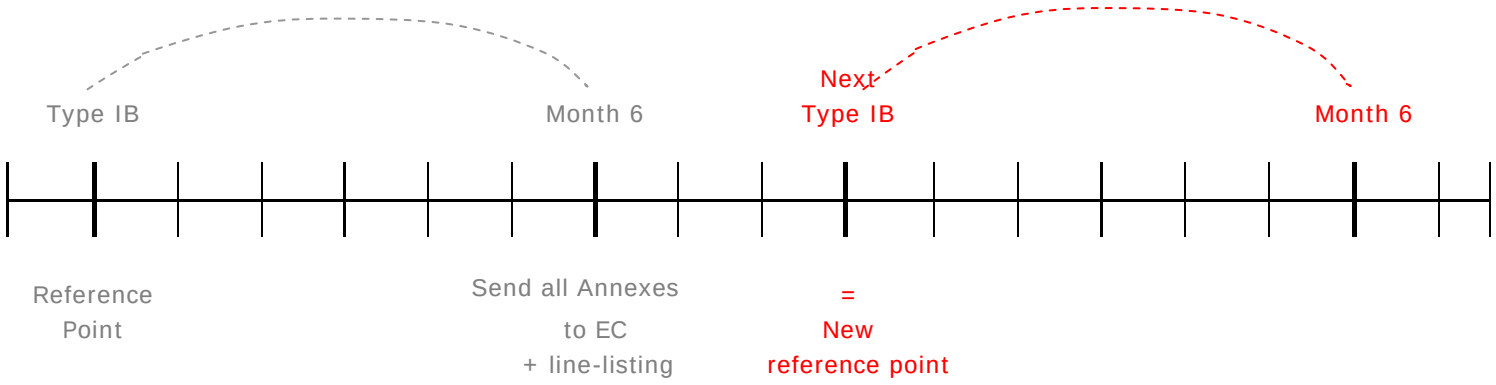
At 'month 6' the Agency will send the complete set of Annexes, based on the latest approved Annexes and reflecting the Type IB change(s) introduced during the past 6 months as well as a line-listing of those Type IA/IB notification(s).

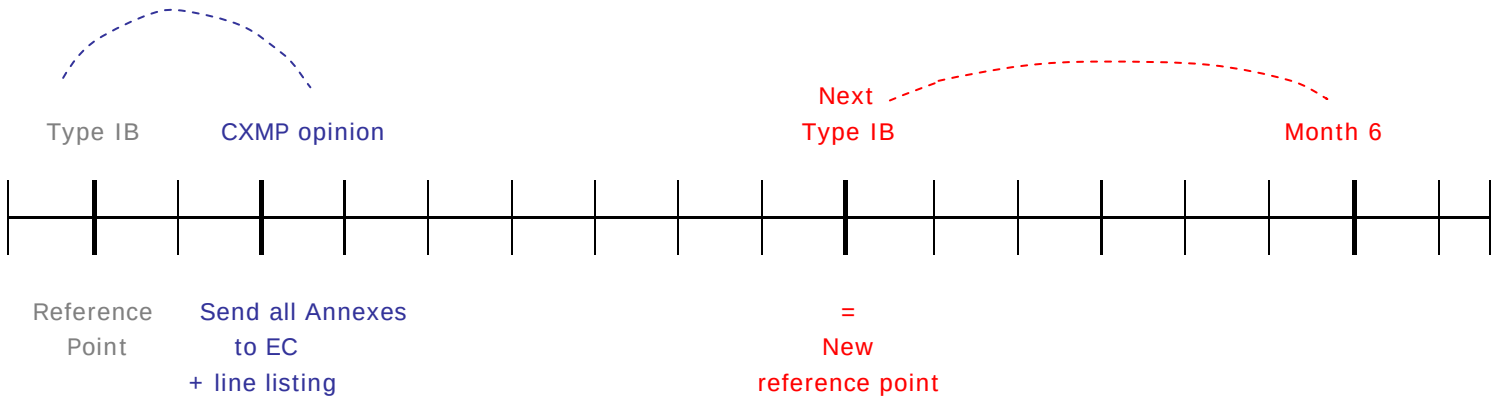
Where a notification contained several Type IB variations concerning one marketing authorisation, the Commission will update the marketing authorisation with one single decision to cover all the approved minor variations.

However, where any Opinion affecting the Annexes is transmitted to the Commission within these 6 months, the changes of the Type IB notification(s) concerned will already be included in the Annexes to the Opinion and will consequently be reflected in the resulting Commission Decision. This Commission Decision will therefore replace the 6-monthly 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*)





Type II variations

1. What changes are considered Type II Variations?

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

The Variations Regulation and the Classification Guideline set-out a list of changes to be considered as Type II variations. In addition, any other change which may have a significant impact on the quality, safety or efficacy of the medicinal product must be submitted as a Type II variation. Please refer also to "When will my variation application be considered a Type II variation or an extension application?".

During validation of an 'unforeseen' variation, submitted by the MAH as a Type IB variation, the Agency may consider that the proposed variation may have a significant impact on the quality, safety or efficacy of the medicinal product. In such case, the marketing authorisation holder will be requested to revise and supplement its variation application so that the requirements for a Type II variation application are met (see also "How shall my Type IB variations be handled (timetable)?).

