

**EMA/CMDh EXPLANATORY NOTES
ON VARIATION APPLICATION FORM
(Human medicinal products only)**

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INTRODUCTION AND GENERAL COMMENTS

This document is intended to provide more clarification on how the new Variation Application Form should be completed. It will be regularly updated as more experience is gained once Commission Regulation (EC) No 1234/2008 has come in to force.

The following provisions from Chapter 1 of the CMDh Best Practice Guides For The Submission And Processing Of Variations In The Mutual Recognition Procedure need to be noted:

‘A grouped application or worksharing application is a single procedure for the variation. It is not bulk or multiple single procedures and a single application form needs to be used for all products involved.

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-sss will be considered to belong to the same marketing authorisation.’

For products authorised via the Centralised Procedure, this corresponds to the usual granting of a Marketing Authorisation, covering all strengths and pharmaceutical forms of the product concerned, which was already applicable prior to the new Variations Regulation (i.e. EU/0/00/000/001-nnn).

Therefore when a single variation is being submitted affecting more than one pharmaceutical form or strength within the above mentioned definition, a single application form should be completed (e.g. for AT/H/1234/001-002/IB/034 only 1 application form is needed instead of the 2 forms that were to be submitted under the previous Variation Regulation).

When a variation is submitted as part of a group of variations which include an extension application, the variation application form needs to be completed for the already authorised product presentations which are affected. The MAA form will need to be completed for the extension application. Note that the procedure will still be handled as one submission and that the variation application form is considered to be an annex to the application form for the extension application.

PAGE 1

Variation number

For Centrally authorised products the European Medicines Agency will assign the variation number. However, in case the MAH knows the next procedural number for the variation application, the number should ideally be included in the application form upon submission. For guidance on the structure of variation procedure numbers, please refer to the Agency's Post-Authorisation Procedural Advice.

For products in MRP the variation procedure number should be assigned by the authorisation holder if only one MA is affected. In cases of worksharing and grouping affecting more than one MA the variation procedure number should be obtained from the Reference Authority or Reference Member State respectively.

In cases of worksharing or grouped applications MRP variation numbers are to be assigned (previously indicated to be virtual variation numbers, see below under PAGE 3): these are however not to be used in the communication by the MAH and involved Member States: only the variation procedure number on the first page should be used as reference in the cover letter, Email headers etc..

For a single variation concerning several strengths within one MA the usual rules apply but under the new Regulation one application form can be used containing more than one MRP variation number. E.g.:

AT/H/0111/001/IB/033

AT/H/0111/003/IB/033

AT/H/0111/004/IB/033

Or alternatively: AT/H/0111/001+003-004/IB/033

Note that for the EU electronic application form the above mentioned alternative option of indication of a range is not appropriate and separate numbers need to be listed.

See Chapter 1 of the CMDh Best Practice Guides for the submission and processing of variations in the Mutual Recognition Procedure for more details. Especially ANNEX II Decision tree for allocating procedure numbers for grouped and worksharing procedures may be of interest.

Concerned Member States

Please tick all boxes for the countries which are involved in the procedures. Further specification on which Member States are involved per particular product should be provided in the table on page 3.

Type of application

On the first page of the application form it should be indicated which type of variations are included in the submission, whether a single or grouped variation is submitted and whether the worksharing procedure is followed. Note that all relevant boxes need to be ticked.

However with regard to **type IB variations** the following is applicable:

For all type IB variations the box "Type IB foreseen" should be ticked, **unless** this concerns a type IB variation where a "z"-category is ticked. These type IB variations should be classified as type IB **unforeseen** variation and the box "type IB unforeseen" should be ticked.

Type IB variations classified as “z”-category following Article.5 recommendations should be submitted as type IB **foreseen** variations.

If for instance a worksharing procedure is followed for a grouped submission containing two Type II, one Type IB foreseen and one Type IB where a “z”-category is ticked (and no Article 5 recommendation is given) variations the following boxes should be ticked:

Type of Application (tick all applicable options)

- | | | | |
|-------------------------------------|---------------------------------|-------------------------------------|---|
| <input type="checkbox"/> | Type IA _{IN} | <input type="checkbox"/> | Single variation |
| <input type="checkbox"/> | Type IA | <input checked="" type="checkbox"/> | Grouping of variations |
| <input checked="" type="checkbox"/> | Type IB unforeseen ² | <input type="checkbox"/> | Including a line extension ⁴ |
| <input checked="" type="checkbox"/> | Type IB foreseen ² | <input checked="" type="checkbox"/> | Worksharing |
| <input checked="" type="checkbox"/> | Type II | | |
| <input type="checkbox"/> | Type II Art. 29 ³ | | |

