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Q&A - List for the submission of variations according to Commission Regulation (EC) 1234/2008

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1. General questions

1.1. What is the definition of MAH?

Answer (Human & Veterinary):

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 concerning products of more than one MAH the applicant should provide an explanation on the link between the MAHs.

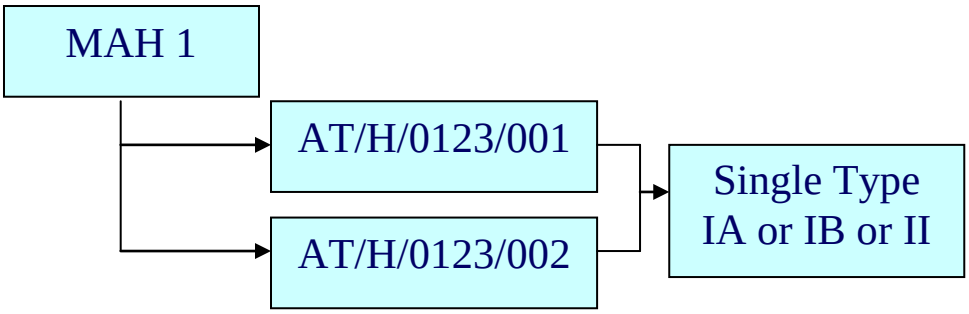
1.2. Question deleted in July 2013

1.3. Question deleted in February 2013

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 (Human & Veterinary):

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.

1.5. Is an update or an addendum to the overall summary (human) or expert report (veterinary) necessary for any kind of type II variations?

Answer (Human & Veterinary):

Yes, the update/addendum to the overall summary (human) or expert report (veterinary) has to be submitted together with the other amended data as necessary documents with every type II variation

application, except for the exceptions listed in the CMDv BPG for Type II Variations (EMA/CMDv/115377/2010) (veterinary).

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 concerned Member States?

Answer (Human & Veterinary):

Variations can be submitted at any time after the end of a marketing authorisation procedure.

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

Answer (Human & Veterinary):

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 in an editable (word) format. 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.

1.8. How should I submit changes to the product information following an administrative renewal (human) or full renewal (veterinary) further to a repeat-use (where only part of the CMS are involved in the renewal)?

Answer (Human & Veterinary):

Changes to the product information resulting from comments of the CMS involved in the renewal procedure should be applied for a single type II variation, under category C.I.z.

However, in case the changes result only in editorial changes, updates in line with the QRD template or adaptation to excipients guideline (human), without any impact on the content of the dossier, they can be included within the scope of another planned variation according to Q/A 3.16 or they can be applied for a single type IB variation, under category C.I.z (if no upcoming variation is planned).

In all cases, the variation application should be submitted to all Member States involved in the procedure.

2. Questions relating to the submission of variations

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

Answer (Human & Veterinary):

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

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 (Human):

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

Answer (Veterinary):

Yes, the applications in general have to be submitted to all concerned member states but in the Veterinary domain some exceptions may apply, see CMDv Information Release - Reduction in Administrative Burdens Relating to Variations - EMA/CMDv/397848/2016; http://www.hma.eu/588.html.

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 (Human & Veterinary):

The electronic 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.

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 (Human & Veterinary):

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.

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 (Human & Veterinary):

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 and will decide on the acceptance. Please see also the BPGs on renewals of CMDh (http://www.hma.eu/95.html) and CMDv (http://www.hma.eu/579.html), respectively.

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

Answer (Human & Veterinary):

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.

Please note that for Type IB variations, national translations updated in accordance with requests for amendment raised in the "Notification with Grounds" have to be submitted in the amended notification as applicable.

2.7. How is the documentation for a grouped variation or worksharing application to be submitted?

Answer (Human):

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. CESP is normally used today but if CD/DVDs are used all eCTDs or NeeS must be 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. See also TIGes/CMB guidance on eCTD and NeeS http://esubmission.ema.europa.eu/tiges/cmbdocumentation.html

Answer (Veterinary):

See Guideline on eSubmissions for Veterinary Products (http://esubmission.ema.europa.eu/tiges/vetesub.htm)

Answer (Human & Veterinary):

However, in exceptional cases 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.

