CMDh BEST PRACTICE GUIDES FOR THE SUBMISSION AND PROCESSING OF VARIATIONS IN THE MUTUAL RECOGNITION PROCEDURE

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INTRODUCTION

The Co-Ordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh) has produced a compilation of the following Best Practice Guides regarding the submission and processing of variation applications within the Mutual Recognition Procedure:

Commission Regulation (EC) No. 1234/2008 is effective 1 January 2010 and replaces 1084/2003/EC. It concerns variations in the Mutual Recognition procedure and Centralised procedure. Since the implementation of Article 28(3) of Directive 2001/83/EC (as amended) applicants have been able to apply for a Marketing Authorisation through the Decentralised procedure. Irrespective of whether the MA was approved via the Mutual Recognition or Decentralised procedure, Regulation 1234/2008/EC and Mutual Recognition Variation procedures will apply to subsequent changes to the MA. Separate guidance is available for Centralised variations.

The following guides have been produced:

Chapter 1: CMDh Best Practice Guide for the allocation of the Mutual Recognition Variation Number for Type I Notifications, Type II variations, Grouping and Worksharing

Chapter 2: Procedure for Automatic Validation of Mutual Recognition Procedures for Variations

Chapter 3: CMDh Best Practice Guide for the Processing of Type IA Minor Variations (Notifications) in the Mutual Recognition Procedure

Chapter 4: CMDh Best Practice Guide for the Processing of Type IB Minor Variations (Notifications) in the Mutual Recognition Procedure

Chapter 5: CMDh Best Practice Guide for the handling of Variations in the Mutual Recognition Procedure: Type II Variations

Chapter 6: CMDh Best Practice Guide for the Processing of Grouped Applications in the Mutual Recognition Procedure

Chapter 7: CMDh Best Practice Guide on Worksharing

Chapter 8: CMDh Best Practice Guide - Recommendations on Unforeseen Variations

These Best Practice Guides are intended to facilitate the practical application of the guidance for the handling of Mutual Recognition variations outlined in Notice to Applicants, Volume IIA, Chapter 5 **[to be updated]**. They provide detail on the actions undertaken by the Reference Member State (RMS), Concerned Member States (CMS) and the applicant at each step of the variation process, and the involvement of CMDh where applicable. The CMDh recommends that the Best Practice Guides are followed by all member states and applicants to ensure that a consistent approach is maintained and that variations are processed in an efficient and timely manner.

Note: separate guidance on the 24-hour urgent safety restriction procedure is available (see http://www.hma.eu/uploads/media/safety.pdf)

CHAPTER 1

CMDh BEST PRACTICE GUIDE FOR THE ALLOCATION OF THE MUTUAL RECOGNITION VARIATION NUMBER FOR TYPE I NOTIFICATIONS, TYPE II VARIATIONS, GROUPING AND WORKSHARING

1. INTRODUCTION

The allocation of the Variation procedure number is partly in the hands of the MAH. This CMDh Best Practice Guide will give detailed guidance on this issue. The MAH is responsible for allocating the variation procedure number for all MR procedures i.e. notifications/variations, renewals and repeat-use procedures. The only exception is the allocation of the variation procedure number for a grouped Type IA notification affecting more than 1 MA or a worksharing application; these procedure numbers can only be allocated by the RMS or Reference Authority. In case of doubt, the RMS or Reference Authority should be contacted.

The allocation of the MRP variation numbers[1] is in the hands of the MAH. There are three situations in which the MRP variation number and the Variation procedure number are not identical:

- a grouped notification or grouped variation affecting one MA
- a grouped notification affecting more than one MA
- worksharing application.

In all other situations, the Variation procedure number is identical to the MRP variation number.

2. THE PRODUCT NUMBER

Each medicinal product within the scope of mutual recognition[2] is characterised by a unique and specific number of the following form

CC/D/nnnn/sss

in which the element (see also Annex I)

CC	is the initial of the Reference Member State (two letter code)
D	is 'H' for medicinal products for human use or 'V' for medicinal products for veterinary use
nnnn	is the 'Medicinal Product Number' characterising the medicinal product
sss	is the 'Speciality Number' characterising the strength and/or pharmaceutical form of a medicinal product

Example:

Name of the Medicinal Product	Product Number
Hilfimmer 10 mg tablets	DE/H/0450/001
Hilfimmer 20 mg tablets	DE/H/0450/002
Hilfimmer 10 mg/ml solution for infusion	DE/H/0450/003
Hilfimmer 10 mg capsules	DE/H/0450/004

[1] In the previous version 6 of this BPG, MRP variation numbers were indicated to be 'virtual variation numbers'

[2] within the scope of mutual recognition are medicinal products (1) authorised in accordance with Directive 87/22/EC ('ex-concertation'), (2) authorised in accordance with Articles 28 and 29 of Directive 2001/83/EC (MRP/DCP) and (3) following a referral, as provided for in Articles 32, 33 and 34 of Directive 2001/83/EC which has led to a complete harmonisation.

If reference is made to all strengths and/or pharmaceutical forms of a medicinal product the following short form may be used, e.g.:

DE/H/0450/001-004

3. THE VARIATION PROCEDURE NUMBER

To characterise notifications/variations for medicinal products within the scope of mutual recognition in a unique and specific way, the Product Number will be extended by two further elements to create the Variation procedure number

CC/D/nnnn/sss/QQ/vvv

Where

QQ is either 'IA' or 'IB' for Type I notifications or 'II' for Type II variations or X for extension applications ('line extensions')[3]
vvvv is a chronological number

Example:

Notification/Variation	Variation procedure number
Type IA	DE/H/0450/001/IA/001
Type IB	DE/H/0450/001/IB/002
Type II	DE/H/0450/001/II/003

If reference is made to all strengths and/or pharmaceutical forms of a medicinal product with an identical variation the following short form may be used, e.g.:

DE/H/0450/001-004/IA/0001

4. THE CHRONOLOGY OF THE VARIATION PROCEDURE NUMBERS

The purpose of this 'chronological number' (element 'vvv' of the Variation procedure number) to be counted on, is to enable the MAH and the competent authority/inspectorate of the Member States to receive information about the history of changes to a medicinal product.

Principles:

1. Irrespective of the type of the Notification/Variation there is a continuous numbering of the submitted notifications/variations.

2. Basis for the continuous numbering is the medicinal product characterised by the 'Medicinal Product Number'.

3. Only identical notifications/variations are entitled to have the same chronological number.

4. No gaps in the continuous numbering are acceptable.

[3] The qualifier X for an extension application will only be used in the case of grouping or if an extension application will be used to change a already granted MA (e.g. the salt of an active substance will be changed to a different salt)

5. The numbering system for notifications/variations is independent from the other existing numbering system for renewals, repeat use-procedures, Article 61(3) notifications and follow up measures (FUMs). New series of numbers should be used for the other independent numbering systems so not to confuse the variations system.

6. After a change of RMS, the numbering of variations/renewals/repeat-use/Article 61(3)/FUM procedures in the new RMS will start with the next sequential number applicable for the respective procedure.

Example:

Notification/Variation	**Renewal**	**Repeat-use**
DE/H/0450/001-004/IA/001 DE/H/0450/001/IA/002 DE/H/0450/003-004/II/003 DE/H/0450/004/IB/004	DE/H/0450/001-004/R/001	
DE/H/0450/001-004/II/005 DE/H/0450/001-004/IB/006		
DE/H/0450/001-002/IA/007		DE/H/0450/003-004/E/001 DE/H/0450/001-002/E/002
DE/H/0450/001-002/II/008	DE/H/0450/001-004/R/002	

5. IDENTICAL NOTIFICATION/VARIATION

If a change applied for is concerning different strengths and/or pharmaceutical forms of a medicinal product, this single notification/variation will receive the same chronological number if the change is identical. An identical Type IB variation is characterised by the identical content of change, whereas an identical Type IA notification or Type II variation is characterised by the combination of the change listed in the Classification Guideline, the procedure type and the identical content of this change.

Examples:

1. To add pack sizes (within the approved limits) with 33 tablets to the SmPC of the medicinal products 'Hilfimmer 10 mg tablets' (DE/H/0450/001) and 'Hilfimmer 20 mg tablets' (DE/H/0450/002).

   As the change is identical for both medicinal products the following Variation procedure numbers will apply:

   for 'Hilfimmer 10 mg tablets': DE/H/0450/001/IA/001
   for 'Hilfimmer 20 mg tablets': DE/H/0450/002/IA/001

   or in a combined short form: DE/H/0450/001-002/IA/001

2. To add pack sizes (within the approved limits) with 33 tablets to the SmPC of the medicinal products 'Hilfimmer 10 mg tablets' (DE/H/0450/001) and pack sizes (within the approved limits) with 55 tablets to the SmPC of the medicinal product 'Hilfimmer 20 mg tablets' (DE/H/0450/002).

As the change has no identical content for the two medicinal products, Variation procedure numbers with different chronological numbers have to be assigned. The preferred way to do this is as follows:

'Hilfimmer 10 mg tablets': DE/H/0450/001/IA/001 (for 33 tablets)
and
'Hilfimmer 20 mg tablets': DE/H/0450/002/IA/002 (for 55 tablets)

3. To add pack sizes (within the approved limits) with 33 tablets to the SmPC of the medicinal products 'Hilfimmer 10 mg tablets' (DE/H/0450/001) and pack sizes (outside the approved limits) with 33 tablets to the SmPC of the medicinal product 'Hilfimmer 20 mg tablets' (DE/H/0450/002).

   Despite the content of the changes seems to be identical (in both cases to add 33 tablets to the SPC), they are in fact not, as the one change is a Type IA Notification (within the approved limits) and the other change is a Type IB Notification (outside the approved limits). Therefore different Variation procedure numbers have to be assigned:

'Hilfimmer 10 mg tablets': DE/H/0450/001/IA/001
and
'Hilfimmer 20 mg tablets': DE/H/0450/002/IB/002

6. VARIATION PROCEDURE NUMBERS FOR GROUPED APPLICATIONS AND WORKSHARING APPLICATIONS

Principles:

1. A grouped application or worksharing application is a single procedure for the variation. It is not bulk or multiple single procedures.

2. For the purpose of handling grouping and worksharing, 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.

3. Only for type IA variations, is it allowed to group variations over more than one MA. If Type IB or Type II variations are grouped over more than one MA, then worksharing needs to be followed.

4. A grouped application or worksharing application needs to be visible in the lifecycle of individual products included in the grouping. It is required to identify the specialities (pharmaceutical strength/form) of a MA that were included in the group. This means that in addition to the Variation procedure number a MRP variation number[4] for each speciality is allocated.

5. A product specific variation sequence number should to be recorded even for grouped variations including >1 MA and worksharing procedures. In these cases, the variation sequence number appears in the allocated MRP variation numbers as created for each speciality (s. point 4 above).

[4] In the previous version 6 of this BPG, MRP variation numbers were indicated to be 'virtual variation numbers'

The following scheme is used for Grouped variations

CC/D/nnnn/QQ/vvv/g

Where:

CC	=	two letter country code of the RMS
D	=	Domain (H)
nnnn	=	product counter (if 1 MA) / xxxx (if > 1 MA)
QQ	=	procedure qualifier (e.g. IA, IB, II, X)
vvv	=	chronological number if 1 MA: next available sequential variation counter if > 1 MA: sequential variation grouping counter (for Type IA only)
g	=	Grouping qualifier (G)

If 1 MA is included in grouping:

- The Variation procedure number is composed of the RMS code, domain, product counter (nnnn) and the next available variation sequence (vvv)
  (e.g. DE/H/0450/IB/070/G).

- This Variation procedure number can be allocated by the MAH itself.

- In addition to the Variation procedure number, for each speciality included in the grouping a MRP variation number[5] is created and maintained in CTS.

  - The MRP variation number consists of the RMS code, domain, product counter and speciality counter, the next available sequential variation counter for the product and is followed by the grouping qualifier.
  - The MRP variation numbers are not to be listed on the cover letter or the first page of application form in the field 'Variation procedure number(s). 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.

If > 1 MA is included in grouping:

- For Type IA Variations, more than one MA may be grouped. In that case the product counter in the Variation procedure number is replaced by a placeholder (nnnn = xxxx), followed by a new variation grouping counter and the grouping qualifier (G).
  (e.g. DE/H/xxxx/IA/004/G).