Or in case a single Type II variation is submitted in a grouped submission with an extension application:

Type of Application (tick all applicable options)

- | | | | |
|-------------------------------------|---------------------------------|-------------------------------------|---|
| <input type="checkbox"/> | Type IA _{IN} | <input type="checkbox"/> | Single variation |
| <input type="checkbox"/> | Type IA | <input checked="" type="checkbox"/> | Grouping of variations |
| <input type="checkbox"/> | Type IB unforeseen ² | <input checked="" type="checkbox"/> | Including a line extension ⁴ |
| <input type="checkbox"/> | Type IB foreseen ² | <input type="checkbox"/> | Worksharing |
| <input checked="" type="checkbox"/> | Type II | | |
| <input type="checkbox"/> | Type II Art. 29 ³ | | |

In the variation application form it is stated that:

A variation is considered ‘unforeseen’ when the proposed variation is not considered a minor variation of Type IB following the Commission classification Guideline, or has not been classified as a Type IB variation in an Article 5 recommendation.

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

Foreseen Type IB variations are therefore those variations which:

1. are listed as examples of Type IB in the Classification Guideline
2. are recommended to be Type IB following an Article 5 procedure
3. are listed as Type IA but do not meet all of the conditions set-out in the Guideline and they are not listed as Type II variations in the Classification Guideline.

Change(s) concern(s):

The following definitions apply:

Change(s) concern(s) (for Type IB and Type II variations only, tick all changes applicable):

- Indication**
- Paediatric Indication**
- Safety**
- Following Urgent Safety Restriction**
- Quality**
- Annual variation for human influenza vaccines**
- Non-food producing target species**
- Other**

The following guidance is on the interpretation of the above terms is provided for variations for medicinal products for human use. There is no specific guidance for medicinal products for veterinary use, however these boxes need to be ticked also in the variation application form for veterinary products.

Indication:

This category should be selected for an application in which a change is a new indication or an amendment to the indication, excluding a paediatric indication.

Paediatric indication:

This category should be selected for an application in which a change is a new paediatric indication or for an amendment to the paediatric indication.

Note: if an extension/change in indication covers both the adult and (part of) the paediatric population both boxes need to be ticked.

Safety:

This category should be selected for an application in which a change relates to a change of the safety information (e.g. section 4.3 to 4.9 of the SmPC). Whether a 30 or 60 day timetable will be followed, to be decided by RMS or the Agency.

Safety following Urgent Safety Restriction:

This category should be selected for an application to adapt the Product information following an Urgent Safety Restriction.

Quality:

This category should be selected for an application in which a change relates to a change in module 3.

Annual variation for human influenza vaccines:

This category should be selected for the annual update for human influenza vaccines. See the guideline on Fast track Procedure for Human Influenza vaccines.

Other:

This category should be selected for an application in which a change does not fall into one of the above categories.

PAGE 2

Name and address of the Applicant/MA holder

Name and address of contact person

For worksharing or grouped Type IA variations affecting more than one MA, in case of individual MAHs belonging to the 'same MAH' (as defined in the Commission Procedural Guideline), a single MA holder* and contact point need to be designated.

* Note that in Chapter 7 of the CMDh Best Practice Guides For The Submission And Processing Of Variations In The Mutual Recognition Procedure it is stated that*The above principle also applies for MRP/DCP products with different companies as MAH in RMS and CMS, since these MAHs do fulfil the definition of the same MAH as given in the Commission Communication 98/C 229/03.*

PAGE 3

PRODUCTS CONCERNED BY THIS APPLICATION

In cases of worksharing or grouped applications product specific MRP variation numbers are to be assigned (previously indicated to be virtual variation numbers): these are however not to be used in the communication: only the variation number on the first page should be used as reference. See the Best Practice Guide on Variations, Chapter 1 section 2.

For products in MRP the following examples are provided.

Example 1) Worksharing

- NL/H/0111/001; CMS: AT, DE, FR, UK (MA-number in The Netherlands: RVG 12345)
- NL/H/0222/001; CMS : AT, DE, FR (MA-number in The Netherlands: RVG 23456)
- DE/H/0333/001; not authorised in NL; CMS: NO
- The Worksharing consist of a Grouped submission (sequential variation numbers respectively: 33 for NL/H/0111, 44 for NL/H/0222 and 55 for DE/H/0333).