2.8. In case the MAH in one or more member state(s) is changed, is a variation in all member states necessary to introduce the new summary of the pharmacovigilance system (human) or DDPS (veterinary) of the new MAH or is a purely national variation in the member state(s) concerned sufficient?

Answer (Human & Veterinary):

In case of the transfer of a MA in one or more member state(s) the new summary of the pharmacovigilance system (human) or DDPS (veterinary) of the new MAH has to be submitted to all member states concerned via MRP variation (as type IA_{IN} notification, C.I.8.a, or under category C.II.7 as applicable). This is also applicable when using the Art. 57 database (human only) as the classification guideline (C.I.8) also requires a "proof that the applicant has at his disposal a qualified person responsible for pharmacovigilance and a statement signed by the applicant to the effect that the applicant has the necessary means to fulfil the tasks and responsibilities listed in Title IX of Directive 2001/83/EC". Therefore, a variation for the introduction of a new summary of the pharmacovigilance system after a change of the MAH still has to be submitted, later changes of the contact details of the QPPV or location of the PSMF do not require variations anymore when they are introduced via the Art. 57 database. A variation to submit the summary of the pharmacovigilance system will not be necessary in cases where the MA is transferred within companies belonging to the same parent company and the same PSMF will continue to be used.

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.

Veterinary: National requirements for transfer of MA see CMDv GUI-31 (http://www.hma.eu/577.html).

Remark: The change in the name and/or address of the MAH (i.e. the MAH remains the same legal entity) for a product authorised through MRP or DCP, is processed at MRP level via a type IA_{IN} No. A.1 variation.

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 (Human & Veterinary):

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.

2.10. After an Art. 30 or 31(1) Referral (human) or an Art. 34 or 35(1) Referral (veterinary) all products included in the Annex I have to adapt to the Commission Decision by a type IA_{IN} notification. How should this variation be submitted to the authorities?

Answer (Human):

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 harmonisation only of the product information a single variation of type IA_{IN} C.I.1.a 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 IA_{IN} has to be submitted consisting of applications according to C.I.1.a and B.V.b.1.a.

Answer (Veterinary):

For Veterinary Medicinal Products see CMDv article “Marketing authorisation transfer to a mutual recognition procedure for a veterinary product” (http://www.hma.eu/589.html).

2.11. a. Question deleted in February 2017

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

Answer (Human):

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 and no later than 3 years for medicinal products with no regulatory activity unless otherwise specified in the implementation plan for the revised QRD templates.

Answer (Veterinary):

MAHs should align the PI with template v.8.1 at the next post-authorisation procedure affecting the PI (e.g. variation, line extension) and at the latest by the time of renewal of the MA (if applicable). Also see implementation plan: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000185.jsp&mid=WC0b01ac058002d9b0

2.12. a. What is meant by “otherwise transmitted” with regard to the notes of category A.8 of the classification guideline?

Answer (Human & Veterinary):

Otherwise transmitted means that the information has been provided within any other formal regulatory procedure e.g. renewals, or if agreed relevant Type IB or Type II variations concerning the B-category changes of the classification guideline. In these cases, no separate variation application for

the change in the audit date has to be submitted. However, the change has to be clearly mentioned in the scope of the application form as well as under "present/proposed".

2.12. b. What is meant by manufacturer of the finished product under documentation requirement 1 of category A8 of the classification guideline?

Answer (Human & Veterinary):

Manufacturer of finished product means any registered EEA manufacturers of medicinal products (finished product and batch release) which hold a valid manufacturing authorisation. This is the same as manufacturing sites which are required to provide a Qualified Person declaration, where a single declaration may be acceptable under certain circumstances – see note under variation no. B.II.b.1.

2.13. How should I submit the results of confirmatory stability studies on production-scale batches (having given a commitment to perform those) where stability data for pilot-scale batches have already been accepted during application for a MA?

Answer (Human & Veterinary):

It is not generally foreseen that these data are submitted to NCAs, either via variation or simple notification. It is the responsibility of the applicant to perform these studies as agreed. However in cases where issues arise during the confirmatory studies with production-scale batches (e.g. unexpected impurities, trends towards out of specification results etc.), the MAH should either submit a variation, if appropriate, (e.g. to correct the shelf-life, storage conditions etc.) or contact the RMS who will then decide whether any corrective action has to be taken.

