1. General questions

**Question 1.1**  
*What is the definition of MAH?*

**Answer:**

According to the Commission Communication 98/C229/03 the definition of the same MAH is as follows:

Applicants belonging to the same mother company or group of companies and applicants having concluded agreements or exercising concerted practices concerning the placing on the market of the relevant medicinal product have to be taken as the same marketing authorisation holder.

Generally, in case of worksharing and grouping of IA variations for several MRP/DCP procedures the applicant should provide an explanation on the link between the MAHs.

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**Question 1.2**  
*When will the Regulation (EC) 1234/2008 apply for purely national authorisations?*

**Answer:**

Regulation (EC) 1234/2008 as amended by Regulation (EC) 712/2012 shall only be applicable for “purely national” procedures from August 4, 2013. After that moment in time, certain products under specific conditions will still be excluded according to Annex VI of Regulation (EC) 712/.

**Question 1.3**
*(Deleted in February 2013)*

**Question 1.4**
*Is it possible to submit an identical variation for different pharmaceutical forms and/or strengths of a marketing authorisation as a single application?*

**Answer:**
For variation applications, the following definition of a marketing authorisation is used: all strengths and/or pharmaceutical forms of a certain product. The following is an example of a single application:

It should be noted that the concept of the global marketing authorisation has been developed for data exclusivity purposes only, and is therefore not applied in relation to the Variation Regulation. Therefore informed consent applications and duplicate applications are regarded as self-standing marketing authorisations.

**Question 1.5**
*Is an update of the overall summary necessary for any kind of type II variations?*

**Answer:**
Yes, the updated overall summary has to be submitted together with the other amended data as necessary documents with every type II variation application.

**Question 1.6**
*Is it possible to submit Variations to a medicinal product authorised via Mutual Recognition or Decentralised Procedure in the situation where the Marketing Authorisation has not been granted in all involved Member States?*
Answer:
The CMDh has agreed that in the situations where not all Member States involved in a MRP or DCP have granted a Marketing Authorisation within 30 days after finalisation of the procedure, Marketing Authorisation Holders can submit Variations after this date, provided that high quality translations of the agreed SmPC, PL and Labelling have been submitted to all involved MSs.

**Question 1.7**
*How should changes be identified in the highlighted SmPC/PL and Labelling texts submitted with applicant’s responses?*

**Answer:**
If comments are made to the SmPC/PL and Labelling during the variation procedure the applicant should propose a new version of the SmPC/PL and Labelling including all revised wording clearly identified, preferably using track-changes function. It is not acceptable if the highlighted texts only identify the changes made in part of the variation procedure, e.g. since clock stop.

It should be clear what changes originate from the initial submission and what changes are proposed as a response to the received comments.

The highlighted final texts circulated by RMS to CMS at the end of procedure should clearly identify all changes approved during the procedure.

2. **Questions relating to the submission of variations**

**Question 2.1**
*When and how should the variation be submitted to RMS and CMS?*

**Answer:**
According to the Regulation (EC) 1234/2008 the same application and the same documentation shall be submitted simultaneously to the RMS and all CMS.

**Question 2.2**
*Is it necessary to submit variation applications to all concerned member states even if they are not concerned by the specific change (e.g. change in the address of the MAH in only one CMS)?*

**Answer:**
Yes, the applications have to be submitted to all concerned member states.

**Question 2.3**
*Which documents have to be submitted for a variation Type IA, IB or II or a grouped application before a procedure is started?*
Answer:
The application form incl. all relevant documentation (e.g. SmPCs, labels and leaflets as required, national product information texts (not applicable for Type II), relevant pages from the Guideline with ticked boxes for conditions and documentation for Type IA and/or Type IB etc.) has to be submitted to the RMS and all CMS. The procedures will not be started before the RMS has received the dispatch list with the dispatch date for all CMS including a statement of the applicant that the fees have been paid, where applicable.

**Question 2.4**
Currently, no variations should be submitted during ongoing Repeat Use Procedures (RUP). What about the annual reports or Type IA variations with immediate notification? Do they have to be submitted before starting a RUP though the 12 months are not full in order to have the dossiers complete?

**Answer:**
Applicants should carefully plan a strategy for their procedures. Annual reports may be submitted earlier than the 12 month deadline in order to have the dossier adequately updated before starting a RUP procedure. Type IA variations with immediate notification have to be submitted before the start of a RUP.