- As the variation grouping counter can not be allocated by the MAH, he has to contact the RMS prior to submission, since the Variation procedure number must be included in the cover letter and on the first page of the application form in the field 'Variation procedure number(s)'. A list of contact points for requests for variation grouping numbers is published on the CMDh website (http://www.hma.eu/69.html#c1726).

- In addition to the Variation procedure number, for each speciality included in the grouping a MRP variation number[6] is created and maintained in CTS.

[5] In the previous version 6 of this BPG, MRP variation numbers were indicated to be 'virtual variation numbers'
[6] In the previous version 6 of this BPG, MRP variation numbers were indicated to be 'virtual variation numbers'

- The MRP variation number consists of the RMS code, domain, product counter and speciality counter, the next available sequential variation counter for the product and is followed by the grouping qualifier.
- The MRP variation numbers are not to be listed on the cover letter or the first page of application form in the field 'Variation procedure number(s). 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.

- Each Grouped variation has a unique number.

Examples:

If a Grouped variation (1 MA), with a Variation procedure number DE/H/0113/IB/058/G is for:
- DE/H/0113/002
- DE/H/0113/003
- (but not DE/H/0113/001)

Then the MRP variation numbers are:
- DE/H/0113/002/IB/058/G
- DE/H/0113/003/IB/058/G

If a Grouped variation (2 MAs) with a Variation procedure number DE/H/xxxx/IA/007/G is for:
- DE/H/0110/001
- DE/H/0110/002
- DE/H/0113/001

Then the MRP variation numbers are:
- DE/H/0110/001/IA/034/G
- DE/H/0110/002/IA/034/G
- DE/H/0113/001/IA/042/G

The following scheme is used for worksharing applications

CC/D/nnnn/QQ/vvv

Where:

CC	=	two letter country code of the Reference authority
D	=	Domain (H)
nnnn	=	the product counter is replaced by the placeholder: xxxx
QQ	=	procedure qualifier for worksharing procedure: WS
vvv	=	sequential worksharing counter

- For the worksharing procedure the Variation procedure number is composed of the Reference Authority code, domain, a placeholder for the product counter (nnnn = xxxx) and new sequential worksharing counter.
  e.g. DE/H/xxxx/WS/002

- As the Variation procedure number can not be allocated by the MAH, he has to contact the Reference Authority prior to submission, if the procedure number was not communicated to the MAH by the CMDh secretariat with the letter of acceptance of the worksharing application. The Variation procedure number must be included in the cover letter and on the first page of the application form in the field 'Variation procedure number(s)'.

- In addition to the Variation procedure number, for each speciality included in the worksharing a MRP variation number[7] is created and maintained in CTS.

  - The MRP variation number consists of the Reference Authority code, domain, product counter, speciality counter of the product followed by the worksharing qualifier and the next available variation sequence of each product included.

  - The MRP variation numbers are not to be listed on the cover letter or the first page of the application form. 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.

- Each worksharing has a unique number.

Example:

If a Work sharing with Variation procedure number DE/H/xxxx/WS/011 is for
- DE/H/0102/001
- DE/H/0113/001
- DE/H/0113/002

Then the MRP variation numbers are:
- DE/H/0102/001/WS/072
- DE/H/0113/001/WS/059
- DE/H/0113/002/WS/059

[7] In the previous version 6 of this BPG, MRP variation numbers were indicated to be 'virtual variation numbers'

ANNEX I
MRP Numbering System
CC/D/nnnn/sss/QQ/vvv/g
e.g. DE/H/0450/001/IA/015/G

Elements	Elements description
CC	Initials of the Reference Member State /Reference Authority AT: Austria BE: Belgium BG: Bulgaria CY: Cyprus CZ: Czech Republic DE: Germany DK: Denmark EE: Estonia EMA: European Medicines Agency (in worksharing only) EL: Greece ES: Spain FI: Finland FR: France HU: Hungary IE: Ireland IS: Iceland IT: Italy LI: Liechtenstein LT: Lithuania LV: Latvia LU: Luxembourg MT: Malta NL: Netherlands NO: Norway PL: Poland PT: Portugal RO: Romania SE: Sweden SI: Slovenia SK: Slovak Republic UK: United Kingdom
D	H = Human V = Veterinary
nnnn	Medicinal Product Number (4 digits)
sss	3 digits Speciality Number (for strength, pharmaceutical form)
QQ	Procedure qualifier which assumes one of the following values: **IA**: for Type IA Notifications **IB**: for Type IB Notifications **II**: for Type II Variations **R:** for Renewal **E:** for Repeat Use **X**: for Extension **WS**: for Worksharing **P:** for Article 61(3) Notifications **FU:** for Follow-up submissions and commitments
vvv	Chronological Number (43 digits)
g	G: Grouping qualifier

ANNEX II

Decision tree for allocating procedure numbers for grouped and worksharing procedures

Grouped variations – numbering scheme

The following scheme is used :

CC/D/nnnn/QQ/vvv/G

Where:

CC	=	two letter country code of the RMS
D	=	Domain (H or V)
nnnn	=	product counter (if 1 MA) / xxxx (if >1 MA)
QQ	=	qualifier (e.g. IA, IB, II, X)
vvv	=	sequential variation * / multi-MA-IA ** counter
G	=	Grouped variation indicator

Examples: UK/H/0254/IB/048/G (for 1 (same) MA)includes
UK/H/0254/001 &
UK/H/0254/002

UK/H/xxxx/IA/003/G (for >1 MA) includes
UK/H/0254/001 &
UK/H/0254/002 &
UK/H/0255/001

* if 1 MA: next available no. from variation sequence

** if >1 MA: next available no. from multi-MA-IA sequence (for Type IA only)

Worksharing procedure – numbering scheme

The following scheme is used :

CC/D/nnnn/QQ/vvv

Where:

CC	=	two letter country code of the Reference authority
D	=	Domain (H or V)
nnnn	=	placeholder : xxxx (is literally meant as 'xxxx')
QQ	=	qualifier (e.g. WS)
vvv	=	sequential worksharing counter (three number digit)*.

Example: UK/H/xxxx/WS/004 includes products
UK/H/0254/001 &
UK/H/0255/001 &
NL/H/1003/001

*new counter starting from 1 for each Reference Authority

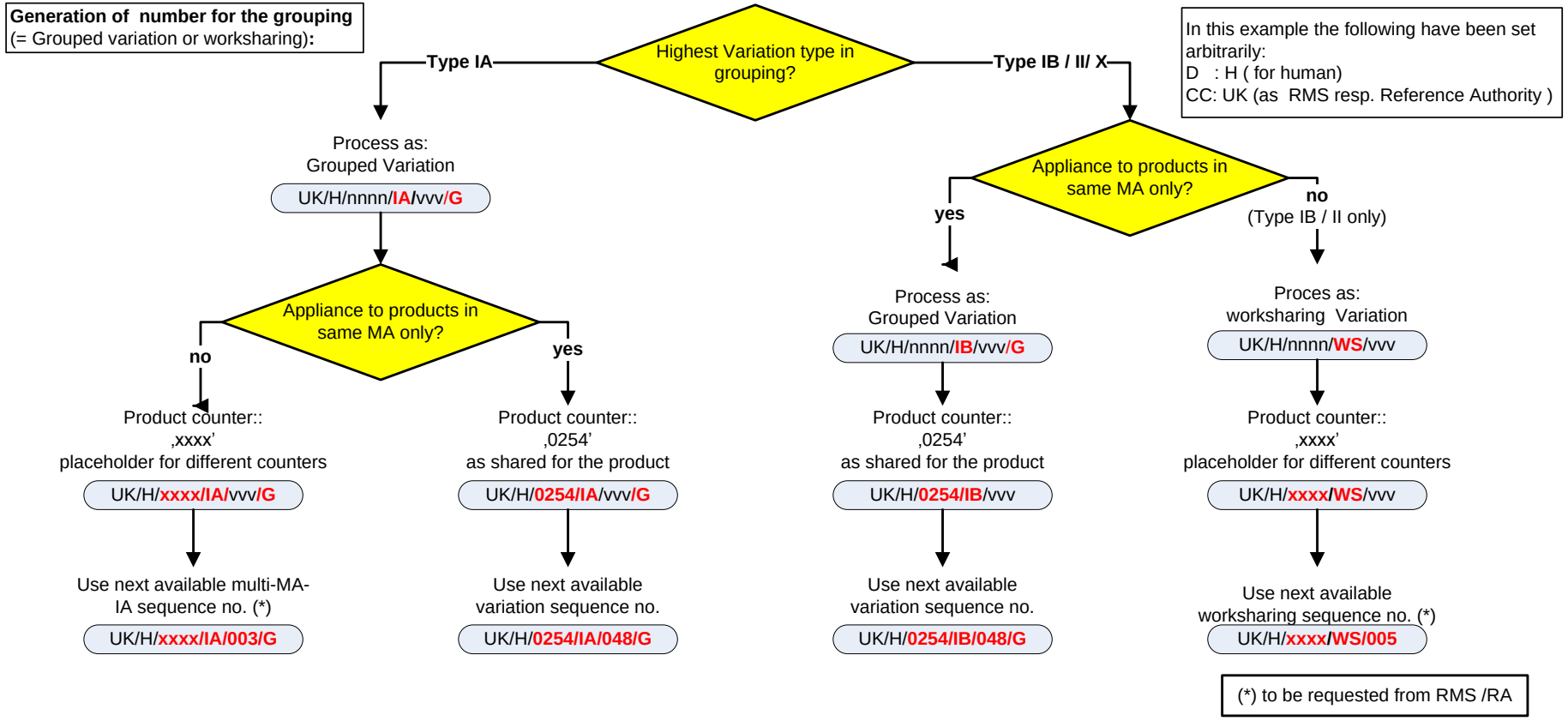
Prerequisites / Definitions:

A **Marketing Authorisation** : all strenghts 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.

Record of:

- The last **sequential number** for the **variations** processed on this MA (common for the product – recorded by RMS & MAH)
- The last **sequential number** for **multiple MAs of Type IA** processed by the RMS (common for the RMS – to be sought from RMS)
- The last **sequential number** for the **worksharing** processed by the RA (common for the Refarence Authority – to be sought from RA)

MA / Product :	UK/H/**0254**/	UK/H/**0255**/	NL/H/**1003**/
Strenght 1 :	UK/H/0254/**001**	UK/H/0255/**001**	NL/H/1003/**001**
Strength 2 :	UK/H/0254/**002**	UK/H/0255/**002**	NL/H/1003/**002**
Form 2 :			NL/H/1003/**003**
last:			*last:*
var-sequ. No.:	**047**	**022**	**015**
	(from UK/H/0254/001/II/047)	(from UK/H/0255/001/II/022)	(from NL/H/1003/001/IB/015)
multi-MA-IA-sequ. No.:	**002**	**002**	**008**
worksharing-sequ. No.:	**004**	**004**	**011**



Virtual Variation numbers

In MR-Variations for each pharmaceutidal form and strength of a product included in the group the variation number as for a single variation is generated and recorded for system internal purposes. These have to be considered/recorded in the variation sequence counter for the calculation of the next available number in the sequence. This in particular is important for a multiple MA type IA variation or a worksharing where the counter for the group is different from the variation sequence.

UK/H/0254/001/IA/048/G
UK/H/0255/001/IA/023/G

UK/H/0254/001/IA/048/G
UK/H/0254/002/IA/048/G

UK/H/0254/001/IB/048/G
UK/H/0254/002/IB/048/G

UK/H/0254/001/WS/048
UK/H/0255/001/WS/023
NL/H/1003/001/WS/016

CHAPTER 2

PROCEDURE FOR AUTOMATIC VALIDATION OF MUTUAL RECOGNITION PROCEDURES FOR VARIATIONS

Completion of CTS records by all Member States is essential for the operation of the procedure (see Best Practice Guide for MRP and DCP).

1. INTRODUCTION

This procedure has been introduced by the CMDh in order to facilitate the initiation of variation procedures according to Regulation (EC) No. 1234/2008 effective 1 January 2010.

Procedures for the allocation of the MR variation procedure number and the submission of the variation apply to all categories of variations. It should be noted that in cases where the CMS have not received the variation application or the fee has not been paid at the time of submission or in accordance with national competent authority requirements, the application will be deemed invalid and the procedure stopped.

2. ALLOCATION OF MR VARIATION PROCEDURE NUMBER

The **MAH** will be responsible for identifying and assigning their own procedure number according to guidance given in Chapter 1. In case of doubt, the RMS or Reference Authority should be contacted.