(See also Question 14 of the Q&As on applications for marketing authorisation; http://www.hma.eu/20.html)

3. Questions relating to the Classification of a variation

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 (Human & Veterinary):

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 may have a significant impact on quality, safety and efficacy of the product, a Type II variation has to be submitted.

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

Answer (Human & Veterinary):

In case more than one manufacturer in one MA has to be deleted a single variation of type IA under classification category A.7 to delete all manufacturing sites may be submitted. However, it has to be

assured that there is still one approved manufacturing site left in the documentation performing the same function as the one(s) concerned by the deletion.

3.3. Which procedure type is applicable for the implementation of product information updates after a PSUR worksharing procedure or single PSUR assessment (PSUSA) and when should the variations be submitted?

Answer (Human):

The implementation of product information updates after a PSUR-WS can be submitted as a type IB variation under category C.I.3.z of the classification guideline provided no new additional data are submitted by the MAH. Although the revised PL wording (which is not usually agreed in the PSUR worksharing procedure) is not considered to be 'new additional data' a notification would not be possible, as there would be no agreed leaflet wording and no harmonised national translations. However, if the implementation of the product information update needs to be substantiated by new additional data submitted by the MAH then a type II variation under category C.I.3.b must be submitted.

In the case of implementation of product information updates after finalisation of a single PSUR assessment (with PRAC recommendation) a variation IA_{IN} under category C.I.3.a may be submitted if harmonised national translations are available irrespective of the medicinal product being part of the procedure and no further adaptation of the currently approved wording to the decision (EC or CMDh decision) is necessary. In cases where the wording has to be adapted this has to be submitted as a type IB under category C.I.3.z. In case the MAH submitted new data for assessment, the variation type to be submitted should be a type II (see also Q/A No. 8 on Pharmacovigilance (http://www.hma.eu/20.html).

For PSUSAs of NAPs the EMA publishes a timetable for submission of the variations which is applicable for all affected products including those that are not listed in the annex to the decision.

For PSUSAs of CAPs or mixed CAPs/NAPs the EC publishes the outcome but without a timeframe for submission. For all products that are involved in these procedures (as listed in the Annex to the EC decision) the Commission decision is to be implemented by the NCAs within 30 days. By analogy to the implementation of referral procedures, the respective variations have to be submitted within 10 days after publication of the Commission Decision on the EC website. For generic products or others not concerned by the PSUSA procedure itself, the changes have to be submitted via a variation procedure within 60 days of the publication of the Commission Decision on the EC website.

It should be noted that in case of type IA_{IN} variations the changes have to be implemented before submission, for type IB variations after approval.

Answer (Veterinary):

MAHs are reminded, especially for safety issues, that once new information becomes available which might entail the variation of the MA, MAHs should submit any variation application resulting from Periodic Safety Update Reports (PSURs) at the same time as the submission of the PSUR, rather than awaiting the assessment of those data.

Where submission of a variation following the assessment of a PSUR is requested, MAHs must submit the corresponding variation application at the latest within 2 months following the adoption of the relevant assessment conclusion.

Implementation of agreed wording changes following the above mentioned procedures may follow a Type IAin variation procedure, C.I.3.z if no additional data are submitted by the MAH and no further adaptation of the approved wording is necessary in the SPC or PL and no linguistic review is necessary. In all other cases a C.I.3.z Type IB should be submitted.

3.4. How should a change to Module 3.2.S or the update of an ASMF, which is part of Module 3 (human) / Part II (veterinary) of a marketing authorisation, be submitted?

Answer (Human & Veterinary):

The update of Module 3.2.S can be submitted as a grouped application according to the highest type of the single changes, if condition 5 or 6, respectively of Annex III of the Variation Regulation applies.

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 Module 3.2.S or the ASMF it is recommended to submit a single variation of type II under category B.I.z. However, it is a prerequisite for the validation of these single variations that the section “present/proposed” is filled out completely and correctly.

In all cases of updates of the ASMF these 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.

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.z)?

Answer (Human & Veterinary):

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.

