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EMA/CMDh explanatory notes on variation application form (Human medicinal products only)

Introduction and general comments

This document is intended to provide more clarification on how the Variation Application Form should be completed.

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-n 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 (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).

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.

Section 1 Application for variation to a marketing authorisation

Type of Authorisation

Please select the type(s) of Authorisation for which the variation application is submitted by ticking the box(es) for National Authorisation in MRP/DCP, EU Authorisation and/or National Authorisation.

Variation procedure number(s)

For EU authorisations the European Medicines Agency will assign the variation number on receipt of the application unless it is grouped IA or Worksharing application. Procedure number for WS and IA groupings needs to be obtained in advance via EMA service desk. For guidance on the structure of variation procedure numbers, please refer to the Agency's Post-Authorisation Procedural Advice.

For products in MRP/DCP the variation procedure number should be assigned by the marketing 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, as applicable.

In cases of worksharing or grouped applications MRP variation numbers are to be assigned: 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.. MRP variation numbers should only be listed in the table 'Products concerned by this application' in the application form.

For a single variation concerning several strengths within one MA 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

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 add all Concerned Member State(s) that are involved in the procedure. Further specification on which Member States are involved per particular product should be provided in section 2 of the application form.

Type of application

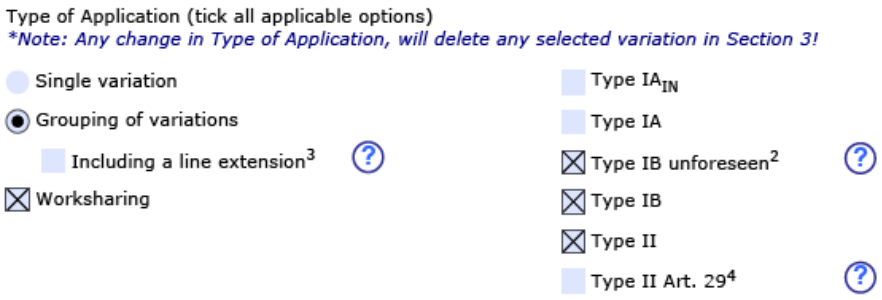
It should be indicated which type of variations are included in the submission, whether a single or grouped variation is submitted and whether the worksharing procedure is followed. Note that all relevant boxes need to be ticked.

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

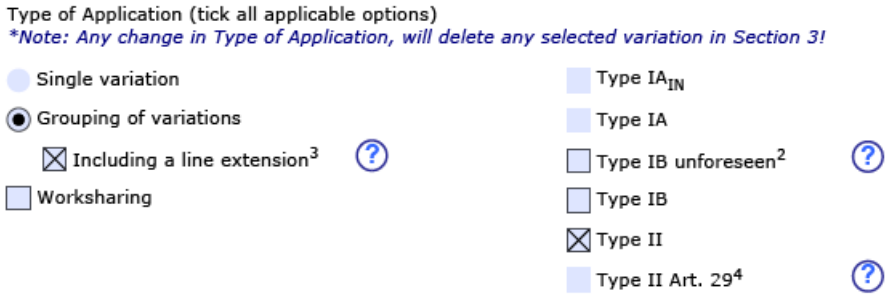
For all type IB variations the box "Type IB" should be ticked, **unless** it concerns a type IB variation where a "z"-category is ticked and which has not been classified as "z"-category following Article.5 recommendations. These type IB variations should be classified as type IB **unforeseen** variation 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 variations.

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



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



In the variation application form it is stated that:

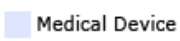
"A variation is considered 'unforeseen' when the proposed variation is not considered a minor variation of Type IB following the Commission Guideline, or has not been classified as a Type IB variation in an Article 5 recommendation.

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."

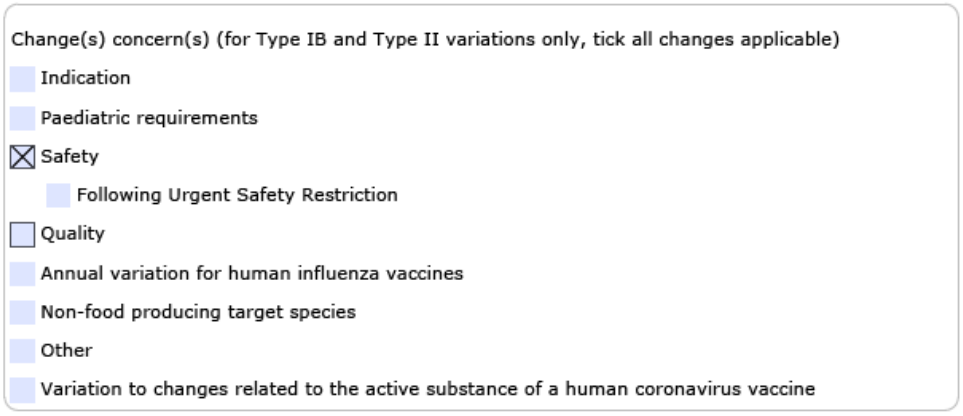
The box "Type IB" should therefore be ticked for those Type IB variations which:

