Chapter 7 - CMDh Best Practice Guide on Variation Worksharing

1. Introduction

Article 20 of Commission Regulation (EC) No 1234/2008 of 24 November 2008 as amended by Commission Regulation (EU) No 712/2012 of 3 August 2012, sets-out the possibility for a marketing authorisation holder to submit the same type IB or type II variation, or the same group of variations affecting more than one marketing authorisations from the same holder in one application. In case a grouped application is applied for a worksharing procedure:

• This may also contain IA changes if these are included in a group containing also type IB or type II variations (see Chapter 6 of this Best Practice Guide).

• The group may not contain a line-extension.

2. Scope

This guidance covers worksharing procedures for:

• a group of products from the same marketing authorisation holder where none of the marketing authorisations is a centralised marketing authorisation. It may include marketing authorisations granted via MRP/DCP as well as purely national marketing authorisations or a mixture of MRP/DCP and purely national marketing authorisations.

• a purely national marketing authorisation held by the same marketing authorisation holder in more than one Member State.

In these cases, the competent authority of a Member State concerned chosen by the Coordination Group shall be the ‘reference authority’.

Some information on the submission of a worksharing procedure for a group of products from the same marketing authorisation holder where at least one of the marketing authorisations is a

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1 As per Commission Communication 98/C 229/03
centralised marketing authorisation is also provided. In these cases, the European Medicines Agency shall be the ‘reference authority’.

This guidance does not cover the case of one or several changes to several different purely national marketing authorisations which concern only one member state.

Harmonisation of the complete initial dossier or SmPC, PL and labelling is not a prerequisite for a worksharing procedure. The variation application form must reflect the ‘present’ and ‘proposed’ situation applicable to all marketing authorisations included in the worksharing procedure.

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 and the reference authority may refuse to process the submission.

For the purpose of handling the worksharing procedure, the following definition of a marketing authorisation is used: all strengths and pharmaceutical forms of a certain product. For MRP/DCP products this would imply that all products belonging to e.g. AT/H/1234/001-n will be considered to belong to the same marketing authorisation. The above principle also applies for MRP/DCP products with different companies as MAH in RMS and CMS, since these MAHs do fulfil the definition of the same MAH as given in the Commission Communication 98/C 229/03.

3. Choice of Reference Authority

Where at least one of the concerned marketing authorisations has been authorised via the centralised procedure, the European Medicines Agency will be the reference authority.

In all other cases, the national competent authority of a Member State concerned chosen by the Coordination Group, based on a recommendation submitted by the holder of the marketing authorisations, shall be the reference authority.

4. Pre-submission activities

In order to facilitate the planning of the procedure, marketing authorisation holders are advised to announce an upcoming worksharing procedure to the preferred reference authority using the specified email addresses as published in the list of CMDh contact points at least 2 weeks before the planned submission, using the template for the letter of intent for the submission of a worksharing procedure (see http://www.hma.eu/265.html). Such pre-submission information should contain the following information:

- List of concerned marketing authorisations.
- Explanation as to why all concerned marketing authorisations are considered to belong to the same holder.  
- Description of the variation.
- List of proposed reference authorities in preferred order.

2 as per Commission Communication 98/C 229/03
• In case the preferred reference authority has not granted a marketing authorisation for all concerned marketing authorisations, the MAH should explain the choice of the preferred reference authority.

• Explanation as to why the holder believes that a worksharing procedure is suitable.

• Planned submission date.

The pre-submission information should be submitted to the preferred reference authority with a request for agreement and information of the worksharing procedure number.

The reference authority will confirm its availability and the procedure number within 7 days to the MAH and the CMDh (via the CMDh secretariat) which will formally confirm the worksharing in the next meeting. Further confirmation by the CMDh secretariat to the applicant is not necessary, however, the agreement of the CMDh with all worksharings applied for will be confirmed and recorded in the meeting minutes.

In cases where the preferred reference authority is unable to agree to act as reference authority it should inform the MAH within a maximum of 7 days. The MAH should afterwards immediately contact the next prioritised reference authority which should then confirm its availability and the procedure number. In case that none of the proposed reference authorities is able to agree to act as reference authority in the worksharing the MAH may forward their request to the CMDh via H-CMDhSecretariat@ema.europa.eu for further discussion.