References

- Commission Regulation (EC) No 1234/2008 (OJ L334 of 12 December 2008)
- Procedural guideline
- Classification guideline

2. Is the Co-Rapporteur involved in Type II Variations?

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

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

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

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

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

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

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

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

References

- Commission Regulation (EC) No 1234/2008 (OJ L334 of 12 December 2008)
- Procedural guideline

4. How shall I present my Type II Variation application?

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

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

- Cover letter.
- The completed EU variation application form, including the details of the marketing authorisation concerned. Where a variation leads to or is the consequence of other variations, a description of the relation between these variations should be provided in the appropriate section of the application form. All proposed changes should be declared in the '**Type of changes'** section of the form, and be clearly described in the "**scope"** section of the form.
- Reference to the part of the Commission Classification Guideline or reference to the published Article 5 Recommendation, if applicable, used for the relevant application.
- Supporting data relating to the proposed variation(s).
- Update or Addendum to quality summaries, non-clinical overviews and clinical overviews as relevant. When non-clinical or clinical study reports are submitted, even if only one, their relevant summary(ies) should be included in Module 2.
- For variations submitted to implement changes requested by the Agency or for generic/hybrid/biosimilar medicinal products, a copy of the request should be annexed to the cover letter.
- In case that the changes affect SPC, labelling and/or package leaflet, the revised product information Annexes must be submitted (see also: Type II variations - "When do I have to submit revised product information? In all languages?").

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

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

References

- Commission Regulation (EC) No 1234/2008 (OJ L334 of 12 December 2008)
- Procedural guideline
- Variation application form

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

Type II variation applications should be addressed and sent to the attention of the Product and Application Business Support (V-PD-BUS) at the following address:

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

Two electronic copies (CD-ROM or DVD) of the Variation application form and supportive documentation should be submitted to the Agency, together with an original, signed cover letter. The Product Team Leader should be indicated in copy ("cc") on the cover letter.

Two electronic copies of the Variation application form and supportive documentation should be submitted simultaneously to the (Co-)Rapporteurs.

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

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

For a full overview of dossier requirements for (Co-)Rapporteur and CHMP members, including delivery addresses, please refer to the following document: PAG dossier requirements.

For the format of the submission, see: "Can or must I submit my post-authorisation application in eCTD format"

6. When shall I submit my Type II Variation application?

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

MAHs are reminded, especially for safety issues, that once new information becomes available which might entail the variation of the MA, MAHs should submit any variation application resulting from the fulfilment of the Follow Up Measures (FUMs) and/or Specific Obligations (SOs) and/or Periodic Safety Update Reports (PSURs) at the same time as the fulfilment of the FUM / SO or submission of the PSUR, rather than awaiting the assessment of those data by CHMP.

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

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

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

References

- Commission Regulation (EC) No 1234/2008 (OJ L334 of 12 December 2008)
- Classification Guideline

7. How shall my Type II application be handled (timetable)?

The EMA will acknowledge receipt of a valid application of a Type II variation and shall start the procedure in accordance with the official starting dates published on the EMA website
The submission deadlines and full procedural detailed timetables are published as a generic calendar on the EMA website (see: "submission deadlines and full procedural timetables").
The published timetables identify the submission, start and finish dates of the procedures as well as other interim dates/milestones that occur during the procedure.

One of the following timetables (TT) shall apply:

For a 60 day TT (= standard time-table):

Condition:

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

Start of evaluation	Day 1
Receipt of (Co-) Rapporteur Assessment Report	Day 30
Comments by other CHMP members	Day 50
Adoption of the CHMP Opinion *[or Request for supplementary information]*	Day 60

For a 30 day TT:

Condition:

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

Start of evaluation	Day 1
Receipt of Rapporteur Assessment Report	Day 20
Comments by other CHMP members	Day 25
Adoption of the CHMP Opinion *[or Request for supplementary info]*	Day 30

In exceptional cases, this timetable could even be shortened.

For a 90 day TT:

Condition:

- For variations concerning changes to or addition of therapeutic indications

Start of evaluation	Day 1
Receipt of (Co-) Rapporteur Assessment Report	Day 60
Comments by other CHMP members	Day 80

MAHs are encouraged to contact the EMA in advance of the submission, in case clarification on the timetable for a specific variation is needed.

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

In case issues are identified which prevent the adoption of an Opinion, the CHMP will adopt a request for supplementary information together with a timetable stating the date by when the MAH must submit the requested data. The clock will be stopped until the receipt of the supplementary information.
Any response to a request for supplementary information must be sent directly to the EMA, all CHMP members and the (Co-) Rapporteur.

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

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

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

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

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

References

- Commission Regulation (EC) No 1234/2008 (OJ L334 of 12 December 2008)
- Procedural guideline

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

Upon adoption of the CHMP opinion, the Agency will inform the MAH and the Commission 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.

Re-examination

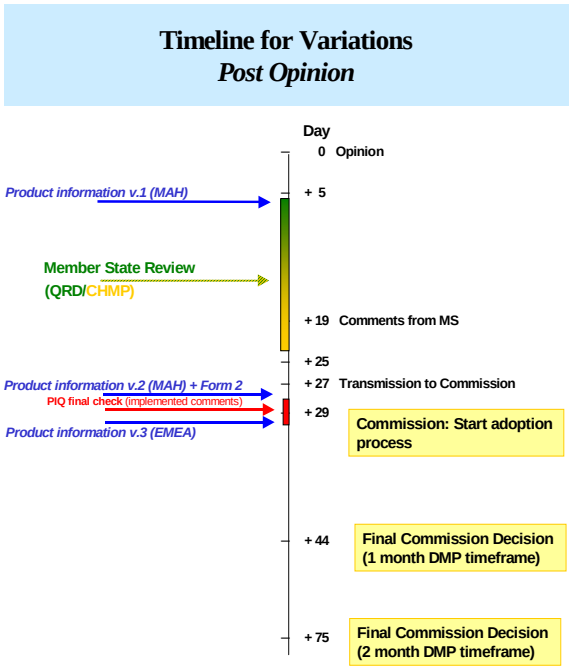
Art. 9(2) of Regulation (EC) No 726/2004, also applies to CHMP Opinions adopted for Type II variation applications. This means that the MAH may give written notice to the Agency/CHMP that he wishes to request a re-examination within 15 days of receipt of the opinion (after which, if he does not appeal,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

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

Decision-Making Process

Upon receipt of the final CHMP opinion, the Commission shall, where necessary, amend the marketing authorisation to reflect the variation within 2 months or within 30 days when the variation leads to a 6-month extension of the supplementary protection certificate.