3. SUBMISSION PHASE

The **MAH** submits the variation and supporting documentation simultaneously to the RMS and CMS. Only the RMS should additionally receive the list of despatch dates (all dates of despatch to the CMS and a statement that the relevant national fees have been paid as required by national competent authorities). This may be sent after the notification/variation submission. Sample text for inclusion in the list of despatch dates is shown in Annex 1.

4. START OF VARIATION PROCESS

The process for acknowledging or as appropriate starting the notification or variation is summarised in the flow charts in Annex II.

4.1 Type IA Notifications

Within 5 calendar days of receipt of the Notification (Type IA and IA_{IN}) and list of despatch dates, the **RMS** completes the CTS record including for transparency a description of the proposed change(s). This may be done by ticking all single changes from the provided list in CTS or by using the free text field. In case of the latter, the application form has to be uploaded to CTS, preferably as a word file. This informs CMS of the start of the notification process i.e. Day 0 as well as of details concerning the changes applied for. Day 0 should be backdated as necessary to coincide with the actual date of receipt of the notification.

CMS should not comment on the validity of the notification in respect of content. **CMS** may only

inform the RMS in case of non-receipt or non-payment of fees. This should be done by indicating the invalid field on CTS and additionally informing the RMS by email. The RMS will take the appropriate action should they be informed of any irregularity.

4.2 Type IB Notifications

Within 7 calendar days of receipt of the variation application, supporting documentation – taking into account any listed examples in the Commission Guideline- , and if applicable a copy of the Article 5 Recommendation, and the list of despatch dates, the **RMS** creates the CTS record, including a text description of the proposed change, as a means of informing CMS about the submission.

CMS should not comment on the validity of the variation in respect of content but may indicate on CTS and by email within 7 calendar days of the CTS record in case the application is invalid due to non-receipt or non-payment of fees. The **CMS** should then inform the RMS on the validity of the application within 7 calendar days of receipt of the possible missing information/fee by the applicant.

The RMS will not start the clock until the **CMS** confirms to the RMS that issues have been resolved and the application is valid. However, the same rules apply for starting the procedure as in the ***MEMBER STATE AGREEMENT UPON CONDITIONS UNDER WHICH THE RMS CAN START THE MRP/DCP*, http://www.hma.eu/91.html.**

If the RMS receives no invalid notification from CMS within the 7 calendar day period, the **RMS** completes the CTS record as a means of informing CMS of the start of the variation process (Day 0). The **RMS** additionally informs the MAH. CMS should not subsequently inform the RMS that the application is not valid.

When the proposed variation is not considered as a minor variation of Type IB following the Commission Classification Guideline[8] or has not be classified as a minor variation of type IB in a recommendation pursuant article 5 of the variation regulation the RMS should confirm within these 7 calendar days whether the proposed change can be considered a minor variation of Type IB, and acceptable as a Type IB notification, or whether it is of the opinion that the proposed change has the potential to have a significant impact on the quality, safety or efficacy of the medicinal product and is not acceptable as a Type IB notification or whether there is a need to consult with CMS on the classification of the proposed change.

When the RMS is of the opinion that the proposed change has the potential to have a significant impact on the quality, safety or efficacy of the medicinal product, the RMS will inform the CMS immediately by email through the MRVE-mailbox mentioning "upgrade" in the email subject in addition to procedure number and product name. In these situations, the validation period can be extended by an additional 7 calendar days to give the RMS and CMS time to discuss this. If the CMS disagree with the RMS, the RMS shall take the final decision on the classification of the proposed variation having taken into account the comments received.

- If it is decided by the RMS that a Type IB notification is still appropriate, the RMS completes the CTS record as a means of informing CMS of the start of the variation process (Day 0). The **RMS** additionally informs the MAH. CMS should not subsequently inform the RMS that the application is not valid.

[8] When one or more of the conditions established in the guideline for a Type IA variation are not met, the concerned change may be considered listed as a Type IB variation unless the change is specifically classified as a major variation of Type II.

- If it is decided by the RMS that the proposed change has the potential to have a significant impact on the quality, safety or efficacy of the medicinal product and that a Type IB notification procedure is not appropriate, the RMS will inform the MAH accordingly, supporting this decision on scientific reasons. The MAH will be requested to revise and supplement the variation application so that the requirements for a Type II variation application are met. The RMS will indicate the upgrade of the variation application to a Type II variation in CTS.

After receiving a request from the RMS to upgrade the proposed variation, the MAH has 21 calendar days to update the application form for a Type II variation, pay the corresponding fee and to submit any supplementary documentation. Once the variation is resubmitted as a Type II variation, the normal timeline for a Type II variation application applies after the procedure has been started by the RMS.

4.3 Type II Variations

The **RMS** enters the procedure into CTS, including a text description of the proposed change, immediately after receiving the variation application as a means of informing the CMS of the variation at an early stage. On receipt of the list of despatch dates the **RMS** circulates to the CMS by e-mail the proposed procedure start date and variation timetable. The procedure start date is normally set at 14 calendar days from receipt of the list of despatch dates to allow CMS to comment on the validity of the application or the proposed timetable.

The **CMS** should inform the RMS within the 14 calendar day period of acceptance of a valid application by indicating on CTS. If no comments are received during the 14 day validation period, the **RMS** notifies the MAH and CMS of the procedure start date. This is Day 0. If a CMS has previously informed the RMS that the application is not valid, the clock will not be started until that CMS confirms to the RMS that the issues have been resolved and the application is valid. The CMS has a duty to update the status of the CTS record accordingly.

The **CMS** should inform the RMS that the application has become valid within 7 calendar days of the missing information being supplied.

4.4 Grouped applications

Grouped applications are handled according to the highest variation type being part of the application and specifying the procedure type as described under 4.1-4.3.

4.5 Worksharing procedure

Worksharing applications are handled according to the procedure as described under 4.3 with the reference authority taking the responsibilities of the RMS.

ANNEX I

Sample information for inclusion in the MAH's list of despatch dates

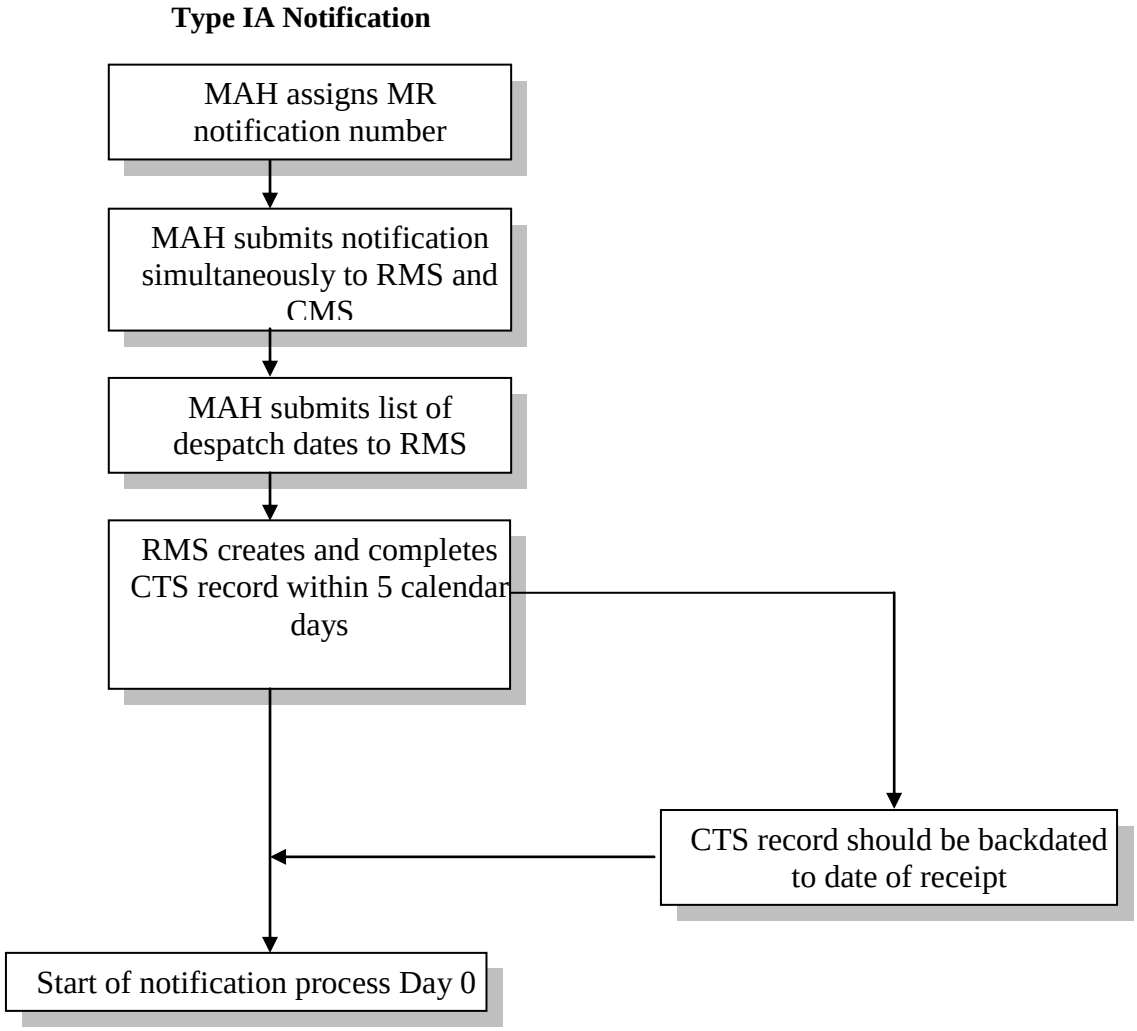
Mutual Recognition Procedure Variation Number
(*e.g. UK/H/0123/001/II/002*)

NAME OF COMPETENT AUTHORITY/AGENCY FOR DESPATCH*	DATE OF SUBMISSION	DATE OF PAYMENT OF FEES, AS APPROPRIATE	MA HOLDER

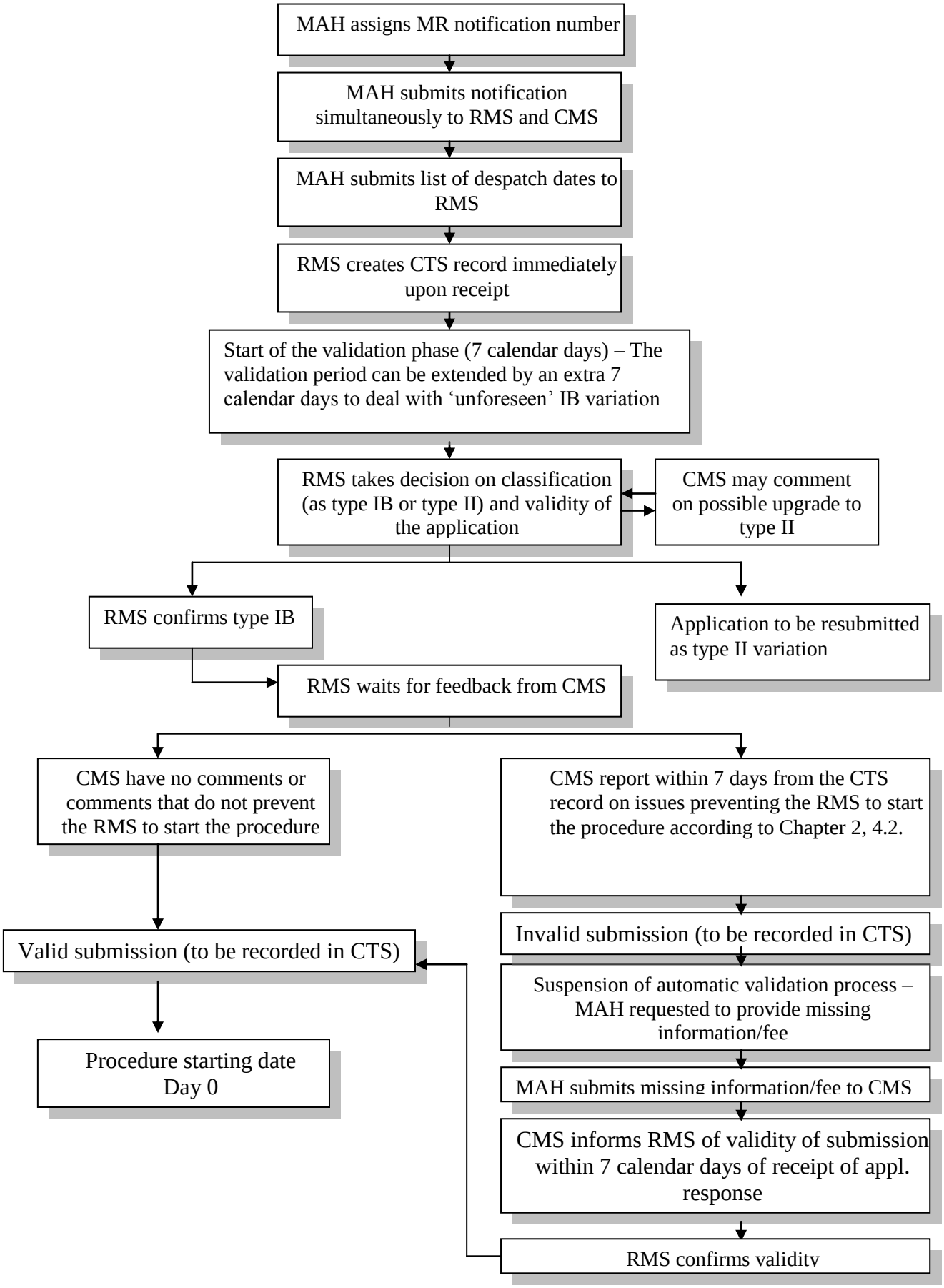
*Note: Address for delivery of the notification/variation to the concerned member states is referenced in Notice to Applicants, Volume IIA, Chapter 7