Following agreement and information of the worksharing procedure number by the preferred reference authority the MAH can already prepare and submit the worksharing application before formal adoption by the CMDh has taken place. However, the responsibility for agreement remains with the CMDh. In the unexpected case the CMDh does not accept the allocated reference authority in its meeting the procedure will not be processed even if already submitted.

The CMDh may – on its own initiative or if requested by the MAH – give advice on the suitability and/or practicability of the proposed worksharing procedure.

All Member States as proposed by the MAH for worksharing procedures for purely national marketing authorisations should accept the submission of this application, if the worksharing fulfils the requirements for a worksharing procedure as laid down in the Commission Regulation 712/2012 of 3 August 2012. It is not possible for a single member state to refuse to participate in such a worksharing proposed by the MAH.

All requests for amendments, e.g. later submission dates, changes to the variations applied for, inclusion of further MAs etc. should be sent to the reference authority who will respond directly to the applicant. In cases where there are substantial changes to the worksharing proposed by the company in the letter of intent, the reference authority may forward the question to the CMDh for discussion.

5. Numbering

Information on the allocation of the procedure number is presented in Chapter 1 of this Best Practice Guide. The procedure number has to be requested from the reference authority before submission of the worksharing application, see above. The MAH will insert the variation procedure number on the first page of the application form in the field ‘Variation procedure number(s)’ and in the cover letter. MRP variation numbers should only be listed in the table ‘Products concerned by this application’ in the application form but not in the cover letter.
6. The Procedure

A variation or group of variations presented for worksharing should be submitted according to the normal rules applicable for variations (see Chapters 3, 4 and 5 of this Best Practice Guide), and should be provided as one integrated submission package covering all variations for all medicinal products. This will include:

- A common cover letter (including variation procedure number).
- A common application form, including the variation procedure number on the first page of the application form in the field ‘Variation procedure number(s)’, the details of the MA(s) concerned and, if applicable, the MRP variation numbers in the table ‘Products concerned by this application’ in the application form. In accordance with “EMA/CMDh Explanatory Notes on Variation Application Form” the table ‘Products concerned by this application’ should list all the EEA Countries where the medicinal product(s) included in the worksharing are authorised, in alphabetical order (i.e. all medicinal products authorised in Austria, all medicinal products authorised in Belgium, etc.).
- Separate supportive documentation sets and revised product information (if applicable) for each medicinal product concerned. This will allow the national competent authority to update the dossier of each marketing authorisation included in the worksharing procedure with the relevant amended/new information.
- For variations that affect the SmPC, labelling or package leaflet, mock-ups or specimens should be provided according to the CMDh “Mock-ups, Specimens and Samples for variations and renewals” (http://www.hma.eu/96.html), or as discussed with the reference authority on a case-by-case basis. In case type IB variation is the highest variation in the worksharing application, both the English texts and the national translations for SmPC, labelling or package leaflet should be submitted for MRP/DCP products and updated national texts should be submitted for products with a purely national marketing authorisation.
- If only purely national marketing authorisations are involved, the proposed changes to the product information should be described in detail in English in the PRESENT-PROPOSED box of the application form.

The MAH shall submit the application and any identical subsequent documentation for the worksharing procedure to all relevant authorities, i.e. the reference authority and all Member States where the products concerned are authorised.

Where the chosen reference authority is the competent authority of a Member State which has not granted a marketing authorisation for all the medicinal products affected by the application, the coordination group on request of the reference authority may ask another relevant authority to assist the reference authority in the evaluation of that application.

Worksharing procedures will be included in CTS for MRP/DCP products, to maintain the life-cycle management of each product.

Worksharing procedures with CAPs mixed with MRP/DCP and/or purely NAPs and worksharing procedures including purely NAPs only will be included in CTS to follow the procedure.

For worksharing procedures with purely NAPs or a mixture of MRP/DCP and purely NAPs, the application form mentioning all products concerned will be uploaded in CTS in order to allow every MS concerned to identify the products included in the worksharing correctly.

The reference authority will validate the application in line with the validation procedure followed for Type II variations (see Chapter 2 of this Best Practice Guide).
As foreseen in legislation for a worksharing procedure, an assessment report will always be prepared by the reference authority and circulated to the concerned Member States for comments.