Although the Variation Regulation has provided for a total decision-making process of 75 days for Type II variations (i.e. 15 days for opinion transmission + 60 days for updating of the MA), the Agency will continue to apply the existing post-opinion timeframes, as set-out in the European Medicines Agency Post-Opinion Linguistic Checking Procedure document. This means that the Agency, in cooperation with the QRD members and the MAH will aim at providing final, checked translations to the Commission by Day +27. (see also: "When do I have to submit revised product information? In all languages?"**)**



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 may only be implemented once the Commission has amended the marketing authorisation and has notified the MAH accordingly. Variations related to safety issues must be implemented within a time-frame agreed between the Commission and the MAH.

Where the Type II variation does not require any amendment of the marketing authorisation, the approved variation may only be implemented once MAH has been informed by the Commission accordingly.

References

- Commission Regulation (EC) No 1234/2008 (OJ L334 of 12 December 2008)
- Procedural guideline
- Re-examination guideline
- The Linguistic Review Process of Product Information in the Centralised Procedure – Human

9. What fee do I have to pay for a Type II Variation?

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 Agency will issue an invoice on the date of the notification of the administrative validation to the applicant and fees will be payable within 45 calendar days of the said notification. The invoice will be sent to the billing address indicated by the MAH and will contain clear details of the product and procedures involved, the type of fee, the amount of the fee, the bank account to where the fee should be paid and the due date for payment. Where more than one procedure is processed in a given month a summary invoice or statement will be issued at the end of each month for payment within 30 days of the end of the month.

To facilitate this operation, applicants/marketing authorisation holders who are demanding a Purchase Order Number on the Agency invoice must quote this Number clearly on the cover letter of a given application. The Agency will no longer accept separate notifications of Purchase Order Numbers, not associated with the dossier. The MAH must state the following sentence on the cover letter of each application:

Please quote Purchase Order Number …….. on the invoice.

If the MAH does not require a Purchase Order Number on the Agency invoice, this must also be clearly stated in the cover letter.

For more information about fees and fee payment in the Centralised Procedure, please consult: http://www.ema.europa.eu/htms/general/admin/fees/feesh.htm

For Type II variations, if the variation is considered 'invalid' (i.e. an assessment process can not 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
- Explanatory note on fees payable to the EMA

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

Mock-ups

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

Specimens

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

Note:

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

The above principles also apply to mock-ups and specimens for Iceland, which have to be sent directly to the Icelandic authorities:

Ms Thorbjorg Kjartansdottir / Ms Gudrun Einarsdottir
ICELANDIC MEDICINES CONTROL AGENCY
Eiðistorg 13-15,
IS - 170 Seltjarnarnes
Tel.: + 354 520 2100, Fax: + 354 561 2170
E-mail: thorbjorg.kjartansdottir@lyfjastofnun.is / gudrun.einarsdottir@lyfjastofnun.is

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)

11. When do I have to submit revised product information? In all languages?

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

At submission (Day 0)

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

After CXMP Opinion (Day +5)

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

After Linguistic check (Day +25)

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

According to Art. 23 of Regulation (EC) N° 1234/2008, Commission decisions on Type II variations will be adopted without a Standing Committee procedure. Consequently, there will be no further revision of the translations of the Annexes after Day +25.

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) · PDF format (clean)

* = 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, labeling 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 CD-ROM/DVD. Highlighted changes should be indicated via 'Tools – Track changes'. Clean versions should have all changes 'accepted'.

Icelandic and Norwegian language versions must always be included.

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

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

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

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

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

12. Will there be any publication on the outcome of my Type II Variation?

The CHMP Press Release and CHMP Monthly Report following each CHMP meeting give information on opinions in relation to new indications, changes to an existing indication, addition or removal of a contraindication. This will include the invented name of the product, the name of the MAH, the indication(s) or contraindication(s) and the date the product was first authorised in the European Union. Where applicable, the CHMP Press Release and/or CHMP Monthly Report also give update on safety information.

Annexed to the CHMP Monthly Report are statistics on the overall total numbers of positive and negative opinions on Type II variations since 1995. In addition, the number and outcome (number of positive or negative Opinions) are given per CHMP meeting for each of the following groups of Type II variations: new indications, SPC changes and Quality changes.

Note:
The policy on transparency for post-authorisation procedures is currently being revised and will be reflected in this document at a later stage.

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

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

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

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

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

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

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

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

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

Even if the variation does not concern an orphan designated product, all MAHs should still check whether their claimed new indication would potentially overlap with the indication of authorised orphan medicinal products, as listed on the Commission Website in the "Community register" of designated orphan medicinal products (http://ec.europa.eu/enterprise/sectors/pharmaceuticals/documents/community-register/index_en.htm), 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 (Enterprise and Industry – Pharmaceuticals)

14. Do I need to address any paediatric requirements in my type II variation application?

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 cover the population aged between birth and 18 years (meaning up to but not including 18-years).

As set out in Article 8 of the Paediatric Regulation, applications submitted from 26 January 2009, 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 on condition (if available, 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.

'New indication' is not defined in the Community legislation. However both the 'Guideline on the elements required to support the significant clinical benefit in comparison to existing therapies of a new therapeutic indication in order to benefit from an extended (11-years) marketing protection', and the 'Guideline on a new therapeutic indication for a well-established substance' provide a definition of what is considered a new indication. For the purpose of the application of Article 8 the same definition applies.

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.

However, the following types of application are exempted from the application of Article 8:

- Generics (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 binding elements of the PIP decision including the timelines for the conduct of the studies or collection of the data are fulfilled. This will follow a two step approach:

- Step 1: check of the compliance at or before validation of the marketing authorisation application. The compliance check should be positively concluded for a marketing authorisation application to be 'valid'.
- Step 2: detection of any non-compliance during the scientific assessment of a valid application.