ANNEX II

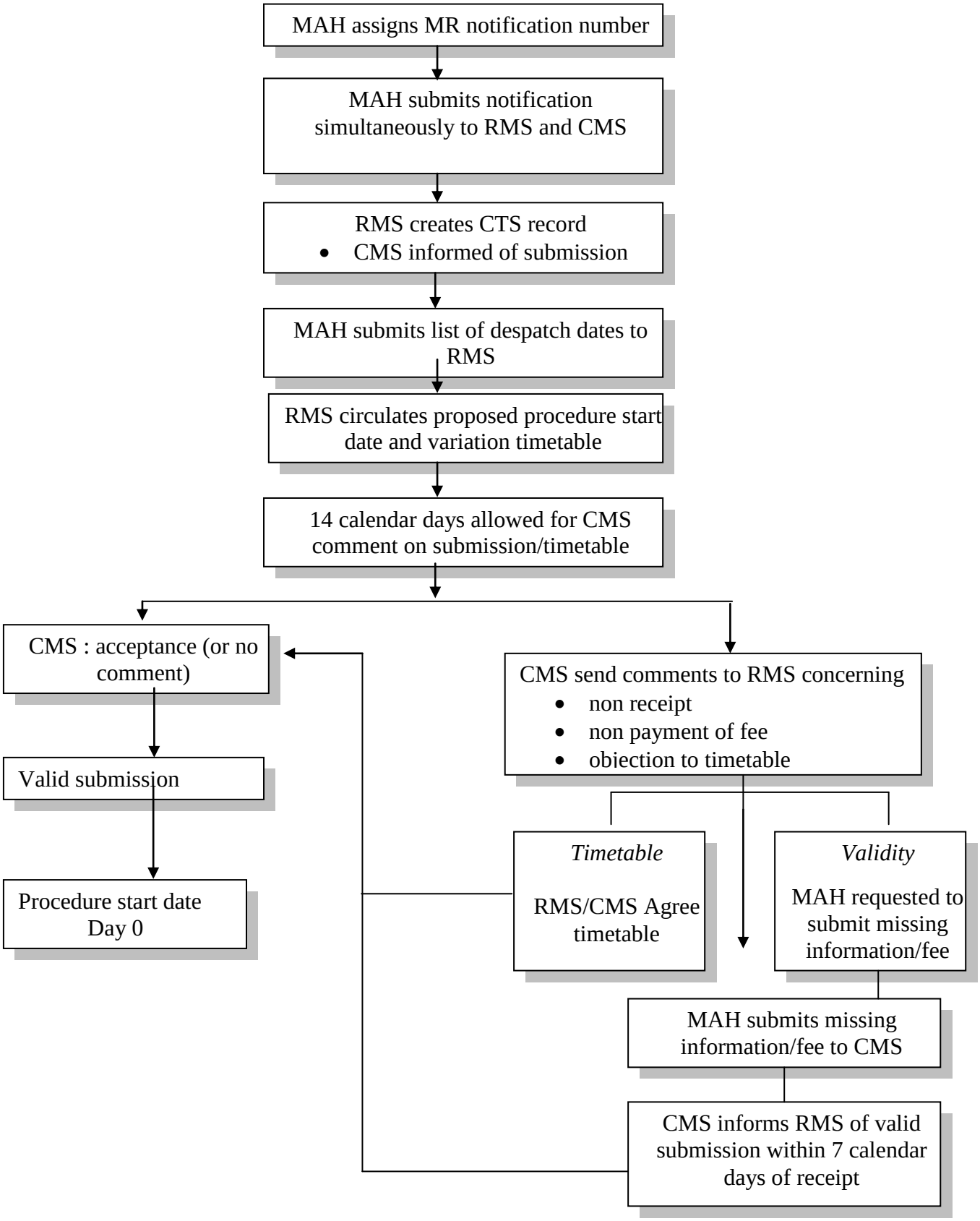
Flowchart for automatic validation: Starting the notification or variation procedure.



Type IB Notification



Type II Variation



CHAPTER 3

CMDh BEST PRACTICE GUIDE FOR THE PROCESSING OF TYPE IA MINOR VARIATIONS (NOTIFICATIONS) IN THE MUTUAL RECOGNITION PROCEDURE

1. INTRODUCTION

This Best Practice Guide has been produced by the CMDh in order to facilitate the processing of Type IA minor variations in the MR procedure. Guidance is given on the role of the Reference Member State (RMS) as co-ordinator of the notification process, and to reflect good practice of the Concerned Member States (CMS) in ensuring a consistent approach is maintained. This will ensure that the notifications are processed in an efficient and timely manner. Moreover, it is considered that the quality of the submission and supporting documentation, which are the responsibility of the marketing authorisation holder (MAH), are crucial to the overall process.

Variation Regulation (EC) No.1234/2008 effective 1 January 2010 identifies the category of variation that can be processed as *Type IA Notifications*. According to the Regulation, a Type IA variation is a category of change which is specifically identified in the Commission guideline on the classification of variations as a Type IA notification and where all the required conditions and data requirements are met.

According to the Regulation minor variations of Type IA do not require prior approval but can be implemented prior to notification to the relevant authorities ("Do and tell"). Type IA notifications are listed in the Commission guideline on the classification of variations and these notifications should be submitted within twelve months following implementation, so called "*annual reports*", taking into account the guidance on possible grouping of variations. However, the notification should be submitted immediately after the implementation of the variation in the case of specific minor variations requiring immediate notification. These notifications are specifically identified as IA_{IN} in the guideline.

It is possible for a MAH to include a Type IA variation in the submission of a Type IA_{IN} variation, or with another upcoming variation, rather than waiting to include it in an annual report. Further information about the grouping of Type IA variations is available in Chapter 6 of this Best Practice Guide; however, the timetable and principles for grouped variations, consisting of Type IA changes only, is the same as the procedure outlined in this Chapter of the Best Practice Guide.

2. MINOR TYPE IA VARIATIONS (NOTIFICATIONS: "DO AND TELL")

Allocation of the MR notification number

Information on the allocation of the MR notification number is presented in Chapter 1 of this Best Practice Guide. In case of doubt, the RMS or Reference Authority should be contacted. The MAH will insert the MR variation number on the application form and in the cover letter. Virtual variation numbers should not be inserted on the application form and in the cover letter.

Start of notification process (Day 0)

The MAH will submit simultaneously to the RMS and CMS an application containing the elements listed in Annex IV of the Regulation, presented as follows in accordance with the appropriate headings and numbering of the EU-CTD format:

- Cover letter.

- Application form, including the MR variation number, a description of the variation(s) submitted and the date(s) of implementation.

- A copy of the relevant page(s) of the Commission Guideline, indicating that all conditions and documentation requirements are met, or a copy of the relevant published Article 5 Recommendation, if applicable.

- Supporting documentation as appropriate.

    - For variations that affect the SmPC and/or labelling or package leaflet, both the English texts and the national translations should be submitted. Mock-ups or specimens should be provided according to Chapter 7 of the NtA, or as discussed with the RMS on a case-by-case basis.

Additionally, the RMS submission should include the list of dispatch dates (all the dates of dispatch to the CMS) and declaration that the relevant national fees have been paid at the time of submission).

The RMS creates the CTS record.

CMS should check they have received the application and relevant fee. The acknowledgement of an acceptable notification which is issued by the RMS on completion of the process will reflect that these documents have been submitted simultaneously to all CMS and that relevant fees have been paid. The notification process start date (Day 0) is set by the RMS on the day of receipt of the above documentation. The RMS completes the CTS record as the means of informing the CMS of the start of the notification process. Day 0 should be backdated as necessary to coincide with the actual date of receipt of the notification.

Review phase (Day 0–30)

The RMS will perform a check of the notification to confirm that the required supporting documentation has been submitted. The MAH's checklist which has been appended to the application form will assist with this. The checklist must have positive confirmation e.g. by manually indicating "YES" or "tick" against each item to indicate that all the required conditions are satisfied and all documentation has been submitted. If all the documentation **has not been provided**, the notification will be deemed unacceptable and the MAH should immediately cease to apply the concerned variation(s) or the MAH may decide to submit a new variation, which will require a new variation procedure number.

Neither RMS nor CMS will perform a full assessment of the supporting data in detail. The RMS will be responsible for undertaking a check (which is more extensive than an administrative check) to establish the acceptance of the notification based on the submitted documentation. CMS should not comment to the RMS or MAH about the acceptance in respect of content. CMS may comment only in the case of non-receipt of documentation or non-payment of fees (highlighted from CTS). Where a Type IA notification affects product information, it is acknowledged that the change will have already been introduced prior to submission. It is the MAH's responsibility to ensure that the text has been correctly updated, including in any required translations. Consequently, the updated product information, including translations will not be the subject of a separate assessment. Therefore, there will be no national phase after the end of the procedure.

For Type 1A variations, there is no request by the RMS for clarification, information or documentation from the MAH and there is no clock-stop or suspension of the process.

Outcome of the notification process

The RMS will make the decision as to whether the notification is accepted or rejected. The following actions will be taken on or before Day 30.

- ***For an acceptable notification***: The RMS will inform the MAH on behalf of the CMS that the Variation is considered acceptable and a letter of *"Acknowledgement of an acceptable Notification"* will be issued. CMS are informed of the outcome by means of the updated CTS record.

- ***For an unacceptable notification*:** The RMS informs the MAH in writing that the Variation is not acceptable and provides brief reasons as well as a course of action. CMS are notified via the updated CTS record, which should also state the reasons for non acceptance.

Examples of suitable text to be used for notification acknowledgement letters issued to the MAH on completion of the process are provided in Annex 1.

For grouped variations a different outcome may apply to the different variations included in the notification, i.e. some changes may be accepted, whilst others may be rejected. In these cases please refer to Chapter 6 if this BPG for details on the possibilities of outcome.

Competent authorities should implement the decision nationally within two months in the case of a variation(s) that does not require immediate notification or six months if the variation(s) does require immediate notification.

ANNEX I

Sample text for acknowledgement notification letters to be issued to the MAH on completion of the procedure

Example 1

ACKNOWLEDGEMENT OF AN ACCEPTABLE NOTIFICATION

The <<*competent authority*>> acknowledges that the Type 1A variation detailed in your application is acceptable. The following change(s) has been notified:

<< *enter change introduced by notification*>>

The notification is considered acceptable on the basis of the Marketing Authorisation Holder undertaking that:

i. The notification of change complies with all conditions specified in the Commission guideline on the classification of variations.

ii all supporting documentation as listed in the Commission guideline on the classification of variations have been provided.

iii the application has been submitted simultaneously to all Concerned Member States and the relevant fees have been paid as required by national competent authorities.

Failure to comply with any of the above may subsequently deem the notification unacceptable.