3.6. Question deleted in May 2015

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 (Human & Veterinary):

The full text of condition 2 is as follows - “The change relates to conventional immediate release oral pharmaceutical forms or to non-sterile liquid based pharmaceutical forms”. Consequently, any conventional 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.

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 (Human & Veterinary):

Variation B.III.2 only relates to active substances, excipients, immediate packaging materials and active substance starting materials. 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 reference is made to the 'current edition' in the dossier of an authorised medicinal product.

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

Answer (Human & Veterinary):

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.z. and submitted to the RMS and all CMS. Editorial changes can be made according to Q/A 3.16.

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

Answer (Human & Veterinary):

In case of MRP/DCP or purely national marketing authorisations submission of a variation is not necessary, if they have been authorised as an independent marketing authorisation. In such cases, a withdrawal notification letter should be sent to the member state(s) concerned and the RMS has to be informed via email. Since in some MS a given pharmaceutical form or strength might have not received a marketing authorisation which is separate to the marketing authorisation for other pharmaceutical forms or strengths, in such cases the deletion of a pharmaceutical form or strength should be submitted as a variation C.I.7, only in those MS(s) according to a national procedure. 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 of doubt applicants may contact the MSs in advance of the submission.

In what concerns the need for update of combined product information further to withdrawal/deletion of a strength/pharmaceutical form, if common combined product information must be updated to delete information concerning strength/pharmaceutical form deleted for all MS, a type IB variation under category C.I.z should be submitted to allow complete review across all section of the combined product information.

If only national versions of combined product information are affected, applicants should confirm with national competent authorities which is the most appropriate procedure for updating the product information.

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 (Human & Veterinary):

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.

However, the adaptation to a product information not being the PI of the reference product to which the original application for marketing authorisation for a generic/hybrid medicinal product refers, has to be justified for the specific product concerned and is therefore regarded as new data provided for this product. Thus, a type II variation C.I.4 would be applicable.

Furthermore, an adaption of a generic/hybrid application to a product information text NOT being the reference product to which the original application for marketing authorisation refers, may NOT be submitted according to category C.I.2 of the Variation Classification Guideline but has to be submitted as a type II variation C.I.4.

3.12. Question deleted in November 2015

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 (Human & Veterinary):

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.

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 (Human & Veterinary):

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.

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

Answer (Human & Veterinary):

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.

3.16. Under which classification category can editorial changes be submitted?

Answer (Human):

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.

Changes to the details of the national reporting systems to communicate adverse reactions as laid down in Appendix V are also regarded as editorial, but if needed this information may also be updated through a national type IA C.I.z procedure.

Answer (Veterinary):

Editorial changes to the product information in Part 1.B (SPC, labelling and package leaflet) can be included within the scope of any upcoming procedure impacting on the product information, clearly stated in the present/proposed section (cf. EMA Veterinary post-authorisation Q&A: Type IA variations; http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/q_and_a/q_and_a_detail_000099.jsp.

Answer (Human & Veterinary):

Concerning other editorial changes of Module 3, 4 and 5, Part II, III and IV please refer to EMA (human) Post-authorisation Guidance Q&A on Editorial Changes.

(veterinary) http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/q_and_a/q_and_a_detail_000099.jsp%20.

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 (Human & Veterinary):

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.

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

Answer (Human):

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

Answer (Veterinary):

A RMP should be submitted as a type IB variation under category C.I.11.z.

3.19. How should the outcome of a PRAC signal recommendation be implemented?

Answer (Human):

In accordance with the "CMDh Recommendation for classification of unforeseen variations according to Article 5 of Commission Regulation (EC) No 1234/2008" the implementation of product information updates after a PRAC signal recommendation may be submitted as type IA_{IN} notification under C.I.z when harmonised national translations are available in all member states. If minor assessment is needed a type IB variation under C.I.z would be applicable. However, if the implementation of the product information update needs to be substantiated by new additional data submitted by the MAH then a type II variation under category C.I.z must be submitted.