For the worksharing procedure for these three dossiers the completed table would be:

(Invented)Name(s):	Active substance(s)	Pharmaceutical form	Strength	MA holder name(s):	MA number(s): ⁸	MRP Variation Number ⁸
NL: WonderPill A 20 mg AT: <to be completed> DE: <to be completed> FR: <to be completed> UK: <to be completed>	<INN>	Tablet	20 mg	PharmaCompany AT: <to be completed> DE: <to be completed> FR: <to be completed> UK: <to be completed>	NL: RVG 12345 AT: <to be completed> DE: <to be completed> FR: <to be completed> UK: <to be completed>	NL/H/0111/001/WS/033
NL: WonderPill B 20 mg AT: <to be completed> DE: <to be completed> FR: <to be completed>	<INN>	Tablet	20 mg	PharmaCompany AT: <to be completed> DE: <to be completed> FR: <to be completed>	NL: RVG 23456 AT: <to be completed> DE: <to be completed> FR: <to be completed>	NL/H/0222/001/WS/044
DE: <to be completed> NO: <to be completed>	<INN>	Tablet	20 mg	PharmaCompany NO: <to be completed>	DE: <to be completed> NO: <to be completed>	DE/H/0333/001/WS/0055

⁸ Indicate the MA numbers affected (a range may be appropriate). For the MRP variation number, which is a product specific number, see the Best Practice Guide on Variations, Chapter 1 section 2, example: NL/H/0123/001-004/IB/033/G.

Example 2) Grouped variation within one MA

- NL/H/0111/001-003; CMS: AT, DE, FR, UK (MA-numbers in The Netherlands: RVG 12345, RVG 12346, RVG 12347)
- Grouped submission includes a Type IB variation (sequential variation number: 33)

For the grouped variation for this MA the completed table could be:

(Invented)Name(s):	Active substance(s)	Pharmaceutical form	Strength	MA holder name(s):	MA number(s): ⁸	MRP Variation Number ⁹
NL: WonderPill A 10 mg AT: <to be completed> DE: <to be completed> FR: <to be completed> UK: <to be completed>	<INN>	Tablet	10 mg	PharmaCompany AT: <to be completed> DE: <to be completed> FR: <to be completed> UK: <to be completed>	NL: RVG 12345 AT: <to be completed> DE: <to be completed> FR: <to be completed> UK: <to be completed>	NL/H/0111/001/IB/033/G
NL: WonderPill A 20 mg DE: <to be completed> FR: <to be completed>	<INN>	Tablet	20 mg	PharmaCompany DE: <to be completed> FR: <to be completed>	NL: RVG 12346 DE: <to be completed> FR: <to be completed>	NL/H/0111/002/IB/033/G
NL: WonderPill A 30 mg AT: <to be completed> DE: <to be completed>	<INN>	Tablet	30 mg	PharmaCompany AT: <to be completed> DE: <to be completed>	NL: RVG 12347 AT: <to be completed> DE: <to be completed>	NL/H/0111/003/IB/033/G

Or, alternatively (note however that for the electronic application form the below mentioned alternative option of indication of a range is not appropriate separate MA and MRP Variation numbers need to be listed):

(Invented)Name(s):	Active substance(s)	Pharmaceutical form	Strength	MA holder name(s):	MA number(s): ⁸	MRP Variation Number ⁸
NL: WonderPill A 10/20/30 mg AT: <to be completed> DE: <to be completed> FR: <to be completed> UK: <to be completed>	<INN>	Tablet	10/20/30 mg 10/30 mg 10/20/30 mg 10/20 mg 10 mg	PharmaCompany AT: <to be completed> DE: <to be completed> FR: <to be completed> UK: <to be completed>	NL: RVG 1234/6/7 AT: <to be completed> DE: <to be completed> FR: <to be completed> UK: <to be completed>	NL/H/0111/001-003/IB/033/G NL/H/0111/001+003/IB/033/G NL/H/0111/001-003/IB/033/G NL/H/0111/001-002/IB/033/G NL/H/0111/001/IB/033/G

⁹ Indicate the MA numbers affected (a range may be appropriate). For the MRP variation number, which is a product specific number, see the Best Practice Guide on Variations, Chapter 1 section 2, example: NL/H/0123/001-004/IB/033/G

For submissions to the Agency, the Annex A of the centrally authorised product(s) concerned should be provided as an Annex to the application form. For worksharing procedures submitted to the Agency, which include nationally authorised products, relevant product and Member State details (including the product specific MRP variation numbers) should be provided as an Annex B to the application form.