Example 2

NON-ACCEPTANCE OF NOTIFICATION

The <<*competent authority*>> cannot accept your Type IA variation as being acceptable because of the following:

<<*enter reason for non-acceptance*>>

ANNEX II

Submission phase	To the RMS and CMS the MAH submits the application accompanied by supporting documentation as appropriate. The MAH submits list of dispatch dates to the RMS.
Day 0	The RMS starts the procedure and completes the CTS record.
Until Day 30	The RMS checks if the notification can be accepted. The CMS only checks if the notification has been received and if the fee has been paid as appropriate.
Day 30	The RMS will inform the MAH on behalf of the CMSs of the outcome of the variation notification. CMS are informed accordingly via the updated CTS record. Where applicable, the MAH provided the RMS during the procedure highlighted and clean versions of the SmPC, labelling or package leaflet in electronic format. The RMS checks the highlighted (changed) text, and circulates these documents together with a statement that it has endorsed the changes made, to the MAH and CMSs
Within 2 or 6 months after acceptance	Competent authorities should implement the decision nationally within: • Two months in the case of a variation(s) that does not require immediate notification or • Six months if the variation(s) does require immediate notification.

CHAPTER 4

CMDh BEST PRACTICE GUIDE FOR THE PROCESSING OF TYPE IB MINOR VARIATIONS (NOTIFICATIONS) IN THE MUTUAL RECOGNITION PROCEDURE

1. INTRODUCTION

This Best Practice Guide was produced by the CMDh in order to facilitate the processing of Type IB Variations in the MR procedure. Guidance is given on the role of the Reference Member State (RMS) as co-ordinator of the notification process, and to reflect good practice of the Concerned Member States (CMS) in ensuring a consistent approach is maintained. This will ensure that the Type IB-Variations are processed in an efficient and timely manner. Moreover, it is considered that the quality of the submission and supporting documentation, which are the responsibility of the marketing authorisation holder (MAH), are crucial to the overall process.

Variation Regulation (EC) No. 1234/2008 effective 1 January 2010 gives a general definition of variations that can be processed as *Type IB Variations.* According to the Regulation, a variation which is not an extension and which is not classified in the guideline referred to in Art. 4 of the Regulation, shall by default be considered a minor variation of type IB. Furthermore, a variation which is recommended as variation of type IB according to Art. 5 of the Regulation, shall be submitted as minor variation of type IB.

Type IB variations may be grouped together with other variations in a single notification. If the highest ranking variation is a Type IB variation, this will be classified as a Type IB variation. Further information about the grouping of variations is available in Chapter 6 of this Best Practice Guide.

An MAH may also submit several Type IB variations to more than one of their marketing authorisations in a single application; this will be dealt with in accordance with the worksharing procedure. Further information about worksharing is available in Chapter 7 of this Best Practice Guide.

In cases of doubt about the classification, the MAH may request the CMDh to provide a recommendation on the classification of the variation according to article 5 of Regulation (EC) No 1234/2008. Further details on the article 5 procedure are given in Chapter 8.

2. TYPE IB VARIATIONS

2.1. Allocation of MR variation number

Information on the allocation of the variation procedure number and the MRP variation number is presented in Chapter 1 of this Best Practice Guide. In case of doubt, the RMS or Reference Authority should be contacted.

2.2. Validation of the application

The MAH will submit simultaneously to the RMS and CMS an application containing the elements listed in Annex IV of the Variation Regulation, presented as follows in accordance with the appropriate headings and numbering of the EU-CTD format:

- Cover letter.

- Application form, including the variation procedure number and the MRP variation number and a description of the variation(s) submitted.

- Checklist of the documentation specified for the proposed change(s) if applicable. This could be directly copied or printed from the Classification Guideline.

- If available, copy of the Art. 5 recommendation for the requested change.

- Supporting documentation as appropriate. For variations requested by a national competent authority, e.g. following assessment of Follow Up Measures (FUMs), Specific Obligations (SOs) and Periodic Safety Update Reports (PSURs), or class labelling, a copy of the request should be annexed to the cover letter.

- For variations that affect the SmPC, labelling or package leaflet, both the English texts and national translations should be submitted. Mock-ups or specimens should be provided according to Chapter 7 of the NtA, or as discussed with the RMS on a case-by-case basis.

Additionally, the RMS submission should include the list of dispatch dates (all the dates of dispatch to the CMS and declaration that the relevant national fees have been paid at time of submission).

The RMS creates the CTS record within 7 calendar days after receipt of the application.

2.3. Start of notification process

After the validation period the RMS completes the CTS record as the means of informing the CMS of the start of the notification process and the timetable. The MAH is informed by the RMS about the start date (Day 0).

2.4. The Evaluation Process (Day 0 to Day 30)

According to the Regulation (EC) No. 1234/2008 the timeframe for the evaluation and the evaluation of the change applied for is in the responsibility of the RMS. This implies, that the RMS has the responsibility to ask the CMS in exceptional cases, where the RMS need an input from the CMS for his decision.

This situation may be given for the following categories of changes:

- Change in the name of the medicinal product (in a CMS)
- Change in pack size
- Change in or introduction of a DDPS (in a CMS)
- Deletion of a pharmaceutical form or indication
- All variations under heading C.I.1-C.I.4 and C.I.6-C.I.7

If the product information is concerned by the change applied for the translation has to be validated during this 30-day period.

If there are objections from CMS regarding the change applied for, it is the responsibility of the CMS to forward this comment to the RMS and to update CTS accordingly within 20 calendar days following the start of the procedure.

Within 30 days from the start of the notification procedure, the RMS will notify the MAH of the outcome of the procedure. If the RMS has not sent the holder its opinion within 30 days, i.e. by Day 30, the notification shall be deemed acceptable.

If the notification cannot be accepted by the RMS, taking into account the CMS comments, the RMS will inform the MAH and the CMSs about the grounds on which the rejection is based ('Notification with Grounds') by Day 30. The clock will stop pending receipt of an amended notification by the MAH, which should be submitted to the RMS and CMS within 30 calendar days. Additionally, the MAH should send a list of the dispatch dates, indicating the dates on which the amended notification was sent to the CMS, to the RMS. The RMS will re-start the procedure on receipt of the list of dispatch dates and inform the MAH accordingly. The RMS will also update CTS to inform the CMS.

Within 30 days of receipt of the amended notification, the RMS will inform the MAH, by means of a 'Notification on a Type IB variation', of its final acceptance/rejection of the variation. If the MAH did not amend the notification within 30 days, as requested, the variation will be rejected and the CMS will be informed accordingly by updating CTS.

2.5. Outcome of the notification process

The RMS will make the decision as to whether the notification is accepted or is rejected. The following actions will be taken on or before Day 30/New Day 30.

- **Approval:** The RMS will inform the MAH that the variation application is approvable, together with the date of approval. CMS are informed of the outcome by means of the updated CTS record.

- **Refusal:** The RMS will inform the MAH and the CMS about the reasons leading to the refusal of the variation application. The RMS will update CTS which should also state the reasons for refusal.

Examples of suitable text for inclusion in approval or refusal notifications issued to the MAH on completion of the procedure are included in Annex 1.

For grouped or worksharing variations a different outcome may apply to the different variations included in the notification, i.e. some changes may be accepted, whilst others may be rejected. In these cases please refer to Chapter 6 or 7 of this Best Practice Guide.

Competent authorities should implement the decision nationally within six months from the end of the procedure; however, the MAH can implement the changes prior to the marketing authorisation being updated by the national competent authority.

ANNEX I

Sample text for inclusion in the approval or refusal notifications issued to the MAH on completion of the procedure

ACKNOWLEDGEMENT OF APPROVAL

The <<*competent authority*>> agrees to the request to vary the Marketing Authorisation detailed in the application. The proposed change is:

<< *enter change applied for*>>

The application is approved on the basis that the application has been submitted simultaneously to all Concerned Member States and the relevant fees have been paid as required by national competent authorities. Failure to comply with this provision may subsequently deem the application invalid.

REFUSAL

The <<*competent authority*>> cannot agree to the proposed variation to the Marketing Authorisation because of the following:

<<*enter reason for non-acceptance*>>

ANNEX II

Submission	• MAH submits variation to the RMS and CMS and a list of dispatch dates to the RMS only. • The RMS creates a CTS record.
Day 0	The RMS starts the procedure, completes the CTS record and circulates an e-mail informing the MAH of the procedure start date.
Until Day 20	CMS notify RMS of their objections as applicable.
Day 30	• If the variation cannot be accepted by the RMS, taking into account the CMS comments the RMS circulates the 'Notification with Grounds' to the CMS and MAH and the clock stops. • If the variation can be accepted by the RMS, taking into account the CMS comments, the RMS circulates an acceptance notification to the MAH and informs the CMS by updating CTS and the procedure ends. Where applicable, the MAH provided the RMS during the procedure highlighted and clean versions of the SmPC, labelling and/or package leaflet in electronic format, The RMS checks the highlighted (changed) text, and circulates these documents together with a statement that it has endorsed the changes made, to the MAH and CMSs.
Clock stop	Within 30 days of receipt of the 'Notification with Grounds', the MAH submits an amended notification to the RMS and CMS and a list of dispatch dates to the RMS only.
New Day 0	The RMS restarts the clock, updates CTS and circulates an email informing the MAH that the procedure has restarted.
New Day 30	• If the variation can be accepted by the RMS, taking into account the CMS comments the RMS circulates an acceptance notification to the MAH and informs the CMS by updating CTS the procedure ends. Where applicable, the MAH provided the RMS highlighted and clean versions of the SmPC, labelling and/or package leaflet in electronic format, The RMS checks the highlighted (changed) text, and circulates these documents together with a statement that it has endorsed the changes made, to the MAH and CMSs. • If the variation cannot be accepted by the RMS, taking into account the CMS comments, the RMS circulates a rejection notification to the CMS and MAH and the procedure ends.
Within 6 months after acceptance	Competent authorities should implement the decision nationally within six months.

CHAPTER 5

CMDh BEST PRACTICE GUIDE FOR THE HANDLING OF VARIATIONS IN THE MUTUAL RECOGNITION PROCEDURE: TYPE II VARIATIONS

1. INTRODUCTION

The Best Practice Guide has been introduced by the CMDh to facilitate the processing of type II variation applications according to Regulation (EC) No.1234/2008 effective 1 January 2010. It aims to provide guidance on the role of the Reference Member State (RMS) as co-ordinator of the procedure, and to reflect good practice of the Concerned Member States (CMS) in handling of type II variations.

The Regulation and the "Commission guideline on the details of the various categories of variations", referred to in Article 4 of the Regulation, set out a list of changes to be considered as Type II variations. In addition, any other change that may have a significant impact on the quality, safety or efficacy of the medicinal product must be submitted as a Type II variation. Such changes may be covered by a recommendation delivered pursuant to Article 5 of the Regulation.

Type II variations require prior approval before implementation.

Type II variations may be grouped together with other variations in a single application if it concerns a single MA. If the highest ranking variation is a Type II variation, this will be classified as a Type II variation. Further information about the grouping of variations is available in Chapter 6 of this Best Practice Guide.

A MAH may also submit several Type II variations to more than one of their marketing authorisations in a single application; this will be dealt with in accordance with the worksharing procedure. Further information about worksharing is available in Chapter 7 of this Best Practice Guide.

2. TIMESCALES

Variations are normally processed according to a 60-day time scale, however the Regulation additionally specifies a reduced or extended (90-day) time scale for Type II variations. The reduced time (recommended 30-days) in the Regulation is intended for variations concerning safety issues. The RMS and MAH should decide when the expedited procedure is appropriate bearing in mind that a 24-hour urgent safety restriction procedure is available (see http://www.hma.eu/uploads/media/safety.pdf). The 90-day process is intended for variations concerning a change to, or addition, of, the therapeutic indications. The detailed procedural timetables for 30-, 60- and 90-day type II procedures are given in the flowcharts at the end of this document. It should be noted that these reflect overall time scales of 30, 90 and 120 days for completion of the procedures (excluding clock-off times).

Flow-charts of the Type II variation procedures are provided in Annex II.

3. ALLOCATION OF VARIATION PROCEDURE NUMBER

Information on the allocation of the variation procedure number and the MRP variation number is presented in Chapter 1 of this Best Practice Guide. In case of doubt, the RMS or Reference Authority should be contacted.

4. SUBMISSION PHASE

The MAH submits simultaneously to the RMS and CMS an application containing the elements listed in Annex IV of the Regulation, presented as follows in accordance with the appropriate headings and numbering of the EU-CTD format:

- Cover letter (including variation procedure number).

- Application form, including the variation procedure number and details of the MA(s) concerned. Where a variation is the consequence of another variation, a description of the relation between these variations should be provided in the appropriate section of the application form.

- A copy of:
  - The relevant published Article 5 Recommendation, if applicable.
  - The recommendation for classification received from the CMDh, if applicable.