3.20. How should the outcome of a Union safety referral procedure be implemented?

Answer (Human & Veterinary):

Change(s) in the Summary of Product Characteristics, Labelling or Package Leaflet intended to implement the outcome of a Union safety referral procedure (submitted in accordance with art 31and art 107i of directive 2001/83/EU or art 35 of directive 2001/82/EC) should normally be submitted as a type IA_{IN} C.I.1.a variation. This is provided that the medicinal product is covered by the defined scope of the procedure (i.e. included in Annex I) and the following condition is fulfilled in accordance with the classification guideline:

"The variation implements the wording requested by the authority and it does not require the submission of additional information and/or further assessment."

Often further assessment is needed. For example, proposed new text can not be implemented without adapting or deleting previously approved text. In some referral outcomes there are optional texts to be implemented depending on the pharmaceutical form.

Therefore, applicants are always encouraged to consider if further assessment would be needed by the authorities when implementing the outcome of a Union referral procedure and in this case submit the application as a type IB C.I.1.a instead.

3.21. Which type of variation should be used for the submission of interim reports of post approval studies?

Answer (Human):

Generally, interim reports do not have to be submitted unless requested specifically by authorities, e.g. as a condition to the MA etc. In case of the submission of interim reports for post approval studies (which are not a condition to a MA) these should be submitted as a type II variation application with category C.1.13, provided that no changes to the SmPC are being proposed based on these results. For the submission of interim reports for post approval studies which are a condition to the MA category C.I.11.b should be chosen. Protocols, interim and final reports on PASS or DUS should be submitted directly to the PRAC.

3.22. Which type of variation should be used for the submission of draft study protocols or final reports for post approval studies?

Answer (Human & Veterinary):

The submission of draft study protocols as well as the final reports for post approval studies should be submitted as a type II variation application with category:

- C.I.13, in case the study is not performed as a condition to the marketing authorisation falling under Article 21a, 22a or 22 of Directive 2001/83/EC or Article 26 of Directive 2001/82/EC (in case changes in the SmPC are foreseen under C.I.4) or
- C.I.11.b, in case it concerns a study performed as a condition to the marketing authorisation falling under Article 21a, 22a or 22 of Directive 2001/83/EC or Article 26 of Directive 2001/82/EC (in case changes in the SmPC are foreseen under C.I.4).

Human: Generally, the MAHs are highly recommended to build consortiums for the planning and processing of clinical studies. Study protocols and results should be submitted via a worksharing procedure so that a harmonised assessment can be the outcome. When submitting such worksharing application a cover letter should be added clearly mentioning all MAHs that are participating in the consortium. However, draft protocols of non-interventional PASS (including DUS) imposed by the PRAC/ RMS/MS (after July 2012) (to the exception of studies to be conducted only in the one Member State that requests the study) should be submitted to the PRAC via the appropriate procedure in accordance with Article 107(n-o) of Directive 2001/83/EC. Please refer to EMA website for further details regarding the submission and assessment of such protocol: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/q_and_a/q_and_a_detail_000134.jsp&mid=WC0b01ac0580796d88

Human and Veterinary: In case the studies are conducted in just one member state the protocols and results have to be submitted via national variation in that member state in case of purely national MAs and as EU variation in case of MRP or DCP MAs. In both cases protocols and results have to be submitted as type II variations under C.I.13 in case the study is not performed as a condition to the MA and as C.I.11.b in case it concers a study performed as a condition to the MA falling under Article 21a, 22a or 22 of Directive 2001/83/EC or Article 26 of Directive 2001/82/EC. In case the study results lead to changes in the SmPC a variation type II under C.I.4 is to be submitted.

3.23. Can a MRP variation be submitted under C.I.2.a (Change in the product information following assessment of the same change for the reference product) as a type IB if the product information of the reference product is not harmonised in all member states concerned?

Answer (Human & Veterinary):

The reference product that is adapted to has to be the reference product from the original application which has to be confirmed in the application form. It has to be identical for all products in the application and approved via MRP/DCP (including products harmonised via an article 30 referral/human or article 34 referral/veterinary) or via the Centralised procedure. The European procedure number of the reference product should also be stated in the application form. If the reference product is approved via the National procedure in several member states and the relevant sections of the product information have not been harmonised e.g. by a worksharing procedure, the variation should be submitted as a type II variation under C.I.2.b.