In general, worksharing procedures will follow a 60-day\(^3\) evaluation timetable. This period may however be reduced by the reference authority having regard to the urgency of the matter, particularly for safety issues, or may be extended by the reference authority to 90 days for Type II variations concerning changes to or additions of the therapeutic indication or grouped applications in case the variations concerned do not fall under the cases listed in Annex III of Commission Regulation (EC) No 1234/2008, as amended.

The 30, 60 and 90 days procedures will follow the same timelines as applicable for type II variations (see Chapter 5 of this Best Practice Guide).

The reference authority prepares a preliminary variation assessment report according to the agreed timetable and circulates it to the member states concerned for comments as well as the MAH for information. The Member States concerned should send their comments to the reference authority on the preliminary variation assessment report and the application within the timeline as agreed in the timetable.

The reference authority can ask for advice from CMDh or any relevant Working Party during the procedure.

In case issues are identified by the reference authority or Member States concerned which prevent the approval of the procedure, the reference authority will send a request for supplementary information (RSI) together with a timetable stating the date by which the MAH should submit the requested data. The clock will be stopped.

As a general rule, a deadline of 60 days (10 days in 30-days procedures and 90 days in 90-days procedures) may apply to respond to the RSI. For longer periods the MAH should send a justified request to the reference authority for agreement. If the justification is not considered acceptable, then the application should be proposed for rejection.

After receipt of the MAH’s response the reference authority will prepare the final variation assessment report within 60 days (10 days in 30-days procedures) and restart the procedure with the circulation of its final variation assessment report to the MAH and the concerned member States. Concerned Member States should send their comments on the final variation assessment report and the application within the timeline as agreed in the timetable. CMS are reminded that generally all comments should be addressed on the PVAR in order to avoid new issues arising in the second phase of the procedure. In general, CMS comments in the second phase should be restricted to those cases when comments on the PVAR have not been adequately addressed in the response or when the response to initial questions raises PSRPH concerns.

Applicants are reminded that the response documents should only contain responses on questions raised by member states. Additional information outside the scope of the variation will not be considered.

For worksharing procedures including purely national marketing authorisations, the MAH is not allowed to withdraw the application in some Member States during the procedure. In case the MAH wishes to withdraw their application they need to withdraw in all Member States (including the reference authority) where the worksharing application has been submitted.

\(^3\) All time lines in this document are based on calendar days, i.e. days should be read as calendar days
Upon finalisation of the review of the variation(s) subject to the worksharing procedure, the reference authority will send its final opinion to the Member States concerned and the MAH (for further details, see section 8).

The European Medicines Agency will provide CMDh with a monthly overview of all on-going worksharing procedures at EMA level in which at least one of the marketing authorisations is a nationally approved marketing authorisation. Member States provide their comments on these procedures through their respective CHMP members.

7. Discussion at CMDh meeting

A systematic discussion of worksharing applications at CMDh meetings is not foreseen. The worksharing applications will be dealt with as normal variations; however whenever the reference authority feels that discussion at CMDh could be useful, the reference authority will propose its inclusion on the agenda.

If in case of one or more variations there is a Member State concerned that cannot approve the reference authority’s opinion as stated in the final variation assessment report on the basis of a potential serious risk to public health, the reference authority refers the procedure to the CMDh, unless the application is withdrawn by the MAH before the finalisation of the procedure.

In case single changes in the worksharing are referred to the CMDh the whole group of changes will be suspended until the referral is finalised, unless otherwise decided by the reference authority. However, the CMDh discussion will only deal with the single changes in question, not with the whole group.

Procedures may only be referred to the CMDh by the reference authority and not by the marketing authorisation holder. Only procedures where the reference authority is the competent authority of a member state can be referred to the CMDh.

The procedures described in the “CMDh Standard Operating Procedure Disagreement in Procedures - Referral to CMDh” are applicable.

8. End of the procedure

The reference authority sends its final opinion to all Member States concerned and the MAH via e-mail.

In case of a favourable decision in the worksharing procedure the reference authority will inform the MAH and the Member States concerned about the approval of the worksharing procedure. The finalisation letter of the reference authority will also list any parts of the worksharing application (e.g. as part of a group, or for a specific medicinal product) which are not considered approvable and/or which have been withdrawn by the holder during the procedure.