**Question 2.5**
Currently, no variations should be submitted during ongoing renewal procedures. What about the annual reports or Type IA variations with immediate notification? Do they have to be submitted before starting renewal though the 12 months are not full in order to have the dossiers complete?

**Answer:**
Applicants should carefully plan a strategy for their procedures. Annual reports may be submitted earlier than the 12 month deadline in order to have the dossier adequately updated before starting a renewal procedure. Type IA variations with immediate notification may in exceptional and urgent cases be submitted during a running renewal procedure. The RMS has to be contacted in advance.

**Question 2.6**
When do I have to submit national translations for a variation procedure?

**Answer:**
For Type IA and Type IB variations the national translation(s) have to be submitted together with the application. For Type II variations national translation(s) have to be submitted within 7 calendar days after the end of the procedure.

**Question 2.7**
How is the documentation for a grouped variation or worksharing application to be submitted?
Answer:
Generally the documentation has to be submitted per product. Especially in the case of
electronic submission every single product file has to be updated according to the next sequence
of the electronic documentation. The common cover letter and common application form must
be included in every single eCTD or NeeS. All eCTDs or NeeS must separated on one CD or
DVD. In case more than one CD or DVD is used, these have to be submitted in a single
package.

However, in case of paper submissions it would be sufficient to submit only one copy of the
documentation for all products in case the documentation is really completely identical. This
does of course not relate to the product information which has to be submitted for each product
separately when concerned.

Question 2.8
In case the MAH in one member state is changed, is a variation in all member states necessary to
introduce the new pharmacovigilance system (DDPS or summary of pharmacovigilance system) of
the new MAH or is a purely national variation in the member state concerned sufficient? And how
can the change of the MAH be submitted to the member states concerned after the 21st of July
2012?

Answer:
In case of the transfer of a MAH in one member state the new pharmacovigilance system of the
new MAH has to be submitted to all member states concerned. In case there is already a DDPS
approved for this medicinal product, a new DDPS of the new MAH may be introduced via
variation procedure as variation type IB (in case the pharmacovigilance system has already been
approved for a different product, C.I.8.b) or type II (in case the pharmacovigilance system has
not yet been assessed, C.I.8.a) (see also Q/A 3.12) or the MAH may decide to switch to the
summary of the pharmacovigilance system (as type IAIN notification, see also Art.5
recommendation).

In case there was no DDPS approved for the medicinal product so far, it is not allowed to
submit a new DDPS after the 21st of July 2012. In this case, a summary of a pharmacovigilance
system can be submitted before or after the transfer (as type IAIN notification, see also Art.5
recommendation). It has to be submitted at the latest with the submission of the next renewal
application or by 21st July 2015.

However, the transfer of the MA to a new MAH is to be handled as an independent purely
national application according to Art. 1(2) of the Regulation (EC) 1234/2008 as there is a
change of the legal entity. The fees are set by each CMS and the management of the procedure
is dealt with by each CMS. The current registered MAH should send a notification to the RMS
to specify which CMSs and MAHs are concerned with this national procedure.

Remark: The change in the name and/or address of the MAH (i.e. the MAH remains the same
legal entity) for a product registered through MRP or DCP, is processed at MRP level via a type
IAN No. A.1 variation.
**Question 2.9**

Is there a need to inform competent authorities, when a notification has been accepted for a European Pharmacopoeia Certificate of Suitability (CEP) by European Directorate for the Quality of Medicines (EDQM) concerning notifications that will not lead to a revised certificate?

**Answer:**

No there is no need to inform the authorities nor to submit a copy of the letter “Acknowledgement of a valid notification” by EDQM to verify that the notification has been accepted by EDQM. Only in cases of updated CEPs, should a variation application be submitted to the competent authorities.

**Question 2.10**

After an Art. 30 or 31(1) Referral all products included in the Annex I have to adapt to the Commission Decision by a type IAIN notification. How should this variation be submitted to the authorities?

**Answer:**

For Art. 30 or 31(1) referrals, all products included in Annex I of the referral will be transferred to MRP. Therefore, the applicant has to choose a new RMS immediately after the CHMP opinion. After receipt of the new MRP number by the future RMS and publication of the Commission Decision the applicant is responsible for allocating the correct variation number and the immediate submission of the type IA\(_{IN}\) variations to all competent authorities concerned.