1. are listed as examples of Type IB in the Variations Guidelines;
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 Guidelines and they are not listed as Type II variations in the Variations Guidelines.

Change(s) concern(s):



This tick box will appear after selecting the human domain at the beginning of section 1. It should be ticked if the variation application (a) affects a device component previously listed in the marketing authorisation of the medicinal product or (b) concerns the introduction of a new device / device constituent part. When selected, a new section 4.d is shown to include details on medical devices and companion diagnostics.



Note: the tick box "Variation to changes related to the active substance of a human coronavirus vaccine" will only appear, if the "Human" and "Type II" box have been ticked.

The following guidance on the interpretation of the above terms is provided for variations for medicinal products for human use.

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 requirements:

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, and for variations related to the implementation of the Paediatric Investigation Plan or related to the implementation of the outcome of the assessment of studies under Article 45/46 of the Paediatric Regulation.

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, is 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.

Variation to changes related to the active substance of a human coronavirus vaccine:

This category should be selected for type II variation applications related to change the active substance of a human coronavirus vaccine.

Other:

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

Name and address of the MA holder

For each Member State involved, the name and address of the MA holder should be provided. For EU authorisations, European Union should be selected from the drop-down list.

For worksharing or grouped variations affecting more than one MA, indicate the MA holder to be used as reference MA holder for the handling of the procedure.

Name and address of contact person

For each Member State involved, the name and address of the contact person should be provided. For EU authorisations, European Union should be selected from the drop-down list.

If different from the MAH, or if different from the authorised contact person, a letter of authorisation should be attached to confirm the delegation.

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

If the contact person is not an authorised contact for one of the products involved, the letter of authorisation should be included in the submission.

* 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.*

Section 2 Products concerned by this application

For all products concerned, the requested details should be included in the electronic variation application form.

For medicinal products for human use, the table should be completed.

For worksharing procedures submitted to the EMA, which include nationally authorised products, relevant product and Member State details should be provided as Annex B to the application form (Using the template on the EMA website).

For worksharing procedures including only NAPs the MAs should be included in the eAF itself and not in a separate annex.

In cases of worksharing or grouped applications product specific MRP variation numbers are to be assigned for MRP/DCP products: 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 3 Types of change(s)

Note: fill out section 1 of the application form first, in order for the proper variations to be loaded. Navigate through the dropdown lists, in order to show the variation. You can select the variation by clicking the relevant checkbox of the variation box. Note: Any change in Type of Application in Section 1, will delete any selected variation!

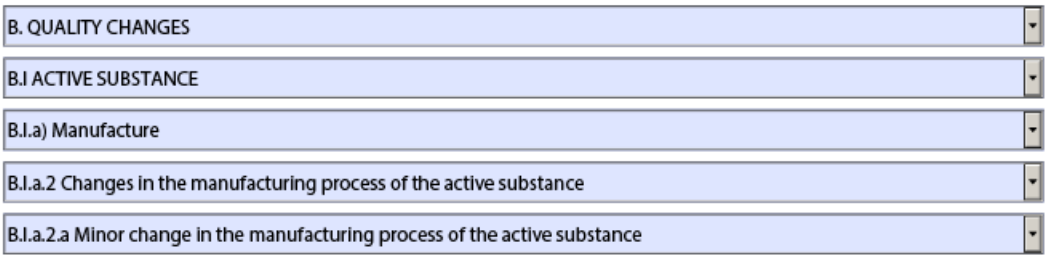
In case of several variations under the same classification the type of change, number and title of each of these variations should be mentioned. E.g. a grouped type II variation application of 3 type II variations C.I.4, this category should be added 3 times and the changes of each type II variation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

For Type IA variations and those Type IB changes listed in the Variations Guidelines the relevant boxes for conditions and documentations need to be ticked as applicable. For Type IA variations, all documents listed in the Guidelines should be provided (unless the Guidelines 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 Guidelines, 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.

Example A

To add a Type IA B.I.a.2.a notification, subsequently the options as indicated below should be selected from the drop-down lists.