The compliance check for Centrally Authorised Medicinal Products will be performed by the Paediatric Committee, following a 30 or up to 60-day procedure. The applicant can choose to apply for the compliance check before submission of their application and to provide the Paediatric Committee compliance opinion as part of the submission package. This approach is strongly recommended, otherwise during validation the Agency will request for the compliance check to be performed by the Paediatric Committee meaning that this will suspend the validation phase until the Paediatric Committee Compliance Opinion is available.

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
- Procedural Advice document related to "Paediatric investigation plans (PIPs), waivers and modifications"
- 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"
- European Medicines Agency website, section "Medicines for children"
- Procedural advice for "validation of new marketing authorisation application, extension/variation application and compliance check with an agreed PIP"

Type II variations/Extension applications

1. When will my variation application be considered a Type II variation or an Extension application?

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

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

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

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

1. Changes to the active substance(s)

2. Changes to strength, pharmaceutical form and route of administration

3. Other changes specific to veterinary medicinal products to be administered to food-producing animals; change or addition of target species

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

As experience has shown difficulties in the classification of 'extension' applications versus 'variation' applications, particularly regarding the items pharmaceutical form and strength, the European Commission has published a guideline clarifying these terms and including relevant examples for such classification. (See also: "Guideline on the categorisation of New Applications (NA) versus Variations Applications (V), January 2002")

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)
- "Guideline on the categorisation of New Applications versus Variations Applications", The Rules governing Medicinal Products in the European Union, Notice to Applicants, Volume 2C

Extension Applications

1. Will my invented name change?

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

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

References

- 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

2. Is the (Co-) Rapporteur involved in Extension Applications?

The 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 Co-Rapporteur would normally be involved.

3. How shall I present my Extension Application?

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

- Cover letter.

- The completed EU 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 1.4.1 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

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

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

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

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

References

- Commission Regulation (EC) No 1234/2008 (OJ L334 of 12 December 2008)
- Procedural guideline

5. How, when and to whom shall I submit my Extension Application?

Extension applications should be addressed and sent to the attention of the Product and Application Business Support (V-PD-BUS) at the following address:

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

Two electronic copies (CD-ROM or DVD) of the complete extension application should be submitted to the Agency, together with an original, signed cover letter. The Product Team Leader should be indicated in copy ("cc") on the cover letter.

The extension application should also be submitted simultaneously to the (Co-)Rapporteur.

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

Upon validation by the Agency, the MAH should forthwith send the extension application to the other CHMP members, including any additional data or information supplied during the validation phase (as appropriate).

For a full overview of dossier requirements for (Co-)Rapporteur and CHMP members, including delivery addresses, please refer to the following document: http://www.ema.europa.eu/htms/human/presub/q23-2.htm (Note: extension submission requirements follow the initial marketing authorisation submission requirements).

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").

For the format of the submission, see: "Can or must I submit my post-authorisation application in eCTD format?"

References

- Commission Regulation (EC) No 1234/2008 (OJ L334 of 12 December 2008)
- "General information", The Rules governing Medicinal Products in the European Union, Notice to Applicants, Volume 2A, Chapter 7

6. How shall my Extension Application be handled (timetable)?

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 SPC, labelling and package leaflet sent by MAH to the Rapporteur, Agency and other CHMP members.
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 a new (Co-) Rapporteur, to co-ordinate the appeal procedure. 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 days 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)
- "Centralised procedure", The Rules governing Medicinal Products in the European Union, Notice to Applicants, Volume 2A, chapter 4.

7. What fee do I have to pay for an Extension Application?

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 Agency will issue an invoice 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. The invoice will be sent to the billing address indicated by the applicant and will contain clear details of the product and procedures involved, the type of fee, the amount of the fee, the bank account to where the fee should be paid and the due date for payment. Where more than one procedure is processed in a given month a summary invoice or statement will be issued at the end of each month for payment within 30 days of the end of the month.

To facilitate this operation, applicants/marketing authorisation holders who are demanding a Purchase Order Number on the Agency's invoice must quote this Number clearly on the cover letter of a given application. The Agency will no longer accept separate notifications of Purchase Order Numbers not associated with the dossier. The applicants/marketing authorisation holders must state the following sentence on the cover letter of each application:

Please quote Purchase Order Number ……. on the invoice.

If the applicants/marketing authorisation holders do not require a Purchase Order Number on the Agency's invoice, this must be clearly stated in the cover letter.

For more information about fees and fee payment in the Centralised Procedure, please consult: http://www.ema.europa.eu/ema.europa.eu/htms/general/admin/fees/feesh.htm.

Where an extension application is considered 'invalid' (i.e. an assessment process can not 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
- "Explanatory note on 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

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

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

At day -10 of the submission of the application:

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

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

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

At the latest 15 working days before launch:

Before the new strength or pharmaceutical form is placed on the market, specimens of the printed outer and immediate packaging and the package leaflet for each new strength and/or new pharmaceutical form in each container type need to be provided to the Agency (using the "Specimen Submission Form" (see EMEA/305821/2006):

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

Mock-ups and specimens for Iceland should not be submitted to the Agency but to the respective authority directly:

Ms Thorbjorg Kjartansdottir / Ms Gudrun Einarsdottir
ICELANDIC MEDICINES CONTROL AGENCY
Eiðistorg 13-15,
IS - 170 Seltjarnarnes
Tel.: + 354 520 2100, Fax: + 354 561 2170
E-mail: thorbjorg.kjartansdottir@lyfjastofnun.is / gudrun.einarsdottir@lyfjastofnun.is

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)

9. When do I have to submit revised product information? In all languages?

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 CD-ROM/DVD as part of the extension application.