For harmonisations only of the product information a single variation of type IAIN C.I.1 has to be submitted. If during the Article 30 or 31(1) procedure not only the product information but also Module 3 has been harmonised a grouped application of type IAIN has to be submitted consisting of applications according to C.I.1.a and B.V.b.1.a.

**Question 2.11.a**

How can I update my product information according to the requirements of the new pharmacovigilance legislation with regard to the implementation of the black symbol and the explanatory statements on additional monitoring and adverse drug reactions reporting?

**Answer:**

The explanatory statements on additional monitoring and ADR reporting have been introduced within the QRD template for MR/DC procedures published in April 2013 on the CMDh website (under Templates). Adaptations to the updated QRD templates may generally be applied for without a separate variation in the course of another regulatory procedure, e.g. renewal or variation application of type IB or type II of the “C” category of the Classification Guideline affecting the product information (see Q/A variations 3.16), so that the necessary update of the product information can be introduced without a separate variation application and no reference to a variation code is required.

However, the implementation of these changes may not be delayed for the products under additional monitoring. In case the black symbol and the statements on additional monitoring and ADR reporting could not have been introduced with a suitable variation by the end of 2013, companies should submit a type IA\(_{IN}\) variation no later than 31 December 2013,
according to Commission Regulation 198/2013. For further information, please see the CMDh Article 5 recommendations (http://www.hma.eu/293.html)

Question 2.11.b
How can I update my product information according to updates in line with the QRD template?

Answer:
It is recommended to implement the updates in line with the QRD template as soon as possible, but no later than 2 years following the publication date of the QRD template for medicinal products with regulatory activity (i.e. no later than April 2015) and no later than 3 years for medicinal products with no regulatory activity (i.e. no later than April 2016).

3. Questions relating to the Classification of a variation

Question 3.1
Which Type of variation should be submitted when the particular change we are applying for is not mentioned in the classification guideline or one or more of the conditions cannot be fulfilled?

Answer:
If a change is not mentioned in the Annex II of the Variation Regulation (EC) 1234/2008 or the classification guideline or the conditions for a specific change could not be fulfilled and the change is not already classified as a Type II variation, this change can be submitted as a Type IB variation by default. However, if the change in the view of the applicant has a significant impact on quality, safety and efficacy of the product, a Type II variation has to be submitted.

Question 3.2
How to apply for the deletion of more than one manufacturing site?

Answer:
In case more than one manufacturer in one MA has to be deleted a grouped application consisting of several type IA variations A.7 for all manufacturing sites has to be submitted. However, it has to be assured that there is still one approved manufacturing site left in the documentation.

Question 3.3
Which procedure type is applicable for the implementation of the Core Safety Profile into the SmPC and the PL after a PSUR worksharing procedure?

Answer:
The implementation of change(s) requested by a National Competent Authority following the assessment of a Periodic Safety Update Report is listed in section C.I.3 of the Classification Guideline. The implementation of a Core Safety Profile can be submitted as a type IB variation provided no new additional data are submitted by the MAH. The revised PL (which is not Q&A submission of Variations
According to Commission Regulation (EC) 1234/2008

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agreed upon in the PSUR worksharing procedure) is not considered to be ‘new additional data’. However, if the implementation of the Core Safety Profile needs to be substantiated by new additional data submitted by the MAH then a type II variation must be submitted.

**Question 3.4**

*How should a change to or update of an ASMF, which is part of Module 3 of a marketing authorisation, be submitted?*

**Answer:**

An update or change of an ASMF as such is not foreseen in the Pharmaceutical Legislation and can only be addressed in connection with a marketing authorisation. The type of the variation is dependent on the type of the single changes introduced in the updated version. The update – including changes of the open as well as the restricted part - can be submitted as a grouped application according to the highest type of the single changes, if condition 5 of Annex III of the Variation Regulation applies.

However, in case of substantial changes in the updated version of the ASMF it is recommended to submit a single variation of type II under category B.I.z.

In all cases, the updated ASMF must be submitted by the ASMF holder (open and closed part to NCA, open part to MAH), the variation as such has to be submitted by the marketing authorisation holder.