- Supporting documentation as appropriate.
  - Update/Addendum to expert reports as relevant.
  - For variations requested by a national competent authority, e.g. following assessment of Follow Up Measures (FUMs), Specific Obligations (SOs) and Periodic Safety Update Reports (PSURs), or class labelling, a copy of the request should be annexed to the cover letter.
  - For variations that affect the SmPC, labelling or package leaflet, only the draft English texts should be submitted. Mock-ups or specimens should be provided according to Chapter 7 of the NTA, or as discussed with the RMS on a case-by-case basis.

Additionally, the RMS submission should include the list of dispatch dates (all the dates of dispatch to the CMS) and declaration that the relevant national fees have been paid at time of submission.

RMS creates the CTS record to inform the CMSs about the new procedure.

5. AUTOMATIC VALIDATION

The automatic validation procedure is described in Chapter 2 of this Best Practice Guide.

6. START OF VARIATION PROCEDURE (Day 0)

Following the validation period the RMS completes the CTS record to inform the CMS on the start of the procedure. The RMS will also inform the MAH of the start date (Day 0).

7. EVALUATION

Generally the 60 days timetable will apply. In special cases the competent authority, in the role of the RMS in a planned variation procedure, should agree with the Marketing Authorisation Holder (MAH) on the timetable of the procedure and aim to synchronise the possible parallel or sequential variation procedures so that overlapping of procedures is avoided, where practical. The 60 and 90-day time frames are maximum time lines thus allowing flexibility for shorter procedures in particular situations. In such exceptional circumstances the MAH should contact the RMS as soon as possible. It is up to the RMS to propose an accelerated time table (e.g. 30-day procedure) to the CMS, which is then part of the automatic validation procedure of this variation. Nevertheless CMS may object to a shortened procedure, in which case the RMS should propose the acceptable timetable. For straightforward changes to the indication the 60-day time frame should be the rule, however the period can be extended to 90 days for variations concerning changes to or addition of therapeutic indication requiring more comprehensive assessment. The agreed timetable included in CTS.

The RMS should ensure that the Preliminary Variation Assessment Report (PVAR) is sent to the MAH and CMSs by the agreed date. The MAH should understand that the PVAR is for information and transparency purposes only at this stage of the procedure. In exceptional cases of a delay, all CMS and the MAH should be informed.

In case the variation concerns the introduction of new DDPS in one or more CMS the RMS may request support in preparation of the PVAR from this CMS.

In the PVAR the RMS should clearly indicate if it endorses the variation in its proposed form, or if it considers that the variation should be rejected or amended. If amendments are required, supplementary information can be requested from the MAH. If the application is considered to be grossly deficient it will be recommended for rejection without a request for supplementary information (RSI).

If the RMS considers the proposed changes to the SmPC, labelling or package leaflet to be unacceptable, they may propose an alternative way forward. When appropriate, the wording of the SmPC, labelling or package leaflet should be harmonised according to SmPCs of other similar products approved during other MR or DC procedures, or in accordance with a Commission Decision following an Article 30 procedure. SmPC changes should be focused on the points directly related to the variation application, or consequential upon it. The revision of other sections of the SmPC, labelling or package leaflet is not acceptable except for minor editorial corrections with the agreement of the RMS. The RMS will highlight such editorial changes in the PVAR.

Following receipt of the PVAR, the CMS should send their opinion about whether to accept or reject the variation to the RMS by the agreed date. The comments should be sent to the RMS via the MRVE mailbox. If a CMS sends no comments by the agreed date, the RMS will consider that the CMS endorses the PVAR of the RMS. CMSs may not raise comments on matters that are unrelated to the submitted variation. If the CMS endorses a proposal of the RMS for straight acceptance or rejection, the procedure can be finalised at the end of the first phase, i.e. without the need for a clock stop as per the agreed dates.

If the CMS does not accept the proposed variation, or the proposal of the RMS, the CMS should give the grounds for its opinion and clearly indicate what supplementary information is required from the MAH.

Additionally, the CMS may propose changes to the SmPC, labelling or package leaflet. The number of these proposals should be kept to a minimum, and the proposals should directly relate to the points subject to the variation. Other sections of the SmPC, labelling or package leaflet may be altered only in separate variation procedures. The CMS should avoid presenting extensive revision of the SmPC and/or other product literature, but concentrate on giving their opinion on the proposal presented by the RMS and MAH.

If the RMS or any of the CMS do not endorse the variation proposed by the MAH, the RMS will send a request for supplementary information (RSI) to the MAH and send the CMS a copy of the request. The RMS should give a clear deadline, as per the agreed dates, to the MAH for submitting the responses to the RSI. The MAH may liaise with the RMS as necessary during the clock-stop period in case of need for clarification. The grounds for extending the clock stop period and the new deadline set should always be communicated to the CMSs.

If the MAH cannot respond within a reasonable timeframe, it is recommended that the variation is withdrawn. The MAH may submit a new variation when data are available.

After receiving the supplementary information from the MAH, the RMS prepares and circulates the Final Variation Assessment Report (FVAR) and revised SmPC, labelling or package leaflet to all CMSs for comment, and to the MAH for information. The RMS should prepare the FVAR and the clock should be re-started within the agreed time frame.

In the case of disagreement between the RMS and CMS, a breakout session can be arranged (e.g. by Vitero). The CMDh Best Practice Guide on Break-Out Sessions is followed.

CMSs should send their comments on the FVAR to the RMS by the agreed date.

8. OUTCOME

Acceptance of variation - In cases where the variation is accepted, the RMS will inform the MAH and CMSs that the variation is considered acceptable together with the date of acceptance. [In cases where the variation results in changes to the SmPC/PL/labelling the MAH should provide the RMS with the highlighted and clean versions of the SmPC/PL/labelling text in electronic format. The RMS is responsible for checking the highlighted (changed) text. The RMS will circulate these documents together with a statement that it has endorsed the changes made.

If applicable, the MAH should send the national translations within seven days of the procedure ending.

These translations may be implemented within 30 calendar days after submission unless any comments of the respective competent authorities have been received.

Competent authorities should implement the decision nationally within two months from the end of the procedure.

Rejection: In cases where the variation is rejected by the RMS and CMS, the RMS will inform the MAH and CMSs that the variation is considered rejected along with a description of the reasoning for the outcome. The MAH and CMS are informed of the outcome by email. The RMS will also update the CTS record, which should state the reasons for rejection.

Disagreement - If one of the CMS can not approve the variation on the basis of a Potential Serious Risk to Public Health (PSRPH), the matter should be referred to CMDh, following the procedure described in the Standard Operating Procedure For Disagreement in procedures Referral to CMDh. The formal referral to CMDh should be made by the RMS, on the basis of a referral request forwarded by those objecting CMSs which raised a PSRPH. To avoid arbitration the MAH may withdraw the variation application from all CMSs and the RMS, not just those that are objecting.

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

For grouped or worksharing variations a different outcome may apply to the different variations included in the application, i.e. some changes may be accepted, whilst others may be rejected. In these cases please refer to Chapters 6 and 7 of this Best Practice Guide.

ANNEX I

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

Example 1

ACCEPTANCE OF VARIATION

The <<*competent authority*>> accepts the Type II variation detailed in your application. The following change has been notified:

<< *enter change applied for*>>

Example 2

REJECTION OF VARIATION

The <<*competent authority*>> rejects your Type II variation, because of the following:

<<*enter reason for non-acceptance*>>

ANNEX II

Flow-charts of the type II variation procedures:

Recommended reduced (30-day) procedure for type II variations

Day 0	Start of the procedure, RMS notifies the timetable to the CMS's by CTS and to the MAH by email
Day 15	RMS circulates the PVAR to the CMS's and to the MAH
Day 20	CMS's send the possible comments on the PVAR to the RMS
Day 21	RMS sends the request for supplementary information to the MAH and the CMS's, clock stop
Clock off period	Should not be longer than 10 + 10 days (10 days for the MAH to provide the responses and 10 days for the RMS to prepare the FVAR)
Day 22	RMS circulates the FVAR to the CMS's and to the MAH
Day 27	CMS's send the possible comments on the FVAR to the RMS
Day 30	End of the procedure, the RMS notifies the completion of the procedure and, when applicable, circulates both highlighted and clean versions of the endorsed, finalised SmPC/PL/labelling to the CMS's and the MAH

60-day procedure for type II variations

Day 0	Start of the procedure, RMS notifies the timetable to the CMS's by CTS and to the MAH by email
Day 40	RMS circulates the PVAR to the CMS's and to the MAH
Day 55	CMS's send the possible comments on the PVAR to the RMS
Day 59	RMS sends the request for supplementary information to the MAH and the CMS's, clock stop
Clock off period	Should not be longer than 60 + 60 days (60 days for the MAH to provide the responses and 60 days for the RMS to prepare the FVAR)
Day 60	RMS circulates the FVAR to the CMS's and to the MAH
Day 75	The possible break-out meeting
Day 85	CMS's send the possible comments on the FVAR to the RMS
Day 90	End of the procedure, the RMS notifies the completion of the procedure and, when applicable, circulates both highlighted and clean versions of the endorsed, finalised SmPC/PL/labelling to the CMS's and the MAH

90-day procedure for type II variations

Day 0	Start of the procedure, RMS notifies the timetable to the CMS's by CTS and to the MAH by email
Day 70	RMS circulates the PVAR to the CMS's and to the MAH
Day 85	CMS's send the possible comments on the PVAR to the RMS
Day 89	RMS 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 RMS to prepare the FVAR)
Day 90	Re-start of the procedure. RMS circulates the FVAR to the CMSs and to the MAH
Day 105	The possible break-out meeting
Day 115	CMS's send the possible comments on the FVAR to the RMS
Day 120	End of the procedure, the RMS notifies the completion of the procedure and, when applicable, circulates both highlighted and clean versions of the endorsed, finalised SmPC/PL/labelling to the CMS's and the MAH

CHAPTER 6

CMDh BEST PRACTICE GUIDE FOR THE PROCESSING OF GROUPED APPLICATIONS IN THE MUTUAL RECOGNITION PROCEDURE

1. INTRODUCTION

Article 7 of Commission Regulation (EC) No 1234/2008 of 24 November 2008 (Variation Regulation) points out that in case that several variations are notified or applied for, separate notifications or applications for each variation sought should be submitted.
However, there are 3 possible exemptions of this rule stated in the Regulation:

1) In case the same holder applies for several identical variations of type IA and/or Type IA_{IN} to the terms of one or several marketing authorisations to the same authority, these may be submitted as one single notification, as pointed out in Article 8 of the Variation Regulation, e. g.
   - One change to several MAs
   - Several identical changes to several MAs
   - Several changes to one MA

2) In case the same holder applies for several identical variations of type IA to the terms of one or several marketing authorisations to the same authority, these may be submitted as one single notification in the form of a so-called Annual Report within a maximum of 12 months after implementation of the first change applied for, as pointed out in Article 8 of the Variation Regulation.

3) Annex III of the Guideline refers to several cases where it is possible to group several variations of type IA, IA_{IN}, IB, II or extension applications to the terms of the same marketing authorisation at the same time into one single application. Furthermore, in case several single variations are not listed in Annex III of the variation regulation the RMS in consultation with the CMS may agree to group these single variations to one procedure.

Therefore, Article 7 in connection with Annex III of the Variation Regulation allows the combination of several changes into one single application.

One MAH could have more marketing authorisations with different RMSs for which the same type IA variation or the same set of type IA variations needs to be submitted. If the MAH wishes to submit these as grouped applications, i.e. as a group containing more than one MA, it is also possible to combine marketing authorisations of more than one RMS in one grouped application. However, there are special rules concerning this procedure mentioned below that have to be considered before submission of such an application. This procedure is restricted to purely administrative changes and other changes of type IA/IAIN that do not contain any product specific information. Furthermore, the flowchart in Annex II of this chapter has to be considered.

For the purpose of handling a grouped application, 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.

2. APPLICATION

The type of variation as well as the timetable of the grouped application is dependent on the "highest" type of the single changes. Submissions should therefore be made according to the following rules:

- A single notification of type IA according to Articles 8 of the Variation Regulation should be submitted in form of a so called Annual Report where all variations are minor variations of type IA. Type IA_{IN} notifications may also be added to the annual reporting if this is submitted immediately and not only 12 months after the first change applied for has been implemented.

- A single notification of type IB according to Articles 9 of the Variation Regulation should be submitted where at least one of the variations is a minor variation of type IB and all variations are minor variations.