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

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

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

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

Upon adoption of the Opinion, the Agency will prepare and send to the MAH the revised English Annex A. After CHMP Opinion (Day 215), the MAH provides the Agency with the electronic versions of the complete set of Annexes in all languages as well as the translations of the revised Annex A as a separate word document.

References

- "The new product information linguistic review process for new applications in the Centralised Procedure" – EMEA/5542/02, European Medicines Agency Website (Application Guidance)

10. Will there be any publication on the outcome of my Extension application?

Information on opinions of extension application is not given in the CHMP press release and CHMP Monthly report, unless they are grouped with a Type II variation in relation to a new indication.

Annexed to the CHMP Monthly Report are statistics on the overall total numbers of positive and negative opinions on Extension applications since 1995.

Note:
The policy on transparency for post-authorisation procedures is currently being revised and will be reflected in this document at a later stage.

References

- CHMP Press Release and CHMP Monthly Report published on the Agency's website

11. Do I need to address any paediatric requirements in my extension application?

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 cover the population aged between birth and 18 years (meaning up to but not including 18-years).

As set out in Article 8 of the Paediatric Regulation, applications submitted from 26 January 2009, 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 Agency granting a class waiver on condition (if available, 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.

'New indication' is not defined in the Community legislation. However both the 'Guideline on the elements required to support the significant clinical benefit in comparison to existing therapies of a new therapeutic indication in order to benefit from an extended (11-years) marketing protection', and the 'Guideline on a new therapeutic indication for a well-established substance' provide a definition of what is considered a new indication. For the purpose of the application of Article 8 the same definition applies.

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.

However, the following types of application are exempted from the application of Article 8:

- Generics (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 binding elements of the PIP decision including the timelines for the conduct of the studies or collection of the data are fulfilled. This will follow a two step approach:

- Step 1: check of the compliance at or before validation of the marketing authorisation application. The compliance check should be positively concluded for a marketing authorisation application to be 'valid'.
- Step 2: detection of any non-compliance during the scientific assessment of a valid application.

The compliance check for Centrally Authorised Medicinal Products will be performed by the Paediatric Committee, following a 30 or up to 60-day procedure. The applicant can choose to apply for the compliance check before submission of their marketing authorisation application and to provide the Paediatric Committee compliance opinion as part of the submission package. This approach is strongly recommended, otherwise during validation the Agency will request for the compliance check to be performed by the Paediatric Committee meaning that this will suspend the validation phase until the Paediatric Committee Compliance Opinion is available.

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

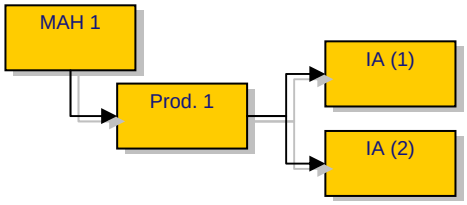
- Regulation (EC) No 1901/2006
- Procedural Advice document related to "Paediatric investigation plans (PIPs), waivers and modifications"
- Commission Guideline on "The format and content of applications for agreement or modification of a paediatric investigation plan and request for waivers or deferrals and concerning the operation of the compliance check and on criteria for assessing significant studies"
- European Medicines Agency website, section "Medicines for children"
- Procedural advice for "validation of new marketing authorisation application, extension/variation application and compliance check with an agreed PIP"

Grouping of variations

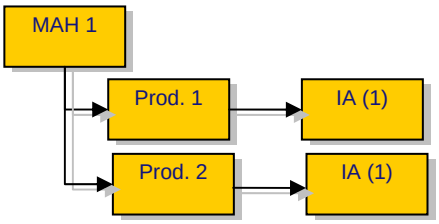
1. What types of variations can be grouped?

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:

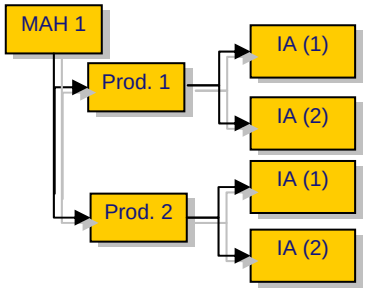
- **Several** Type IA or IA_{IN} affecting **one** medicinal product.
  This means for instance that a Type IA variation which is normally not subject to immediate notification, can be included in the submission of a Type IA_{IN} variation.



- **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.

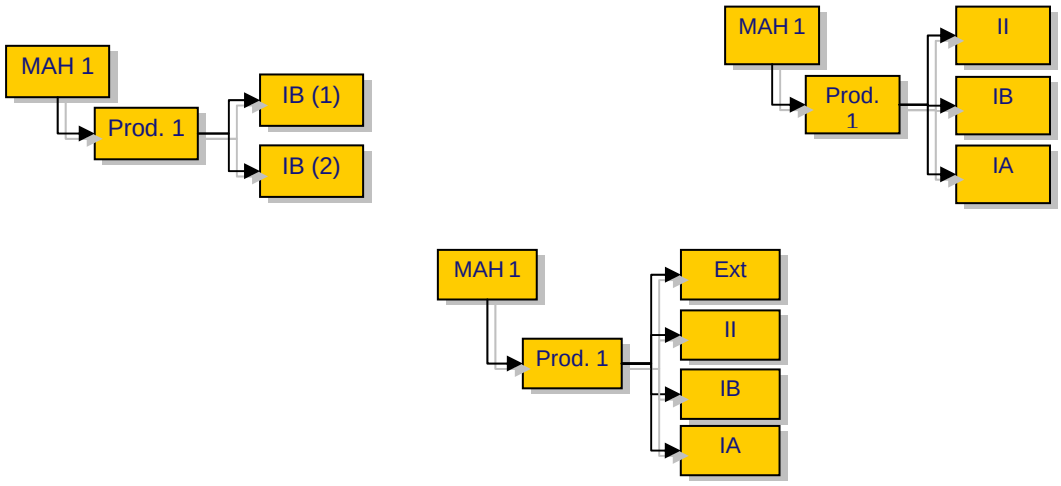


Applicants belonging to the same mother company or group of companies and applicants having concluded agreements or exercising concerted practices concerning the placing on the market of the medicinal product(s) concerned, have to be taken as "the same marketing authorisation holder"[2].