**Question 3.5**

*What is necessary for submitting a type IB variation according to Classification Guideline C.I.1.b), C.I.2.a), C.I.3.a)?*

**Answer:**

Under “**Precise Scope and Background for Change**” in the application form the applicant should declare that he adapts the SmPC, PL and labelling identically to the reference text as foreseen in the respective variation without any other changes to the product information.

**Question 3.6**

*Which procedure should apply for the implementation of the updated version of the Core SmPC/Core PL for seasonal influenza vaccines when the new version will be used for the next annual strain update. Is it possible to submit a single Type II variation for the annual strain update (B.I.a.5) including the adaption on the new version of the Core SmPC/PL?*

**Answer:**

Yes. The implementation of the updated version of the Core SmPC/PL and the annual strain update can be submitted as a single Type II variation, taking into account the specificity of this procedure.
Question 3.7
What is intended by “non-sterile liquid based pharmaceutical forms” in condition 2 of change category B.II.b.4 (change in batch size of finished product) ?

Answer:
The full text of condition 2 is as follows - “The change relates to standard immediate release oral pharmaceutical forms or to non-sterile liquid based pharmaceutical forms”. Consequently, any standard immediate release oral pharmaceutical form is already covered under the condition. However, as far as non-sterile liquid based pharmaceutical forms are concerned, this should be interpreted as applying to formulations that have the characteristics of liquids and are not for oral administration e.g. topical solutions and lotions. Consequently, creams, gels, suppositories and ointments are excluded.

Question 3.8
When general monographs of the Ph.Eur. or product specific monographs of a national pharmacopoeia of a Member State are updated how should variations affecting the finished product be submitted?

Answer:
Variation B.III.2 only relates to active substances, excipients and active substance starting material. Changes to comply with Ph.Eur. or with a national pharmacopoeia of a Member States affecting the finished product should be submitted according to the relevant variations listed under B.II.d.

The wording of the change Type IA, no. B.II.d.1.a (Tightening of specification limits) should be read in the context of the general title of the change B.II.d.1 (Change in the specification parameters and limits of the finished product) and the definition of ‘specification parameter’ (means the quality attribute for which a test procedure and limits are set e.g. assay) in the introductory note of the ‘Communication from the Commission — Guideline on the details of the various categories of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products (2010/C 17/01).

There is no need to notify the competent authorities of an updated monograph of the European pharmacopoeia or a national pharmacopoeia of a Member State in the case that compliance with the updated monograph is implemented within six months of its publication and reference is made to the ‘current edition’ in the dossier of an authorised medicinal product.

Question 3.9
How should I submit changes to the product information to adapt to the results of a repeat use procedure?

Answer:
Changes to the product information resulting from comments of the new CMS during a repeat use procedure should be applied for in one single type II variation under category C.I.
**Question 3.10**

*How should a deletion of a pharmaceutical form or strength be submitted?*

**Answer:**

According to the EC Classification Guideline deletion of a pharmaceutical form and/or strength is a variation no. C.I.:

<table>
<thead>
<tr>
<th>C.I.7 Deletion of:</th>
<th>Conditions to be fulfilled</th>
<th>Documentation to be supplied</th>
<th>Procedure type</th>
</tr>
</thead>
<tbody>
<tr>
<td>a) a pharmaceutical form</td>
<td>1, 2</td>
<td>IB</td>
<td></td>
</tr>
<tr>
<td>b) a strength</td>
<td>1, 2</td>
<td>IB</td>
<td></td>
</tr>
</tbody>
</table>

**Documentation**

1. Declaration that the remaining product presentation(s) are adequate for the dosing instructions and treatment duration as mentioned in the summary of product characteristics.
2. Revised product information

**Note** In cases where a given pharmaceutical form or strength has received a marketing authorisation which is separate to the marketing authorisation for other pharmaceutical forms or strengths, the deletion of the former will not be a variation but the withdrawal of the marketing authorisation.

The situation could arise that in some MS included in a MRP/DCP the deletion of a pharmaceutical form or strength is a variation, and in the other MS included in a MRP/DCP a withdrawal of a marketing authorisation.