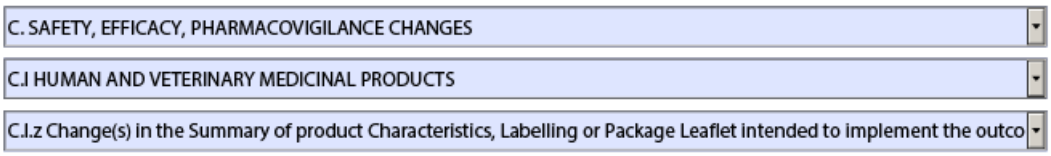


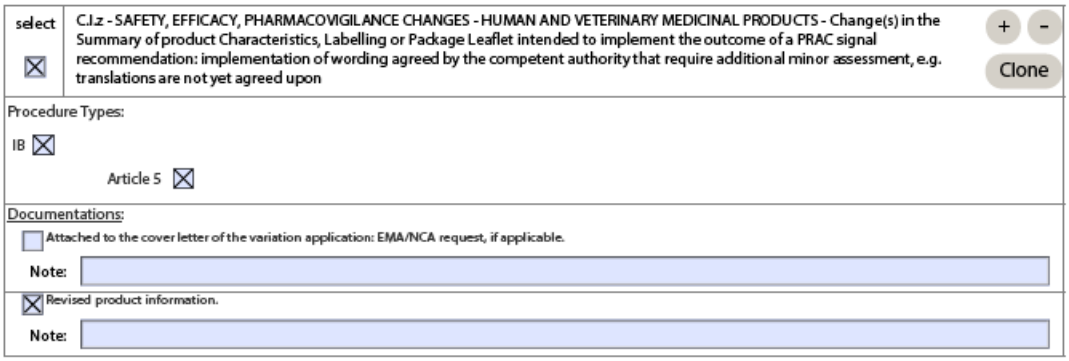
The selected category including the conditions and required documentation will then appear in the AF.

To select the notification, the select box should be ticked. Other boxes need to be ticked as applicable, and the implementation date needs to be provided.

Example B

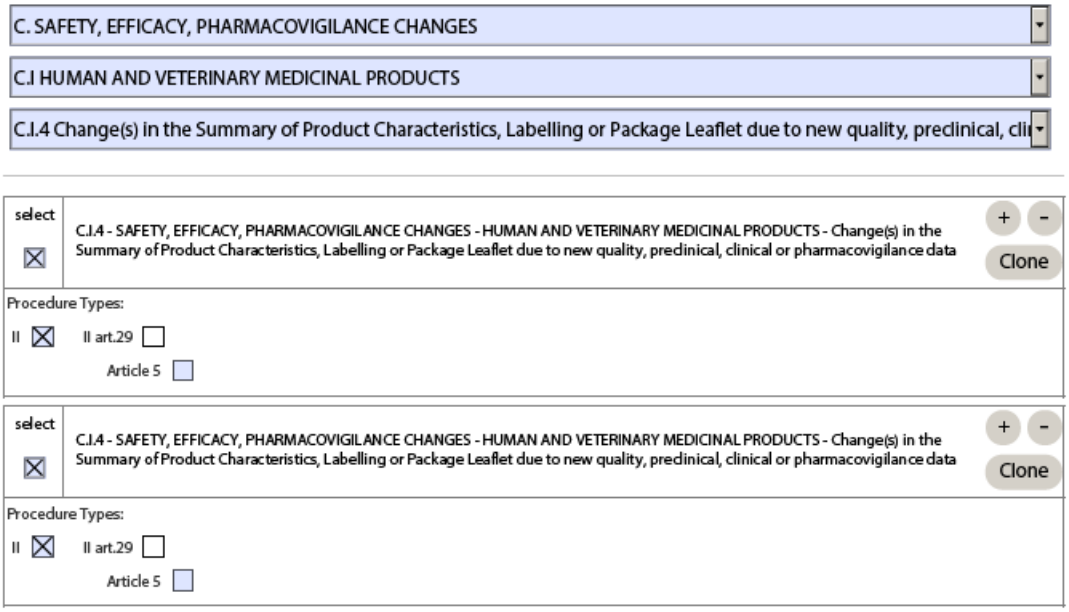
To add a Type IB C.I.z variation to implement the outcome of a PRAC signal recommendation: implementation of wording agreed by the competent authority that require additional minor assessment, e.g. translations are not yet agreed upon, the relevant variation category should be selected and added using the drop down lists in the application form and by ticking the tick boxes as required.