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

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

Article 7.2(b) of the Variations Regulation sets-out the possibility for a marketing authorisation holder to group several types of variations affecting **one medicinal product**, under a single notification/application.



The cases for which this is allowed are listed in Annex III of the Regulation. Any other grouping of variations must first be 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)
- Procedural Guideline

2. What groups of variations would be considered acceptable?

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 had 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 Annex III of the Variation Regulation.

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 variations which are consequential to this major variation of type II.	The current interpretation of 'consequential' will apply: "A consequential variation is regarded as a change, which is an unavoidable and direct result of another change (i.e. the 'main change') and not simply a change which occurs at the same time." Example: Type II for new indication + Type IB or IA for addition of a new pack size required for the use in this new indication Grouping of non-consequential quality changes may also be acceptable, under Article 7.2(b) "other groups to be agreed with the Agency".
11	All variations in the group are consequential to the assessment of a given periodic safety update report.	This group will concern all changes reflecting the wording to be implemented following assessment of a given PSUR, as is currently the case. The Agency will continue to consider that implementation of a PSUR changes is one variation. But, such a single variation should only concern one PSUR.
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 reflecting the wording to be implemented following assessment of a FUM as is currently the case. "conducted under the supervision of the holder" will be interpreted as any post-authorisation study FUM submitted by the MAH. The Agency will continue to consider that implementation of a FUM is one variation. But, such a single variation should only concern one FUM.

Table 2: Grouping examples according to Article 7.2(b) of the Variation Regulation.

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 Type IA Change in ATC Code	 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)
Implementation of agreed wording change(s) requested by the CHMP for which <u>no new additional data are submitted</u> 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

3. How shall I present a grouped variations application?

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.

- 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 it is an allowed grouping in Annex III of the variations regulation or the grouping has been agreed with the Agency.
- The completed 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)?".

References

- Procedural guideline
- eCTD Variations Q&A document

4. What procedure number will be given to grouped variation applications?

- Several Type IA/IA_{IN} variations affecting **one** medicinal product:

The usual procedure number for Type IA variations will be given, with the addition of the suffix "/G". The 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 can not be allocated to one single product, the procedure number will therefore contain "xxxx" as a place-holder for the product number.

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

This 'high-level' procedure number can be obtained from the Agency shortly before submission.

For each medicinal product concerned by the group of variations, the usual product-specific sequential procedure number will be given, which includes a reference to the "IG" group to which it belongs.

Example: EMEA/H/C/prod_nb/IG002/21 (i.e. it was the 21st procedure for this product, which was submitted as part of a Type IA/IA_{IN} group affecting several medicinal products "IG/002")

- 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 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. Can grouped variations be subject to a worksharing procedure?

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. In such case, the review of the Type IA/IA_{IN} variation will be performed as part of the worksharing procedure.

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

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

For example:

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

In case of grouped Type IA/IA_{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 the Extension, 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 the Type II variation, 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.

7. How and when will the marketing authorisation be updated for grouped variations; when can I implement the approved changes?

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

Similarly, grouped variations can be implemented according to the provisions corresponding to the 'highest' type of Opinion/Notification issued at the end of the procedure (except for Type IA variations which are by definition already implemented before notification).

For instance, if a positive opinion on a Type II variation is adopted which also includes 3 Type IB variations, the decision-making procedure for a Type II opinion will apply.

If, however, the MAH withdraws the Type II, the Agency will issue a Type IB notification of outcome which will be subject to the 6-monthly MA updating procedure, and the Type IB notification can be implemented without awaiting the 6-monthly MA update.

Where a group of variations to the terms of one MA have been approved, the Commission will update the MA with one single decision to cover all the approved variations for the product concerned, following the timeframes for the 'highest' variation reflected in the Opinion/ Notification.

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 decision-making timeframes for Type IA/IA_{IN} variations.

8. What fee do I have to pay for grouped variations?

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 can not be started), an administrative fee may be charged by the Agency.

For more information about fees and fee payment in the Centralised Procedure, please consult: http://www.ema.europa.eu/htms/general/admin/fees/feesh.htm.

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" (EMA Website / General / Admin)

Worksharing of variations

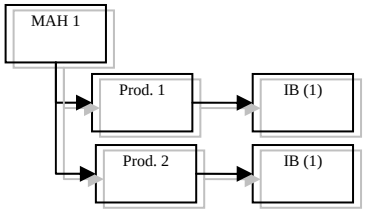
1. What is worksharing and what types of variations can be subject to worksharing?

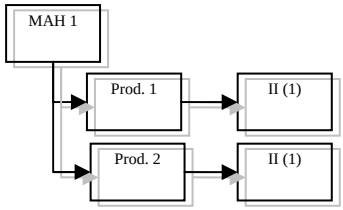
Article 20 of Commission Regulation (EC) N° 1234/2008 (the 'Variations Regulation') sets-out the possibility for a MAH to submit the same Type IB or Type II variation, or the same group of variations affecting more than one marketing authorisation from the same MAH in one application.

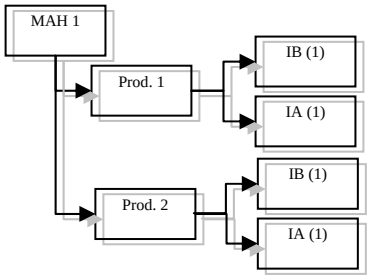
Applicants belonging to the same mother company or group of companies and applicants having concluded agreements or exercising concerted practices concerning the placing on the market of the medicinal product(s) concerned, have to be taken as "the same marketing authorisation holder"[3].