The CMDh agreed the following:
- The variation should be submitted to all MS included in the MRP/DCP.
- On the cover letter and in the application form it should be clarified in which MS a variation is required for the deletion of the pharmaceutical form or strength, i.e. to which MSs the variation applies.
- In the MS where a withdrawal application is required, the withdrawal application should be submitted in parallel.
- In case the deletion of a pharmaceutical form or strength is a withdrawal application in the RMS and all CMS, then no variation application needs to be submitted.
- It is the responsibility of the applicant to identify before submission which MS requires a variation and which MS requires a withdrawal application.
- In case all strengths and pharmaceutical forms of one product are withdrawn in one or more member states, then no variation application needs to be submitted but a withdrawal letter has to be sent to the member states concerned.

**Question 3.11**

*Which type of variation should be submitted for the implementation of changes in the SmPC, not already covered by the Classification Guideline, for which no new quality, pre-clinical, clinical or pharmacovigilance data are provided by the applicant?*
Answer:
An update of the SmPC to implement change(s) in the Summary of Product Characteristics not already covered by the Classification Guideline and for which no new data are provided by the applicant should be submitted as a C.I.z, type IB variation.

Question 3.12
In variation C.I.8 (Introduction of a new Pharmacovigilance system) a distinction is made whether a Pharmacovigilance system has or has not been assessed by ‘the relevant national authority’. How should the new DDPS be submitted?

Answer:
The CMDh has published a declaration form for the submission of DDPS that have already been approved by one of the member states (http://www.hma.eu/91.html). This form should be added to all variation applications according to C.I.8.b, where a competent authority of the EEA (including Iceland, Norway, Liechtenstein and the EMA) has already approved the current version of the DDPS.

In those cases where the current version of the DDPS has not yet been approved by any competent authority of the EEA (including Iceland, Norway, Liechtenstein and the EMA), a type II variation according to C.I.8.a should be submitted.

The change of a DDPS due to a transfer is possible only in those cases where a DDPS was already approved before 21st of July 2012. The DDPS has to be replaced by a summary of the pharmacovigilance system with the submission of the next renewal application or at the latest by 21st July 2015.

Question 3.13
If the correct category for a special change is not listed in the classification guideline and the applicant is not sure about the correct variation type, is it possible to liaise with the RMS?

Answer:
Generally it is the duty of the applicant to identify the correct variation type and to classify the variation procedures by themselves and to choose the correct variation type incl. the IB by default variation. Only in exceptional cases it is, however, necessary to contact the RMS, e.g. for grouping applications not listed in Annex III of the Regulation. Any advice received by the RMS has then to be submitted in writing as addendum to the application form together with the variation application.

Question 3.14
What is understood by “manufactured by complex manufacturing processes” in change code B.II.b.4 (change in batch size of the finished product)?
Answer:
Complex manufacturing processes is intended to cover situations where the actual manufacture of the finished product involves a process which includes one or more processing steps that may give rise to scale up difficulties. These will be considered on a case by case basis.

Where relevant, if a change is submitted as a Type IB variation, it is up to the applicant to provide adequate justification for not considering a manufacturing process as a “complex” one, in terms of scale up.

**Question 3.15**
*How should a change in the name of a manufacturing site responsible for batch release and other activities be submitted?*

**Answer:**
A change in the name of a manufacturing site responsible for batch release AND other activities may be submitted as a single application as per scope A.5.a) --> type IA-IN.

**Question 3.16**
*Under which classification category can editorial changes be submitted?*

**Answer:**
Editorial changes in the SmPC (and corresponding PIL/labelling), updates in line with the QRD template, adaptation to excipient guidelines, etc. without any impact on the content of the dossier, can be included within the scope of another planned type IB or type II variation under chapter C that affects the product information. No separate variation submission is necessary and no reference to a variation code is required.

**Question 3.17**
*We wish to register a new site of active ingredient manufacturer by Type IA change code B.III.1 notification, as the manufacturer holds a Ph Eur Certificate of Suitability (CEP). The CEP does not state a re-test period but we have stability data to support this. Can we tick condition 4 and include the stability with the Type IA change code B.III.1 notification?*

**Answer:**
The Type IA notification procedure is intended to be a simple and rapid process for minor changes and does not include the assessment of data. In this case, the stability data will need to be assessed. This can be done by either submitting a Type IB change code B.I.d.1 variation to change the re-test period of the active substance in parallel with the Type IA change code B.III.1, or as a group with the Type IA change (the resultant group would default to a Type IB procedure time table).