- EXAMPLE of a completed ANNEX BDE/H/0155/001; CMS: CY, FR
- DE/H/0165/001; CMS : AT, BE, FR, PT
- The Worksharing consist of a Grouped submission (sequential variation numbers respectively: 38 for DE/H/0155 and 34 for DE/H/0165).

<u>Member State</u> <u>EU/EEA</u> ¹⁰	<u>MRP variation number</u>	<u>Marketing Authorisation</u> <u>Holder</u> ¹¹	<u>(Invented) name</u> ¹²	<u>Active</u> <u>substance(s)</u>	<u>Strength(s)</u> ¹³	<u>Pharmaceutical Form</u> ¹⁴
Austria	DE/H/0165/001/WS/034	<to be completed>	<to be completed>	<INN>	20 mg	Film-coated tablets
Belgium	DE/H/0165/001/WS/034	<to be completed>	<to be completed>	<INN>	20 mg	Film-coated tablets
Cyprus	DE/H/0155/001/WS/038	<to be completed>	<to be completed>	<INN>	20 mg	Film-coated tablets
Germany	DE/H/0155/001/WS/038	PharmaCompany	WonderPill A	<INN>	20 mg	Film-coated tablets
Germany	DE/H/0165/001/WS/034	PharmaCompany	WonderPill B	<INN>	20 mg	Film-coated tablets
France	DE/H/0165/001/WS/034	<to be completed>	<to be completed>	<INN>	20 mg	Film-coated tablets
France	DE/H/0155/001/WS/038	<to be completed>	<to be completed>	<INN>	20 mg	Film-coated tablets
Portugal	DE/H/0165/001/WS/034	<to be completed>	<to be completed>	<INN>	20 mg	Film-coated tablets

¹⁰ List all the EEA Countries where the medicinal product(s) included in the worksharing are authorised, in alphabetical order (i.e. all medicinal products authorised in Austria, all medicinal products authorised in Belgium, etc.)

¹¹ Name and address of the Marketing Authorisation Holder in each EEA Countries where the medicinal product is authorised

¹² As registered in the respective official language of the EEA Country (no strength or pharmaceutical form should be mentioned unless it is an integral part of the authorised (invented) name)

¹³ It is possible to combine in the same row several strengths for the medicinal product in each Country. A separate row should however be used for each pharmaceutical form.

¹⁴ Information in English - use current standard terms from the Ph. Eur.

PAGE 5

TYPE(S) of CHANGE(S)

In case of several variations under the same classification the type of change, number and title of each of these variations should be mentioned. E.g. a grouped type II variation application of 3 type II variations C.I.4, this category should be repeated 3 times and the changes of each type II variation should be explained under the precise scope and background for change.

For Type IA variations and those Type IB changes listed in the Classification Guideline a copy of the relevant section from the Classification Guideline needs to be provided as an annex to the variation application form and the relevant boxes for conditions and documentations need to be ticked. For Type IA variations, all documents in the guideline should be provided (unless the guideline indicates that their absence may be appropriate or can be justified). For Type IB variations, to ease validation applicants are advised to provide all documents suggested in the classification guideline, including the documentation required for Type IA variations, but which are submitted as a Type IB variation since not all of the Type IA conditions are met.

For Type IA variations following an Article 5 recommendation a copy of the conditions* needs to be provided and the relevant boxes for conditions need to be ticked.

Only the main header of the change from the Classification Guideline with the specific variation applied for needs to be selected. So from the list of changes presented as:

	B.I. a.2 Changes in the manufacturing process of the active substance	Procedure type		
<input type="checkbox"/>	a) Minor change in the manufacturing process of the active substance, except changes referred to in c), d) and e) below	<input type="checkbox"/> IA	<input type="checkbox"/> IB ⁹	Implement. Date:
<input type="checkbox"/>	b) Substantial change to the manufacturing process of the active substance which may have a significant impact on the quality, safety or efficacy of the medicinal product.	II		
<input type="checkbox"/>	c) The change refers to a biological / immunological substance or use of a different chemically derived substance in the manufacture of a biological/immunological medicinal product and is not related to a protocol.	II		
<input type="checkbox"/>	d) The change relates to an herbal medicinal product and there is a change to any of the following: geographical source, manufacturing route or production.	II		
<input type="checkbox"/>	e) Minor change to the restricted part of an Active Substance Master File.	IB		
<input type="checkbox"/>	z) Other variation	<input type="checkbox"/> IA <input type="checkbox"/> II	<input type="checkbox"/> IB	<input type="checkbox"/> Art 5 Implement. Date:

⁹ If one of the conditions is not met and the change is not specifically listed as Type II.