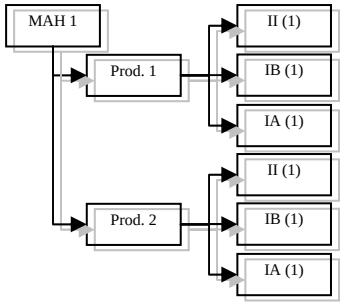
Extensions are excluded from worksharing.

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









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

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

Purely national marketing authorisations are excluded from the worksharing procedure.

References

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

- Commission Regulation (EC) No 1234/2008 (OJ L334 of 12 December 2008)
- Procedural Guideline

2. What variation(s) would be considered acceptable for worksharing?

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

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

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

Clinical/Pharmacovigilance

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

Quality

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

Additional examples will be regularly included in this document, to reflect accumulated experience.

3. What pre-submission steps will apply to a worksharing procedure?

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

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

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

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

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

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

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

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

4. How shall I present a variation application under worksharing?

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

- One common cover letter, clearly indicating that the application is submitted for a worksharing procedure together with a short overview of all medicinal products concerned, with their respective Rapporteurs and RMSs, as well as an overview of the submission format for the different products, if applicable (e.g. eCTD, NEES). In case MRP/DCPs are part of the worksharing procedure, the MAH should also include a confirmation that the worksharing applications have been submitted to all Member States where the products concerned are authorised (= RMSs and CMSs) and that the relevant national fees have been paid. A formal letter with the worksharing applicant and contact person for the worksharing procedure should be provided with the worksharing application.
- One completed EU variation application form, listing all medicinal products concerned and declaring all variations included in the group in the section 'type of changes', as well as a justification for the proposed worksharing (and grouping if applicable) in the 'precise scope and background' section of the application form. The response from the Agency on the acceptability of the worksharing application, further to the submission of the letter of intent should be attached to the application form.
- 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

- Procedural guideline
- eCTD Variations Q&A document

5. How and to whom shall I submit my variation application under worksharing?

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:**

Variation applications for worksharing, should be addressed and sent to the attention of the Product and Application Business Support (V-PD-BUS) at the following address:

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

For Centrally Authorised medicinal products (eCTD mandatory):

Two electronic copies (CD-ROM or DVD) containing the relevant eCTD sequence for each product, should be submitted to the Agency, together with an original, signed cover letter. The coordinating Product Team Leader should be indicated in copy ("cc") on the cover letter.

For nationally authorised medicinal products (eCTD not mandatory):

Two electronic copies (CD-ROM or DVD) of the Variation application form and supportive documentation for each product should be submitted to the Agency. 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 CHMP 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.

- **Submission to the Rapporteur and CHMP members:**

When the submission address for Rapporteur/CHMP members is identical to the submission address for the national competent authorities, no additional copies of the application should be sent separately to the Rapporteur/CHMP member concerned. However, the cover letter should be addressed to both the national competent authority and the CHMP member concerned.

When the submission address for Rapporteur/CHMP members is different from the submission address for the national competent authorities, 2 copies of the full variation application for all products concerned should be provided separately to the CHMP member concerned upon validation by the Agency.

For submission addresses for national competent authorities, please refer to Chapter 7 of the Notice To Applicants Volume 2A. For submission addresses for CHMP members, please refer to the overview table on the Agency's website (http://www.ema.europa.eu/htms/human/presub/dossierrequirements.pdf)

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

6. What procedure number will be given to variation applications under worksharing?

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

Example: EMEA/H/xxxx/WS/003

For each medicinal product concerned by the worksharing procedure, the usual product-specific sequential procedure number will be given, which includes a reference to the "WS" procedure to which it belongs.

Example: EMEA/H/C/prod_nb/WS003/21 (i.e. it was the 21st procedure for this product, which was submitted as part of the 3rd worksharing procedure received by EMEA "WS/003")

Whether the worksharing relates to a single variation or a group of variations, is not indicated in the procedure number (i.e. no need for an additional suffix "/G")

MAHs are reminded that Agency's procedure numbers are allocated by the Agency upon receipt of the application. For worksharing procedures**,** the 'high-level' procedure number can be obtained from the Agency shortly before submission. However, in case of delayed submission, the indicated worksharing number may already have been allocated to another worksharing procedure submitted in the mean time.

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

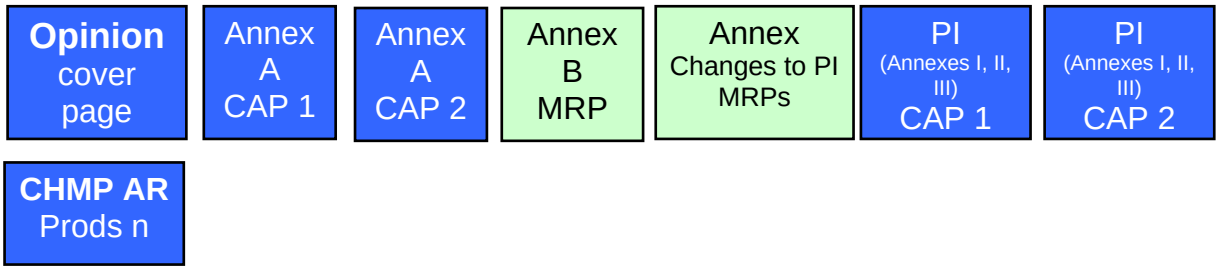
The MAH must submit the variation application for worksharing, at the latest by the recommended submission dates published on the Agency's website (See also "Human Medicines – Procedural Timetables / Submission dates").

In general, variations submitted for worksharing will follow a 60-day evaluation timetable. This period may however be reduced having regard to the urgency of the matter, particularly for safety issues, or may be extended to 90 days for Type II variations concerning changes or additions to the therapeutic indication. Implementation of agreed changes for which no new additional data are submitted by the MAH may also follow a 30 day timetable, provided that only centrally authorised medicinal products are part of the worksharing and this is agreed by the Agency.