In case of an unfavourable decision, the reference authority will inform the MAH as well as the Member States concerned about refusal of the worksharing application (including the grounds for the unfavourable outcome).

In case of disagreement where the reference authority is the competent authority of a member state a CMS can on grounds of Potential Serious Risk to Public Health (PSRPH) request the reference authority to refer the application to CMDh.

The request from CMS should be sent no later than Day 90 (Day 30 in 30-days procedures and Day 120 in 90-days procedures). See also section 7.

For the approval of grouped variations that are part of a worksharing procedure, reference is made to section 6 of Chapter 6 of this Best Practice Guide.
The outcome of a worksharing procedure has always to be identical for all member states and medicinal products involved in the procedure.

Following the circulation of the final opinion:

- In worksharing procedures in which the European Medicines Agency acted as reference authority, the Member States concerned shall approve the final opinion, inform the European Medicines Agency and amend accordingly the marketing authorisations concerned within 60 days, provided that the documents necessary for the amendment of the marketing authorisations have been transmitted to the Member States concerned.

- In worksharing procedures in which the competent authority of one of the Member States acted as reference authority, the Member States concerned will amend, within 30 days following the approval of the opinion of the reference authority (i.e FVAR) or, where a referral has been triggered, the notification of the agreement of the coordination group or the Commission decision (as applicable), the marketing authorisation(s) accordingly, provided that the documents necessary for the amendment of the marketing authorisation(s) have been transmitted to the Member States concerned.

Type IB variations may be implemented by the MAH immediately following receipt of the finalisation letter of the reference authority.

Type II variations may be implemented by the MAH 30 days following receipt of the finalisation letter of the reference authority under the condition that the documents necessary for the amendment to the marketing authorisation have been provided to the Member States concerned, and unless a CMDh referral has been initiated. If a change to the SmPC, labelling or package leaflet was part of the worksharing application, the MAH should submit within 7 days after circulation of the finalisation letter high quality translations (in all relevant community languages) of the information texts to all member states concerned. These translations may be implemented within 30 days after submission unless any comments of the respective competent authorities have been received. All other changes can be implemented immediately following receipt of the finalisation letter of the reference authority, unless a CMDh referral has been initiated.

Variations related to safety issues must be implemented within a time-frame agreed between the reference authority and the holder.

Where harmonisation of a section of the SmPC of a purely national marketing authorisation has been achieved through a worksharing procedure, any subsequent variation submission affecting the harmonised section shall be transmitted simultaneously to all Member States concerned, preferably within a new worksharing procedure.

NB: Examples of suitable text for inclusion in the acceptance, acceptance/rejection or rejection notifications issued to the MAH on completion of the procedure are included in Annex 1.

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4 Applicable as of 4 August 2013
**Flow chart - Worksharing Procedure where the reference authority is the competent authority of a member state**

<table>
<thead>
<tr>
<th>Recommended reduced (30-day) procedure</th>
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<tbody>
<tr>
<td><strong>Day 0</strong></td>
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<tr>
<td><strong>Day 15</strong></td>
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<tr>
<td><strong>Day 20</strong></td>
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<td><strong>Day 21</strong></td>
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<tr>
<td><strong>Clock off period</strong></td>
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<tr>
<td><strong>Day 22</strong></td>
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<tr>
<td><strong>Day 25</strong></td>
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<tr>
<td><strong>No later than day 30</strong></td>
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<td><strong>Day 30</strong></td>
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<td><strong>Day 30</strong></td>
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<table>
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<tr>
<th>60-day procedure</th>
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<tbody>
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<td><strong>Day 0</strong></td>
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<td><strong>Day 40</strong></td>
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<td><strong>Day 55</strong></td>
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<tr>
<td><strong>Day 59</strong></td>
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<tr>
<td><strong>Clock off period</strong></td>
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<td>Day 60</td>
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<td>Day 75</td>
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<td>Day 80</td>
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<td>No later than day 90</td>
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### 90-day procedure