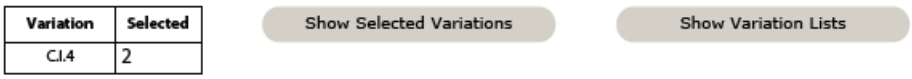


Example C

To add two type II C.I.4 variations, the relevant variation category should first be selected and added using the drop-down lists in the application form and by ticking the tick boxes as required.



The category can be duplicated using the + button.



Note that the number of selected C.I.4 variations at the start of section 3 will now read 2.

Further explanation

Since Type IA variations are 'do and tell' variations the implementation date of the change concerned needs to be specified. 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 cannot 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 Variations Guidelines and the change is not listed as a Type II variation this is considered

to be a Type IB variation and this should be indicated on the application form. The Type IA category should be selected as described above, but instead of the box for IA the box for IB should be ticked.

To apply for variations not listed in the Guidelines, MAHs should select a z-category variation under the specific Guidelines section concerned at the lowest possible level i.e. either within a specific variation or under the appropriate Guidelines 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 'Type IB' and not as 'Type IB unforeseen' variations on the first page of the application form.

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/NCA 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. The ASMF reference number should be included in the precise scope if affected by the variation.

For worksharing procedures, the justification should refer to the letter of intent.

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 eCTD. For SmPC, labelling and package leaflet changes, underline or highlight the changed words presented in the table or provide as a separate Annex.

If applicable, the D-U-N-S (Data Universal Numbering System) number and/or EU or National ASMF reference number should be provided. A national ASMF number should only be provided if an EU ASMF reference number is not available.

OTHER APPLICATIONS

This section on other ongoing or pending applications should only be completed for submissions relating to one MA and should contain a concise and general description of the changes.

Section 4 (a-d)

Note: Whether section 4 (a, b, c, d) will be displayed in the AF and, if so, which subsections, depends on the options that were selected in the preceding part of the AF.

Section 4a Orphan medicinal product information

This section should be completed for all type IB and type II variations for human medicinal products concerning a new indication (including paediatric indication) for the product at issue.

Section 4b Paediatric requirements

This section should be completed for type IB and type II variations for human medicinal products concerning a new indication or for variations related to PIP implementation.

Section 4c Extended data exclusivity / market protection

This section should be completed for type II variations with a claim for extended data exclusivity / market protection.

Section 4d Change to the design or intended purpose of the medicinal device component, or introduction of a new device / device constituent part

This section should be completed if the variation application (a) affects a device component previously listed in the marketing authorisation of the medicinal product or (b) concerns the introduction of a new device / device constituent part. Information should be provided on the type of device applicable, the device identification and classification, the manufacturer of the device, the documentation to confirm compliance to the Medical Device Regulation and the Notified Body involved.

Annexed documents

All applicable boxes should be ticked.

Declaration of the Applicant / Signature

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 section 2 above.

For MRP/DCP/purely nationally authorised products the MAH should also declare:

1. If the same type II variation application for the same medicinal product[1] has also been submitted in other Member State(s) not involved in the current procedure. If yes, the applicant has to specify in which Member State it has been submitted and when; the status of the variation should also be stated. If the same variation has been submitted in several Member States, the section should be duplicated by using "+" button.
2. If the product information of the concerned MA(s) has/have been (partially) harmonised by an Article 30 or 31 referral or through a dedicated type II worksharing variation as detailed in Q4.21 of the CMDh Q&A on variations.

[1] For an explanation of what constitutes the "same medicinal product" in this context, see section E.3 of Commission communication on the Community marketing authorisation procedures for medicinal products (Official Journal C 229, 22/7/1998 p. 4 - 17).

- This section should be completed only for type IB and type II variation applications affecting the product information section 4 and/or 5 of the SmPC and corresponding information in the Package Leaflet. This section is therefore not applicable for type IA variations, quality variation or purely administrative changes to the product information.
- This section should be completed only if the product at issue has been included in the scope of a harmonisation procedure i.e. a referral or a dedicated worksharing variation as detailed in Q4.21 of the CMDh Q&A on variations). Therefore, any other WS procedures or information on generic medicinal products that have been harmonised with the originator should not be listed here.
- Also in the case the former harmonisation concerns only a subsection or single sentence „yes" should be ticked as it is foreseen in legislation that harmonisation once achieved should be kept in the future.
- If only part of the strengths have been harmonised "yes" should be ticked and it should be specified in the free text field that the referral or dedicated harmonization WS has concerned only one / several of the strengths.

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. If the contact person is not an authorised contact for one of the products involved the letter of authorisation should be included in the submission.