* the conditions are included in the publication of the advice by CMD(h/v) or the Agency.

The following information needs to be included in the application form when applying for variation B.2.c).

	B.I. a.2 Changes in the manufacturing process of the active substance	Procedure type
<input checked="" type="checkbox"/>	c) The change refers to a biological / immunological substance or use of a different chemically derived substance in the manufacture of a biological/immunological medicinal product and is not related to a protocol.	II

Further explanation

	B.I.a .2 Changes in the manufacturing process of the active substance	Procedure type		
<input checked="" type="checkbox"/>	a) Minor change in the manufacturing process of the active substance, except changes referred to in c), d) and e) below	<input checked="" type="checkbox"/> IA	<input type="checkbox"/> IB ⁹	Implement. Date: 01-01-2010

⁹If one of the conditions is not met and the change is not specifically listed as Type II.

Since Type IA variations are ‘do and tell’ variations the implementation date of the change concerned needs to be specified in the last column. For all other variations the implementation date needs to be provided at the end of the application form. When a Type IA change is part of a grouped submission with Type IB or Type II changes or if a Type IA change is included in a worksharing procedure and when a specific implementation date can not be included here (i.e. when the Type IA change has not yet been implemented by the MAH) reference should be made to the **Declaration of the Applicant** section of the application form (i.e. ‘*See Decl. Appl.*’).

Where the change applied for does not meet all the conditions of a particular Type IA variation as given in the Classification Guideline and the change is not listed as a Type II variation this is considered to be a foreseen Type IB variation and this should be indicated on the application form. Such variation is to be included as follows:

	B.I.a .2 Changes in the manufacturing process of the active substance	Procedure type		
<input checked="" type="checkbox"/>	a) Minor change in the manufacturing process of the active substance, except changes referred to in c), d) and e) below	<input type="checkbox"/> IA	<input checked="" type="checkbox"/> IB ⁹	Implement. Date:

Other variations

	B.I.a 2 Changes in the manufacturing process of the active substance	Procedure type	
<input type="checkbox"/>	z) Other variation	<input type="checkbox"/> IA <input type="checkbox"/> IB <input type="checkbox"/> II	<input type="checkbox"/> Art 5 Implement. Date:

To apply for variations not listed in the guideline, MAHs should declare such other variation (“z”) under the specific guideline section concerned at the lowest possible level i.e. either within a specific variation or under the appropriate guideline section title, as appropriate, including its proposed classification. Please indicate whether the variation has been subject to an Article 5 procedure.

These changes can only be submitted as a Type IA variation, when such classification has been recommended following an Article 5 procedure.

Note that ‘other variations’ recommended to be Type IB via an Article 5 procedure, should be considered as foreseen Type IB variations on the first page of the application form.

PAGE 6

PRECISE SCOPE AND BACKGROUND FOR CHANGE, AND JUSTIFICATION FOR GROUPING, WORKSHARING AND CLASSIFICATION OF UNFORESEEN CHANGES (if applicable)

The actual changes that are being applied for should be stated in a concise way and a brief explanation provided of why the change is required. For grouping, where applicable, the justification should include a reference to Annex III of the Commission Regulation, or to examples published by CMD or the Agency, or to any pre-submission contacts with the RMS or the Agency (as appropriate).

For example, where variations within a group are considered by the applicant to be consequential to each other (cases 2 and 3 in Annex III of the Commission Regulation), this should be clearly stated and appropriately justified by the applicant in this section of the application form.

For worksharing procedures, the justification should refer to the pre-submission contacts with CMD or the Agency.

For type IB variations where the “z”- category is ticked - except type IB variations classified as “z”-category following Art.5 recommendations - a justification for classification as a type IB has to be given

In the **present/proposed table**: specify the precise present and proposed wording or specification, including dossier section number(s) at the lowest possible level according to CTD. For SPC, labelling and package leaflet changes, underline or highlight the changed words presented in the table or provide as a separate Annex

OTHER APPLICATIONS

This section should only be completed for submissions relating to one MA and should contain a concise and general description of the changes.

PAGE 9

Declaration of the Applicant

All applicable boxes need to be ticked, the implementation date for the Type IB and Type II variation(s) need(s) to be indicated here, as appropriate. The implementation date for Type IA changes is normally to be indicated in the **TYPE(S) of CHANGE(S)** section of the form (see also 'Page 5' above).

PAGE 10

In case of worksharing/grouping for more than one MA a single MA holder and contact point need to be designated and the box declaring that the main signatory is authorised on behalf of all designated contact points (as specified in the dossiers) needs to be ticked.