However, these type II variations would be accepted with a limited data package. An update of the overview and a sound justification for all proposed changes (e.g. explaining why a certain reference text has been selected for a specific change) would be regarded as sufficient documentation in these cases. As a general rule the highest level of safety information as included in the reference product's product information should be chosen.

3.24. Which type of variation should be submitted for the change in the name and/or address of a manufacturer/importer of the finished product (including batch release or quality control testing sites), e.g. in case the change in name and/or address is due to change of the holder of the manufacturing authorization?

Answer (Human & Veterinary):

According to EU legislation, a Manufacturing Authorisation is only issued to cover manufacturing sites located in the EEA region. A change of holder concerns a change in the legal entity and requires the issue of a new Manufacturing Authorisation. In these situations, such a change can only be submitted under category A.5, provided the specified condition is fully met and a copy of a new Manufacturing Authorisation is presented. This means that there is no physical change to the actual manufacturing site and that additionally all manufacturing operations remain the same. Manufacturing operations cover the manufacturing activities for which the site is responsible, including if relevant manufacturing processes and controls, as well as the relevant GMP related responsibilities and relationships with other companies. Therefore, at the point of transfer of the Manufacturing Authorisation, to be acceptable under A.5 any changes should be purely administrative in nature.

In the event that the specified condition is not met, rather than automatically defaulting to a Type IB under category A.5, depending upon the nature of what is changing, exceptionally the change should be presented under the relevant B Category, normally B.II.b.1 or B.II.b.2 and be suitably supported.

3.25. How should Marketing Authorisation holders handle changes to its dossiers, linked to Ph. Eur. monograph updates resulting from the implementation of the new policy concerning the expression of the degree of hydration?

Answer (Human & Veterinary):

Ph. Eur. monographs for both drug substances and excipients are being updated to reflect a change in policy in terms of the expression of the degree of hydration. These will start from January 2017, when reference to anhydrous will be removed from a number of monographs (https://www.edqm.eu/sites/default/files/pharmeuropa_changes_in_titles_for_the_9th_edition_2016.pdf) and there will be future changes linked to the degree of hydration, which will only be implemented if there is another change required to the relevant monograph.

The change in name of an active substance or excipient impacts the product information (where relevant the SmPC, PL and label) and also Module 3/Part II information. Consequently, Marketing Authorisation variations will be required.

In order to reduce the regulatory burden, the changes may be included as part of another relevant regulatory procedure without any prior agreement e.g. variation impacting the SmPC and product information. For transparency, the changes should be clearly highlighted and the background to the changes explained in the submission.

However, in the event that there is no expected opportunity to include the changes as part of another suitable regulatory procedure, the change in name of the active substance or excipient should be submitted as a single Type IA IN under change code A3. Marketing Authorisation holders should note that any required changes should be implemented within 5 years of the relevant updated monograph coming into force.

3.26. Which variation should be submitted for the change in supplier of sterilised primary container components, which are to be used in the aseptic manufacture of medicinal products and what supporting information should be provided?

Answer (Human & Veterinary):

The terminal sterilisation of primary packaging components, which are subsequently used during aseptic processing of medicinal products, is a critical process and the sterility of the primary container is a critical quality attribute to ensure the sterility of the medicinal product. Therefore, in cases of pre-filled syringes and other types of sterilised containers which are filled under an aseptic process (e.g. ophthalmic preparations) and where no other sterilisation process is performed after filling and sealing of the primary packaging, the variation should be submitted as Type IB variation, under category B.II.b.1.z.

The variation submission should include assurance on GMP or ISO compliance of the site where the sterilisation of the containers is performed. In addition, details of the sterilisation method should be provided and in the event that the method does not use the reference conditions stated in the Ph. Eur., validation data should be provided, as outlined in the Q&A published on EMA website under packaging, "What data is required for sterilisation processes of primary packaging materials subsequently used in an aseptic manufacturing process?" (http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/q_and_a/q_and_a_detail_000072.jsp).

It should be noted that anyway the sites responsible for the sterilisation of the containers and/or their components are expected to be included in section 3.2.P.7 of the dossier.