| Day 0 | Start of the procedure, the reference authority notifies the timetable to the CMS's by CTS and to the MAH by email |
| Day 70 | Reference authority circulates the PVAR to the CMS's and to the MAH |
| Day 85 | CMS's send the possible comments on the PVAR to the reference authority |
| Day 89 | Reference authority sends the request for supplementary information to the MAH and the CMS's, clock stop |
| Clock off period | Should not be longer than 90 + 60 days (90 days for the MAH to provide the responses and 60 days for the reference authority to prepare the FVAR) |
| Day 90 | Reference authority circulates the FVAR to the CMS's and to the MAH |
| Day 105 | The possible break-out meeting |
| Day 110 | CMS's send the possible comments on the FVAR to the reference authority |
| No later than day 120 | If a CMS does not agree with the final opinion of the reference authority on grounds of potential serious risk to public health, the reference authority is requested to refer the application to CMDh. |
| Day 120 | The reference authority circulates the final opinion to the CMS's and the MAH. If applicable, it is the responsibility of the applicant to provide the updated SmPC/PL/labelling (both annotated version in which all changes approved during the procedure have been marked, and clean versions to the RMSs/MSs involved in the WS procedure) |
| Day 120      | If not referred to CMDh, the final opinion is considered approved by CMS | versions to the RMSs/MSs involved in the WS procedure |
ANNEX I

Sample text for inclusion in the acceptance, acceptance/rejection or rejection notifications issued to the MAH on completion of the procedure

Example 1

Acceptance of the Worksharing (grouped) Variation

The reference authority, having considered the application for a worksharing (grouped) variation, recommends approval of the variation to the terms of the Marketing Authorisation, concerning the following change(s):

<Specification change(s) including category number of classification guideline>

If applicable:

[Please note the following change(s) was/were withdrawn from this application during the procedure:

<Specification of this / these changes>

All Member States concerned are in agreement with the reference authority.

Request to Applicant

In case of changes to the product information

Applicants are reminded to submit the national translations taking into consideration the recommendations of the Best Practice on the submission of high quality national translations no later than 7 days after the procedure is closed.

In case of approval new or update RMP

The applicant is requested to send the list of safety concerns included in the approved RMP to CMDh secretariat, e-mail address: H-CMDhSecretariat@ema.europa.eu by using the form published by CMDh (http://www.hma.eu/464.html)

In case of harmonisation of a section of the SmPC of purely national marketing authorisations

Where harmonisation of a section of the SmPC of a purely national marketing authorisation has been achieved through a worksharing procedure, any subsequent variation submission affecting the harmonised section shall be transmitted simultaneously to all Member States concerned, preferably within a new worksharing procedure.

Example 2

Acceptance/Rejection of the Worksharing (grouped) variation

The reference authority, having considered the application for a worksharing (grouped) variation, recommends approval of the variation to the terms of the Marketing Authorisation, concerning the following change(s):

<Specification of change(s) including category number of classification guideline>

However, the reference authority, having considered the variation application, refuses the following change(s):

<Specification of change(s) including category number of classification guideline>
for the reasons given below:

<Reason for refusal>

If applicable:

[Please note the following changes were withdrawn from this application during the procedure:

<Specification of these changes>]

All Member States concerned are in agreement with the reference authority.

**Request to Applicant**

**In case of changes to the product information**

Applicants are reminded to submit the national translations taking into consideration the recommendations of the Best Practice on the submission of high quality national translations no later than 7 days after the procedure is closed.

**In case of approval new or update RMP**

The applicant is requested to send the list of safety concerns included in the approved RMP to CMDh secretariat, e-mail address: H-CMDhSecretariat@ema.europa.eu by using the form published by CMDh (http://www.hma.eu/464.html)”

**In case of harmonisation of a section of the SmPC of purely national marketing authorisations**

Where harmonisation of a section of the SmPC of a purely national marketing authorisation has been achieved through a worksharing procedure, any subsequent variation submission affecting the harmonised section shall be transmitted simultaneously to all Member States concerned, preferably within a new worksharing procedure.

**Example 3**

**Refusal of the Worksharing (grouped) Variation**

The reference authority, having considered the application for a worksharing (grouped) variation, refuses all the changes detailed in the variation application for the following reasons:

< Reason for refusal>

If applicable:

[Please note the following changes were withdrawn from this application during the procedure:

<Specification of these changes>]

All Member States concerned are in agreement with the reference authority.