- A single application of type II according to Articles 10 of the Variation Regulation should be submitted where at least one of the variations is a major variation of type II and none of the variations is an extension.

- A single application for an extension application according to Article 19 of the Variation Regulation should be submitted where at least one of the variations is an extension.

- A grouped procedure will be submitted as one single application with one variation procedure number and only one CTS record. This variation procedure number has to be introduced on the first page of the application form. The MRP variation numbers are not to be listed on the cover letter or the first page of application form in the field 'Variation procedure number(s). 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 (see also Chapter 1).

In case an applicant intends to submit a grouped application with variations of type IA or IAIN or a grouped variation of type IA/IAIN for a group of products with different RMS he has to contact the RMS chosen as "Lead-"RMS for this grouped application and to request his acceptance to act as this. If the chosen RMS accepts to act as "Lead-"RMS he informs the applicant and issues a variation procedure number according to the principles as laid down in Chapter 1 with his own initials in the country code. The Lead-RMS then sends an email to all member states concerned in the grouped application via the MRVE-mailbox to inform them about the intended submission including the proposed changes, the acceptance of the "Lead-"RMS and the variation procedure number. The heading of these emails should contain the wording "IA-supergroup". Member states may comment, if necessary, within one week on this announcement. If member states, which are RMS in one of these procedures, cannot agree they have to inform the "Lead-"RMS accordingly stating their reasons for their refusal. The "Lead-"RMS as well as the applicant have to consider these reasons and must not integrate these procedures in the grouped application. The applicant has to send separate applications per RMS in all cases where the RMS does not accept to participate as concerned member state in a "Lead-"RMS-procedure.

3. VARIATION NUMBERING

Information on the allocation of the variation procedure number is presented in Chapter 1 of this Best Practice Guide. For grouped type IA variations in which >1 MA is included, the variation procedure number has to be requested from the RMS or Reference Authority before submission. In case of doubt, the RMS or Reference Authority should be contacted. The MAH will insert the variation procedure number on the application form 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 (see also Chapter 1).

4. VALIDATION OF THE APPLICATION

The MAH will submit simultaneously to the RMS and CMS an application containing the elements listed in Annex IV of the Regulation, presented as follows in accordance with the appropriate headings and numbering of the EU-CTD format.

- Cover letter (including variation procedure number).

- Application form, including the variation procedure number and the MRP variation number and the details of the MA(s) concerned. Where a variation is the consequence of another variation, a description of the relation between these variations should be provided in the appropriate section of the application form.
  In case an extension application is part of the grouped application the application form for a new application has to be submitted with the additional variation application form introducing the changes applied for as annex.

- A copy of:

  - a checklist of the conditions specified for the proposed change(s), if applicable. This could be directly copied or printed from the Classification Guideline.
  - the relevant published Article 5 recommendation, if applicable.
  - a recommendation for classification received from the CMDh, if applicable.

- Supporting documentation as appropriate.

  - For variations requested by a national competent authority, e.g. following assessment of Follow Up Measures (FUMs), Specific Obligations (SOs) and Periodic Safety Update Reports (PSURs), or class labelling, a copy of the request should be annexed to the cover letter.

  - For variations that affect the SmPC, labelling or package leaflet, mock-ups or specimens should be provided according to Chapter 7 of the NtA, or as discussed with the RMS on a case-by-case basis. In case a type IA or type IB variation is the highest variation in the group, both the English texts and the national translations for SmPC, labelling or package leaflet should be submitted.

Additionally, the RMS submission would include the list of dispatch dates (all the dates of dispatch to the CMS) and declaration that the relevant national fees have been paid at time of submission.

In case of a grouped application for procedures with more than one RMS the applicant has to add the following information to his submitted documentation:

- List of concerned marketing authorisations.
- Explanation as to why all concerned marketing authorisations are considered to belong to the same holder[9].
- Description of the variation.
- Preferred "Lead-RMS" authority.
- In case the preferred "Lead-RMS" authority has not granted a marketing authorisation for all concerned marketing authorisations, the MAH should explain this choice
- Planned submission date.

[9] as per Commission Communication 98/C 229/03

The table on page 3 of the application form has to contain all the correct sequential MRP variation procedure numbers for each RMS procedure. If the product information is concerned the applicant has to assure that all national translations have been sent to the member states concerned and confirm this to the "Lead-"RMS. The "Lead-"RMS is responsible for the validation of the procedure. All procedures concerned will be entered into CTS under the respective procedure number. (The sequential numbering of the MRP variation number will be automatically issued by the CTS system. It is in the responsibility of the "Lead-"RMS to check if this number is consistent with the number in the table on page 3 of the application form.) Member states concerned may comment, if national translations of the product information have not been received or are not acceptable. The "Lead-"RMS has to refuse the procedures in those cases. The "Lead-"RMS is responsible for the evaluation and finalisation of the procedure.

5. HANDLING AND TIMELINES OF GROUPED APPLICATIONS

The highest variation type of the grouped application determines the rules and timelines of the grouped variations. The grouped application is handled in the same way as the respective application type for a single variation of the highest type. The principle of Type IA notification applies also when the Type IA variation is part of a grouped application. The Type IA change may be implemented before submission of the grouping. In case a Type IA change is dependent on the outcome of other changes in a grouped application this change may be submitted with an implementation date in the future and the change will be implemented as soon as the complete grouped application is approved.

According to Article 19 a grouped variation in which the highest type is an extension application will be handled according to the timeline of a new application procedure.

6. FINALISATION OF PROCEDURES

Grouped applications are finalised according to the same procedure as single variations of the same procedure type. In order to avoid an unnecessary reassessment of already evaluated and agreed changes, the outcome will concern the single changes applied for and not the grouped application as a whole.
It should also be possible for the MAH to withdraw single changes from the grouped application when it becomes obvious that these are regarded as non-approvable.

In case all single variations are regarded as approvable, the RMS will circulate an approval letter for the grouped application to the MAH. The CMS will be informed via CTS.
In case single variations are not approvable or withdrawn by the MAH, a combined letter will be circulated by the RMS stating the refused or withdrawn single changes including reasons leading to the refusal as well as listing all approved changes of the grouped application. This letter will be addressed to the MAH and introduced as data file into CTS for information of the CMS.
If all single changes are refused a refusal letter for the whole grouped application stating reasons for the refusal of every single change will be circulated by the RMS to the MAH. CMS will be informed via CTS. The refusal letter will not be introduced as data file into CTS.

The outcome of the grouped variation is to be introduced in CTS by the RMS.

- The procedure will be introduced as <u>approved</u> in case all single changes are regarded as approvable.

- The procedure will be introduced as partially <u>approvable</u> in case single changes are refused or withdrawn. In this case detailed information about approved and refused or withdrawn changes will be given in the letter to the MAH which will be saved in the CTS data file.

- In case the whole group has to be refused / withdrawn the grouped procedure is introduced as refused / withdrawn in the CTS system.

The procedure for the submission and approval of a revised SmPC, labelling or package leaflet, in cases where these documents were affected by the variation(s), is the same as the one outlined in Chapters 3, 4 and 5 of this Best Practice Guide. This also applies to the procedure for implementing the decision(s) nationally.

In case of grouped applications of Type IA for products with more than one RMS the outcome, "valid, invalid or partially approved" will be introduced in CTS. Reasons for (partial) invalidation have to be mentioned in the outcome letter and this has to be uploaded in CTS. The applicant and all other member states being the RMS in one of the procedures concerned will be informed about the outcome via email (member states to MRVE-Mailbox).

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.

7. REFERRALS

If in case of one or more type II variations or extensions within a group there is a CMS that can not approve the application on the basis of a potential serious risk to public health, the RMS will refer the procedure to the CMDh, unless the application is withdrawn by the MAH before the finalisation of the procedure.

The Member State in disagreement shall give a detailed statement of the reasons for its position to all Member States concerned and to the MAH. The RMS collects the reasoning and refers the whole matter to CMDh.

Generally, in case single type II changes are referred to the CMDh the whole group of changes will not be approved until the referral is finalised. However, the CMDh discussion will only deal with the single changes in question, not with the whole group. In individual cases, where single changes are very urgent and completely independent from the referred change, the MAH may request to implement these changes in advance before approval of the whole group with his RMS. The RMS has to take a decision on this request.

Procedures may only be referred to the CMDh by the RMS and not by the marketing authorisation holder.

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 GROUPED VARIATION

The <<*competent authority*>> accepts all the changes detailed in your application. The following changes have been notified:

<< *enter changes applied for*>>

The variations are considered acceptable on the basis that the application has been submitted simultaneously to all Concerned Member States and the relevant fees have been paid as required by national competent authorities. Failure to comply with this provision may subsequently deem the variations invalid.

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

Example 2

ACCEPTANCE/REJECTION OF THE GROUPED VARIATION

The <<*competent authority*>> accepts some of the changes detailed in your application including the following:

<< *enter changes applied for*>>

The above variations are considered acceptable on the basis that the application has been submitted simultaneously to all Concerned Member States and the relevant fees have been paid as required by national competent authorities. Failure to comply with this provision may subsequently deem the variations invalid.

However, the <<*competent authority*>> rejects the following changes for the reasons given below:

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

Example 3

REJECTION OF THE GROUPED VARIATION

The <<*competent authority*>> rejects all the changes detailed in your application for the following reasons:

<<*enter reason for non-acceptance*>>

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

ANNEX II

Flowchart for submission of Type IA-"Supergroups" with more than one RMS

Pre-Submission phase - Day 14	The applicant contacts the RMS chosen as "Lead"-RMS and informs him about the planned grouped application including the proposed changes and the concerned MRP procedure numbers.
Pre-Submission phase – Day 7	The "Lead"-RMS issues the variation procedure number and sends an email to the applicant and all member states concerned via the MRVE-mailbox with the heading "IA-supergroup". Member states, which are RMS in one of the procedures concerned, may comment within one week if they refuse to participate in the procedure stating their reasons. The applicant has to consider that before submitting the documentation.
Submission phase	To the RMS and CMS the MAH submits the application accompanied by supporting documentation as appropriate. The MAH submits list of dispatch dates to the RMS.
Day 0	The RMS starts the procedure and completes the CTS record.
Until Day 30	The RMS checks if the notification can be accepted. The CMS only checks if the notification has been received, if the fee has been paid as appropriate and his own national translations are correct.
Day 30	The RMS will inform the MAH on behalf of the CMSs of the outcome of the variation notification. CMS are informed accordingly via the updated CTS record. The RMS checks the highlighted (changed) text, and circulates a statement that it has endorsed the changes made, to the MAH and CMSs The applicant and those member states being the RMS in one of the procedures concerned will be informed about the outcome via email (member states to the MRVE-mailbox).
Within 2 or 6 months after acceptance	Competent authorities should implement the decision nationally within: • Two months in the case of a variation(s) that does not require immediate notification or • Six months if the variation(s) does require immediate notification.

CHAPTER 7

CMDh BEST PRACTICE GUIDE ON WORKSHARING

1. INTRODUCTION

Article 20 of Commission Regulation (EC) No 1234/2008 of 24 November 2008 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[10] where none of the marketing authorisations is a centralised marketing authorisation. 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 centralised marketing authorisation is also provided. In these cases, the European Medicines Agency shall be the 'reference authority'.

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.

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 fulfill the definition of the same MAH as given in the Commission Communication 98/C 229/03.

[10] As per 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 shall be the reference authority. Any recommendation submitted by the holder of the marketing authorisation shall be taken into account.

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 Coordination Group at least 3 months in advance of 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[11].
- Description of the variation.
- Preferred reference authority.
- 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.

Worksharing of MR/DC procedures with more than one RMS
In case the intended worksharing procedure includes MR/DC procedures with more than one RMS, the pre-submission information should be submitted to the CMD via H-CMDhSecretariat@ema.europa.eu. The CMDh secretariat forwards the pre-submission information to the preferred reference authority via the CMDh member.

Pre-submission information submitted two weeks in advance of the next CMDh meeting, will be discussed at that meeting[12]. A list of CMDh meetings is published on http://www.hma.eu/115.html. Pre-submission information submitted less than two weeks in advance of the CMDh meeting, will be discussed in the 2nd CMDh meeting following submission.

At the latest two weeks after the CMDh meeting, CMDh will inform the MAH whether the worksharing request has been accepted, which national competent authority will act as reference authority, and the variation procedure number to be used in the worksharing application. 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.