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

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

8. How and when will the marketing authorisations be updated following a worksharing procedure? When can I implement the approved changes?

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

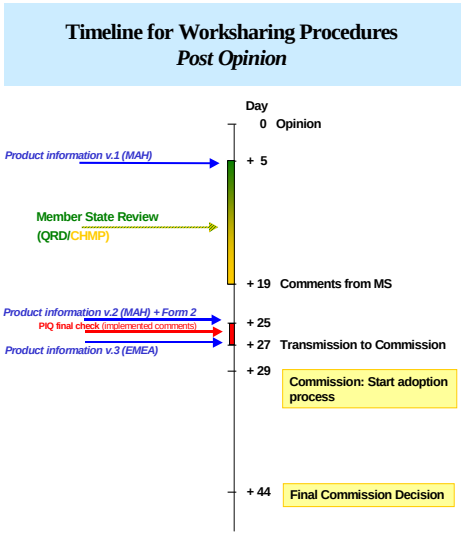
Re-examination
Art. 9(2) of Regulation (EC) No 726/2004, also applies to CHMP Opinions adopted for worksharing procedures. This means that the MAH may give written notice to the Agency/CHMP that he wishes to request a re-examination within 15 days of receipt of the opinion (after which, if he does not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

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

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

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

The Agency, in cooperation with the QRD members and the MAH will aim at providing final, checked translations for all centrally authorised products included in the worksharing procedure to the Commission by Day +27. (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 30 days, unless a referral procedure in accordance with Article 31 of Directive 2001/83/EC is initiated within 30 days following receipt of the final opinion.

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

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

Type II variations (including those which contain grouped Type IB variations) approved via a worksharing procedure, may be implemented 30 days after receipt of the favourable CHMP opinion.

Variations related to safety issues must be implemented within a time-frame agreed between the marketing authorisation holder and the Commission.

References

- Commission Regulation (EC) No 1234/2008 (OJ L334 of 12 December 2008)
- Procedural guideline

9. What fee do I have to pay for variation applications under worksharing?

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

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

For more information about fees and fee payment in the Centralised Procedure, please consult: http://www.ema.europa.eu/htms/general/admin/fees/feesh.htm

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" (EMA Website / General / Admin)

9. When do I have to submit revised product information? In all languages?

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 which a 60 or 90-Day timetable applies

At submission (Day 0)

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

After CXMP Opinion (Day +5)

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

After Linguistic check (Day +25)

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

Only one centrally authorised medicinal product will undergo a linguistic check. In the cases where the changes to the product information may vary between products, the product with the most complex changes will generally be the one subject to linguistic check.

According to Art. 23 of Regulation (EC) N° 1234/2008, Commission decisions on worksharing procedures will be adopted without a Standing Committee procedure. Consequently, there will be no further revision of the translations of the Annexes after Day +25.

b. Variations for which a short (e.g. 30-Day) timetable applies

At submission

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

After CXMP Opinion (Day +5)

- 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 (usually relating to Type IB variations only), a linguistic check will be performed during the procedure. It is therefore expected that the texts provided at Day +5 will be the final texts.

Overview:

Day	Lang. *	60- or 90-Day Timetable	Short (e.g. 30-Day) Timetable
0	EN	· Electronically · Word format (highlighted) · One CAP	· Electronically · Word format (highlighted) · One CAP
	Other EEA	/	· Electronically · Word format (highlighted) · One CAP
+5	All EEA	· Electronically · Word format (highlighted) · One CAP	· Electronically · Word format (highlighted) · PDF format (clean) · All CAPs
+25	All EEA	· 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, labeling and PL texts for all strengths and pharmaceutical forms of the product concerned, as well as Annex II. The complete set of Annexes must be presented sequentially (i.e. Annex I, II, IIIA, IIIB) as one document for each official EU language. Page numbering should start with "1" (bottom, centre) on the title page of Annex I. The 'QRD Convention' published on the Agency's website should be followed. When submitting the full set of Annexes in PDF format, this should be accompanied by the completed formatting checklist which provides guidance on how to correctly prepare the PDF versions.

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

Icelandic and Norwegian language versions must always be included.

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

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

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

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

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

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

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

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

This can be done either in case of a marketing authorisation being granted under INN name (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)
- "Guideline on the acceptability of invented names for human medicinal products processed through the centralised procedure" (CPMP/328/98)

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

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

Therefore, Marketing Authorisation Holders are advised to submit the new proposed IN at the latest 4-6 months prior to their intended implementation of the new name and Type IA_{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)
- "Guideline on the acceptability of invented names for human medicinal products processed through the centralised procedure" (CPMP/328/98).

3. How shall I present my IN change application?

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	• Cover letter
Module 1.2	• Variation Application form with the following attachements:
	• A copy of the relevant page(s) of the Classification Guideline. As requested in the application form, MAHs must tick the boxes in front of each condition and required documentation. It is recommended to add a reference to the location of each required document in the submitted dossier (e.g. 'Appendix 1', 'Appendix 2'…).
	• A copy of the Agency's letter of acceptance of the new name
Module 1.3	• 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?"

Two electronic copies of the application should be sent to the Agency to the attention of the Product and Application Business Support (V-PD-BUS), as well as to the Rapporteur at the time of submission. See also "How and to whom shall I submit my type IB variation notification?"

The Product Team Leader should be indicated in copy ("cc") on the cover letter.

For a full overview of dossier requirements for (Co-)Rapporteur and CHMP members, including delivery addresses, please refer to the following document: PAG dossier requirements.

References

- Commission Regulation (EC) No 1234/2008 (OJ L334 of 12 December 2008)
- 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" (CPMP/328/98).

4. Do I need to submit amended mock-ups/specimens with my variation?

Mock-ups

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

Specimens

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

References

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