As far as the Type IB variation is concerned, the applicant should confirm that stability data was generated in the same packaging material as was stated in the CEP dossier provided to EDQM. In addition, for those CEPs issued before 1st Sept 2011 and where no packaging material is stated in the CEP, details of the packaging materials used in the stability studies
should be provided (description of the immediate container closure system, including the identity of materials of construction and if appropriate a brief description of any non-functional secondary packaging components).

As change code B.I.d.1 is a Type IB notification, condition 4 of the Type IA notification will have to be ticked, as omission of re-testing before manufacture will not be acceptable until the new re-test period has been approved.

Question 3.18
How should I submit a new RMP or an updated RMP to update my dossier?

Answer:
Please see Q&A under Questions & Answers, Pharmacovigilance Legislation, question 2.

4. Questions relating to grouping and worksharing

Question 4.1
Can the same variation for more than one marketing authorisation be submitted on one application form?

Answer:
Yes, in case of worksharing applications and type IA notifications for several MRP/DCP marketing authorisations one single application form is to be submitted for all marketing authorisations of the same holder concerned.

Question 4.2
If there are different Marketing Authorisations holders for the same MRP product in the CMS, may these products participate in grouping and worksharing?

Answer:
Generally, all MAHs belonging to the same MRP or DCP are regarded as the same MAH and the procedure may participate in grouping and worksharing.

Question 4.3
Is it possible to submit one grouped application for different marketing authorisations?

Answer:
A marketing authorisation in the sense of variations is defined as one MRP or DCP product including all strengths and forms. Several marketing authorisations of the same MAH can be grouped together in the case of Type IA notifications (also applicable as “annual report”) if the changes applied for are identical. A grouping of more MAs is not possible for Type IB and Type II variations. The CMS in all the concerned marketing authorisations may differ. Please see also detailed information in chapter 6 of the Best Practice Guide.
**Question 4.4**  
*When has an ‘annual report’ to be submitted?*

**Answer:**  
The so-called “annual report” is no specific procedure but a submission of single or grouped Type IA variations within a maximum of 12 months after the implementation of the first Type IA change which is part of this submission. It is up to the applicant if and when to submit an annual report. The submission of Type IA notifications in the form of an annual report is not mandatory. The annual report for Type IA notifications not requiring an immediate notification has to be submitted at the latest 12 months after implementation of the first Type IA variation.

**Question 4.5**  
*Can harmonisation of Module 3 be done by worksharing?*

**Answer:**  
Module 3 harmonisation is surely an option for worksharing as worksharing does not require product harmonisation in advance. The aim is to have a harmonised result. However, currently the procedure may only be used for MRP/DCP licences as the Regulation (EC) 1234/2008 is not yet applicable for purely national licences (see also question 1.2).

**Question 4.6**  
*Is it possible to group Type IA variations for a CP and a DCP product if the Rapporteur and RMS are from the same Competent Authority?*

**Answer:**  
No, CP and MRP/DCP products may only be combined in a worksharing procedure, not in any other type of procedure.

**Question 4.7**  
*Is the reference authority for a worksharing procedure automatically the RMS of one the products concerned?*

**Answer:**  
The reference authority for a worksharing application is chosen by the CMDh, based on a proposal by the applicant. However, the reference authority has to be a MS concerned in at least one of the procedures.

**Question 4.8**  
*A product is registered through MRP/DCP and a different product name is proposed in several MSs. Is it possible to submit a change in the product name (variation A.2.b, type IB) in more than one MS as a grouped application concerning one marketing authorisation?*
**Answer:**

A change in the product name in more than one MS of a MRP/DCP marketing authorisation can be submitted as a grouped application consisting of several type IB variations in case a different product name in each MS is proposed, since it falls under situation 4 listed in Annex III of the Variation Regulation (all variations in the group relate solely to changes of administrative nature to the SmPC, labelling and package leaflet).

If the product name in each MS is identical and the same change is applied for in all MS, then the change in product name can be submitted as a single variation.

**Question 4.9**

_A product is registered through MRP/DCP. Is it possible to submit a change in the name and/or address of the marketing authorisation holder (variation A.1, type IA) in more than one MS as a grouped application concerning one marketing authorisation, even if the name and/or address is different in each MS?_

**Answer:**

A change in the name and/or address of the marketing authorisation holder in more than one MS of a MRP/DCP marketing authorisation can be submitted as a grouped application consisting of several type IA variations.