Worksharing of MR/DC procedures with the same RMS
In case the intended worksharing procedure only includes MR/DC procedures with the same RMS and the MAH proposes the RMS to be the preferred reference authority, the pre-submission information should be directly submitted to the RMS. The RMS takes the decision whether or not the intended submission can be agreed as a worksharing procedure.
- If not agreed upon, the RMS requests that the MAH submits its pre-submission information together with the reasons for non-acceptance by the RMS to CMDh as described above under the paragraph

[11] as per Commission Communication 98/C 229/03
[12] It is recommended to avoid discussions in August, due to the holiday period.

"Worksharing of MR/DC procedures with more than one RMS". The procedure described in that paragraph will then be followed. The RMS of the procedures involved in the worksharing procedure will remain the proposed Reference Authority. The MAH should then wait to submit the worksharing application until they have received confirmation of the CMDh whether the worksharing request has been accepted.
- If the worksharing request is agreed upon, the RMS communicates this to the MAH, provides the procedure number to the MAH and indicates that they may then submit the variation to RMS and all CMSs.
The RMS will forward the pre-submission information together with the procedure number on the agreed worksharing request to the CMDh Secretariat for inclusion in the agenda for information of the next CMDh meeting and will inform the CMDh Secretariat of their agreement with the proposal.

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, if the procedure number was not communicated to the MAH by the CMDh secretariat with the letter of acceptance of the worksharing application. 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 the MRP variation numbers in the table 'Products concerned by this application' in the application form.
- 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 Chapter 7 of the NtA, or as discussed with the RMS 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.

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.

The reference authority will validate the application in line with the validation procedure followed for Type II variations (see Chapter 5 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-day13 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.

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 the draft 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 draft 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 together with a timetable stating the date by which the MAH should submit the requested data. The clock will be stopped until receipt of the supplementary information.
As a general rule, a clock-stop of 60 days (10 days in 30-days procedures and 90 days in 90-days procedures) may apply. For longer clock-stops 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 finalise the draft assessment report within 60 days (10 days in 30-days procedures) and restart the procedure with the circulation of its final draft assessment report to the MAH and the concerned member States. Concerned Member States should send their comments on the final draft assessment report and the application within the timeline as agreed in the timetable.
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.

Worksharing procedures will be included in CTS, to maintain the life-cycle management of each product.

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

13 All time lines in this document are based on calendar days, i.e. days should be read as calendar days.

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 States concerned that can not approve the Reference Authority's final opinion on the basis of a potential serious risk to public health, the Reference Authority refers to 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.

The procedures described in the CMDh Standard Operating Procedure Disagreement in Procedure Referral to CMDh are applicable.

8. END OF THE PROCEDURE

In case of a favourable decision in the worksharing application 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, unless they had 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).

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 reference authority sends its final opinion to all Member States concerned.

- 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 30 days, unless an art. 31 referral is initiated within 30 days following receipt of the opinion. For practical reasons it is agreed that if a Member State concerned 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.

- In worksharing procedures in which the competent authority of one of the Member States acted as reference authority, the Member States concerned shall approve the final opinion, inform the reference authority and amend accordingly the marketing authorisations concerned within 30 days. For practical reasons it is agreed that if a Member State concerned can not approve the final opinion of the reference authority, that Member State should sent a request to the reference authority to initiate a CMD referral procedure 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 send a request to the

reference authority to initiate a CMD referral within 10 days after distribution of the final opinion, the final opinion is considered approved by the Member State.

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 positive opinion 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.

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

All other changes can be implemented 10 days following receipt of the finalisation letter of the Reference Authority, unless an art 31 referral or a CMD referral is initiated within 10 days after distribution of the final opinion.

CHAPTER 8

BEST PRACTICE GUIDE
CMDh RECOMMENDATIONS ON UNFORESEEN VARIATIONS

1. INTRODUCTION

Article 3, paragraph 1 of Commission Regulation (EC) No 1234/2008 (variation regulation) refers to Annex II where a classification of minor variations, type IA and major variations, type II, is laid down. The classification of extensions of a marketing authorisation is laid down in a list in Annex I. Article 4 of the variation regulation confers on the Commission the obligation to establish guidelines on the details of the various categories of variations (classification guideline). These guidelines shall be regularly updated, taking into account inter alia the recommendations of the CMDh and CMDv or, in the case of centralised marketing authorisations, the EMA.

Article 5 of the variation regulation provides the basis for a marketing authorisation holder (MAH) to request the Reference Member State (RMS), EMA (in case of centralised marketing authorisations) or a national competent authority of a Member State (NCA) (in case of purely national marketing authorisations) to deliver a recommendation on classification of an unforeseen variation before submission of the variation. This recommendation shall be consistent with the Commission guidelines and be delivered to the MAH, EMA, CMDh and CMDv within 45 days following the receipt of the request.

Article 5 of the variation regulation also provides the basis for a NCA to request the CMDh or CMDv to deliver a recommendation on classification of an unforeseen variation before examination of the variation. This recommendation shall be consistent with the Commission guidelines and be delivered to the MAH, EMA and all NCAs within 45 days following the receipt of the request.

Cooperation between the two coordination groups and the EMA is envisaged by the legislation. The recommendations will be published once adopted.

It should be noted that the recommendation of the CMDh is not a (pre-) assessment of the future variation application but a recommendation of the classification of a variation. The recommendation relate to the situation described in the request.

2. SCOPE

This guidance covers medicinal products for human use that have been authorised through the mutual recognition, decentralised or purely national procedures. The request shall apply only to variations whose classification is not provided for in the a.m. annexes (unforeseen variations). The CMDh cannot "reclassify" a variation already listed in the annexes/guidelines.

3. SUBMISSION AND VALIDATION OF REQUEST FROM MAH

A request for a recommendation of a classification from a MAH shall be submitted to the relevant authority prior to submission of the variation. To facilitate the retrieval of the requests MAHs are requested to use the following standardised wording in the subject field of the email:

<MRP> - <Product name>-Art. 5 variation classification request.

The application form for Article 5 requests published on the CMDh website (http://www.hma.eu/265.html) should be used. It is important that the request includes a detailed description of the product and a detailed description of the proposed variation of the terms of the authorisation, as the time available to request additional information is very limited. The request should include information detailing whether a similar variation has been previously submitted to a NCA and if so how it was classified and in accordance with which guidance. The request should in addition include a justification of why the variation is considered to be unclassified according to the variation regulation.

It is the responsibility of the relevant authority to validate the request with respect to the classification guideline.

Invalid request: If the relevant authority considers the variation to fall under the scope of a foreseen variation, if a recommendation has already been issued or if the variation should clearly be classified as type IB by default according to the classification guideline, the authority will deem the request invalid and inform the MAH thereof.

Valid request: If the relevant authority considers the variation to be unclassified, it is recommended that the request is forwarded to the coordination group for discussion in order to avoid any discrepancies in recommendations. This should be done at the latest within 25 days following receipt of the request in order to have no less than 45 days left for the CMDh phase. The timetables for Article 5 recommendations as published by the CMDh (http://www.hma.eu/293.html) have to be considered and the requests have to be forwarded by the relevant authority in advance of the next start date.

4. SUBMISSION OF REQUEST TO CMDh FROM NCA

A request for a recommendation of a classification from a NCA shall be submitted to the CMDh secretariat electronically (H-CMDhSecretariat@ema.europa.eu) prior to examination of a variation or following a valid request from a MAH. The NCA request should comply with the submission details described under section 3 above.

The CMDh is obliged to deliver a recommendation within 45 days of the receipt of the request. In order for the CMDh to have the opportunity to discuss the request at one of their monthly meetings specific submission dates should be adhered to.

5. HANDLING OF REQUEST AND COOPERATION WITH CMDv AND EMA

The NCA that received the request from a MAH or that triggered the Article 5 procedure will be the Rapporteur.

The CMDh secretariat shall without delay send the request to all CMDh members, the secretariat of CMDv and the contact point at EMA, for information. The mailbox devoted to the procedure should be used.

The procedure will be started according to the timetables published on the CMDh website (http://www.hma.eu/293.html).

Where the CMDh secretariat receives notification of a request submitted to CMDv or EMA, they will circulate details of that request to CMDh members. The CMDh Rapporteur will be the same MS that has received the request by the MAH. The Rapporteur should circulate a short statement to the designated mailbox whether the request is applicable to variations handled by the CMDh or not. In case the variation is applicable to CMDh, CMDh members will provide comments to the Rapporteur, who in turn would coordinate and forward a CMDh response to the CMDv secretariat or EMA contact point as appropriate. The CMDh response must be sent to the CMDv secretariat no later than Monday

the week before the CMDv meeting where the Article 5 recommendation will be discussed. Comments to a request submitted to EMA must be sent no later than day 28 after receipt of the Article 5 request.

6. THE RAPPORTEUR

The Rapporteur shall propose a recommendation for a classification with an appropriate justification. The proposed recommendation will reflect the consideration of the facts presented to it in the request from the MAH or the NCA, but must be consistent with the Commission guidelines on categories of variations.

The proposal for a recommendation for a classification should be sent to the designated mailbox at least 2 weeks before the Monday of the monthly CMDh meeting.

7. MEMBER STATES AND CHMP WORKING PARTIES COMMENTS

All CMDh members, CMDv members and the EMA may send comments on the Rapporteur's proposal for a recommendation for a classification. In addition one representative from a relevant CHMP working party may also comment through the designated mailbox on behalf of that working party. The comments should be sent at least 1 (one) week before the Monday of the monthly CMDh meeting. If a CMDh or CMDv member, EMA or the relevant CHMP working party have a divergent view from the Rapporteur this should be properly justified.

If no divergent opinions are expressed during the above written procedure there may be no need for discussion at the CMDh meeting.

8. DISCUSSION AT CMDh MEETING

The EMA, members of CMDv and European Commission shall be invited to the discussion at CMDh. National experts may attend in the same manner as for referral procedures. No participation from the MAH is anticipated.

In case of divergent opinions among members of the CMDh the voting procedure in the Rules of Procedure shall apply (http://www.hma.eu/205.html).

In cases where there remains a divergent opinion between CMDv/CMDh/EMA, the recommendation, including the arguments, shall be sent to the European Commission for information.

It should be noted that CMDh is not empowered to issue a decision but to deliver a recommendation according to Article 5 of the variation regulation. However it is anticipated that the MAH will accept and follow the recommendation of the CMDh.

After the CMDh discussion, the Rapporteur updates the recommendation to reflect the outcome of the discussion and sends the final agreed CMDh recommendation including the information for publication to the designated mailbox at day 44/45.

9. THE RECOMMENDATION

In case the Article 5 request has been submitted to a NCA by a MAH, the NCA will communicate the outcome of the CMDh procedure to the MAH by day 45.

The recommendation should include the conditions applicable for the recommended classification of the variation but not the required documentation.

There is no possibility to appeal a recommendation issued by the CMDh.

10. PUBLICATION OF RECOMMENDATIONS

Recommendations from CMDh shall be published on the CMDh website together with links to corresponding information on the CMDv and EMA websites. It should also be mentioned in the monthly CMDh press release, to ensure ease of accessibility. Information of a commercial confidential nature has to be deleted.

11. ANNEX II – CLASSIFICATION OF VARIATIONS

It is the responsibility of the Commission to initiate regular updates of the guideline referred to in Article 4 point (a) and Annex II of the variation regulation taking into account the recommendations adopted by the CMDh, CMDv and EMA.

ANNEX

Flow chart for Recommendations on unforeseen variations

Day -25	MAH sends a request to NCA electronically.
Between day -25 and day 0	NCA (= the Rapporteur) performs validation of request and, if valid, forwards it to the CMDh. If not valid, the request will be refused and the applicant informed accordingly. The Rapporteur circulates the valid request to the CMDh secretariat (H-CMDhSecretariat@ema.europa.eu)
Day 0	CMDh secretariat circulates the request together with the appropriate timetable to: • the Rapporteur • CMDh members via the designated mailbox • CMDv • EMA contact point
Day 25	The Rapporteur makes a proposal for the classification of the variation. The Rapporteur circulates this proposal to the designated mailbox.
Day 32	The Rapporteur receives the comments from: • CMDh members • CMDv (if applicable) • EMA contact point
Day 38/39	Discussion at the CMDh plenary meeting. Final position on the recommendation.
Day 44/45	The Rapporteur circulates the updated final recommendation via the designated mailbox. In cases where there remains a divergent opinion between CMDv / CMDh / EMA the CMDh secretariat sends the recommendation including the arguments to the European Commission for information.
Day 45	The NCA (Rapporteur) communicates the outcome to the MAH.
	The recommendation is published on the CMDh website.