**Question 4.10**

_If the addition of a new manufacturing site requires substantial changes in the manufacturing process, how should these changes be submitted?_

**Answer:**

As all the changes in the manufacturing process are related to the new manufacturing site, all these changes may be submitted in one grouped application according to the highest type of the single changes applied for.

**Question 4.11**

_Must all changes in a grouped application according to article 7.2(b) of the Regulation (EC) 1234/2008 apply to all strengths and pharmaceutical forms that have been included in this group?_

**Answer:**

Yes, all the changes in one variation application must apply to all the products that are listed in the application form. It is not allowed that single changes of this grouped application do only concern parts of the list of products.

**Question 4.12**

_If it is intended to conform to the current legislation and Module 1 has to be updated therefore, how can this update of Module 1 be submitted?_
Answer:
In order to conform to the current legislation all changes for the update of Module 1, including changes or addition of Braille, readability user testing, environmental risk assessment, summary of pharmacovigilance system or risk management plan, may be submitted as one single variation of type II under category C.I.z.

Question 4.13
Is it allowed to submit different class labellings agreed by PhVWP/CMDh as a grouped application?

Answer:
Please see the document ‘Examples for acceptable and not acceptable groupings for MRP/DCP products’

Question 4.14
How can a generic MA be adapted to the most current version of the SmPC, if the results of several procedures, e.g. PhVWP recommendations and PSUR worksharing, have to be considered?

Answer:
The applicant has to submit one variation application according to C.I.3.a for each single change applied for. The single change is defined by one data package triggering the variation. All these single changes may be combined in one grouped application, see also Examples for acceptable and not acceptable groupings for MRP/DCP products, http://www.hma.eu/96.html.

It is not acceptable to wait for the originator having adapted to all these changes and to submit a single variation C.I.2.a in order to adapt to the originator.

Question 4.15
Can I introduce or update the summary of the pharmacovigilance system and a change in the QPPV within one single variation application or is a grouped application necessary?

Answer:
The introduction/update of a summary of the pharmacovigilance system and concurrent changes in the QPPV can be submitted as a single IA\textsubscript{IN} variation under classification category C.I.z provided the changes affecting the QPPV are clearly mentioned in the scope and in the ‘present / proposed’ sections of the variation application form.

5. Questions regarding the approval and implementation of variations

Question 5.1
Is there a possibility for an appeal by the MAH in case of rejection of type IB or type II variations?
Answer:
According to the Regulation (EC) 1234/2008 a referral to the CMD is only possible in case of potential serious risk to public health seen by a CMS. Therefore, there is no possibility for the applicant in case of an MRP or DCP procedure for any type of variation to refer the matter to the CMD or the CHMP.

Question 5.2
What is meant by “implementation” for Type IA variations?

Answer:
For quality changes, implementation is when the Company makes the change in its own Quality System.

This interpretation allows companies to manufacture conformance batches and generate any needed stability studies to support a Type IAIN variation before making an immediate notification\(^1\) because the change will not be made in their own Quality System until these data are available.

For changes to the pharmacovigilance system, ‘implementation’ is when the Company makes the change in its pharmacovigilance system (i.e. when it internally approves the DDPS or summary of pharmacovigilance system incorporating the changes).

For product information, it is when the Company internally approves the revised product information. The revised product information will then be used in the next packaging run.

Question 5.3
If a Type IA variation is part of a group containing Type II, do I have to wait for the implementation of the IA variation until the group assessment is completed?

Answer:
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.

Question 5.4
In case SmPC changes are applied for in a Type II variation when can I implement the national texts?

Answer:
30 days after submission of high-quality national translation(s) of the product information the changes are implicitly approved. A Member State has to comment on the national translation(s) within 29 days or otherwise the proposed translations are implemented.

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\(^1\) For example the type IAIN for addition, deletion or replacement of components in the flavouring or colouring system requires stability data on at least two pilot scale or industrial scale batches.
**Question 5.5**

In case a type IA or type IA_{IN} variation affects the package leaflet, how should the ‘Date of revision of the text’ be detailed in the printed version of the package leaflet?

**Answer:**

For Type IA and IA_{IN} variations the „Date of revision of the text“ will correspond to the implementation date (i.e. when the Company internally approves the revised product information). (see also Question 5.2)