3.27. Which type of variation should be submitted for the change in the name and/or address of: a manufacturer (including where relevant quality control testing sites), or an ASMF holder, or a supplier of the active substance, starting material, reagent or intermediate used in the manufacture of the active substance (where specified in the technical dossier) where no Ph. Eur. Certificate of Suitability is part of the approved dossier, or a manufacturer of a novel excipient (where specified in the technical dossier) when the condition mentioned in the guideline that the manufacturing site and all manufacturing operations remain the same is not met?

Answer (Human & Veterinary):

Normally, when conditions for IA or IA_{IN} variations are not met, the same change code applies as type IB when the specific change is not listed as type II variation. In the specific event that the specified condition of change code A.4 is not met, i.e. with the change in the name and/or address of the manufacturer the manufacturing site or operations do not remain the same, rather than automatically defaulting to a Type IB under category A.4, depending upon the nature of what is changing, exceptionally the change should be presented under the relevant B Category, normally B.I.a.1, and be suitably supported.

3.28. Which type of variation (Type IA N°A.7 or type IA B.III.1.a.4) should be submitted to delete one approved manufacturer of the active substance where Ph.Eur. Certificate of suitability is part of the approved dossier?

Answer (Human & Veterinary):

The A.7 type IA variation clearly indicates that the manufacturing site of an active substance is being deleted, whereas by using B.III.1.4 type IA variation the applicant can delete the Ph. Eur. certificate of suitability without deleting the API manufacturer – It is possible if more than one certificate exists per material.

3.29. How should I submit the transfer of test methods for testing of biological medicinal products to a new or already authorized testing site? Which variation classification category is applicable and what type of supporting documentation is expected?

Although, the need to submit a variation to approve an existing QC testing site for additional testing activities after analytical test transfer has been completed is not specifically foreseen by the current EC Variation Classification Guideline submission of a variation following by analogy the existing foreseen variation category B.I.a.1.j, B.II.b.2.b or B.II.b.2.c.3 may be necessary as outlined below under ii.

i. In case of **physical, chemical and microbiological test methods** to be transferred to a **new** testing site (i. e. not yet listed in the dossier) submission of a variation is required (category B.II.b.2).

The documentation to be submitted is defined in the EC Variation Classification Guideline.

ii. In the case of biological, immunological, or immunochemical test methods (e.g. in vivo bioassays, in vitro bioassays, enzymatic assays, binding assays, neutralisation assays, immunochemical assays) to be transferred to a **new** testing site or to an **already approved** testing site, a variation of type B.I.a.1 or B.II.b.2 is to be submitted.

The documentation should include at a minimum, the method transfer protocols in accordance with Eudralex Volume 4 Chapter 6 article 6.39 (which pre-define the acceptance criteria), from the old site to the new site (or new test laboratory). Depending on the variability of the specific method and the potential risk, to the quality, safety or efficacy of the product, posed by the proposed change, additional data such as a summary of the analytical method transfer test results may be required.

4. Questions relating to grouping and worksharing

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

Answer (Human & Veterinary):

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. In addition this is also acceptable for grouped Type IB and II variations only involving purely national marketing authorisations within only one member state.

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 (Human & Veterinary):

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.

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

Answer (Human & Veterinary):

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 (except for purely national marketing authorisations within only one member state). The CMS in all the concerned marketing authorisations may differ. Please see also detailed information in chapter 6 of the Best Practice Guide or CMDv/BPG/016 for Grouping of Variations.

4.4. When has an ‘annual report’ to be submitted?

Answer (Human & Veterinary):

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.

4.5. Can harmonisation of Module 3/Part II be done by worksharing?

Answer (Human & Veterinary):

Module 3/Part II harmonisation is surely an option for worksharing as worksharing does not require product harmonisation in advance. The aim is to have a harmonised result. See also Q/A 4.16.

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

Answer (Human):

No, CP and MRP/DCP and purely national products may only be combined in a worksharing procedure, not in any other type of procedure. As a worksharing procedure is not applicable for type IA notifications there is no possibility to submit a combined application for type IA changes for purely national, MRP/DCP and CP products.

Answer (Veterinary):

Within the framework of supergrouping of type IA variations, MRP/DCP and purely national products may be combined, please refer to "Reduction in Administrative Burdens Relating to Variations", http://www.hma.eu/588.html.

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

Answer (Human & Veterinary):

The reference authority for a worksharing application is chosen by the CMDh or CMDv, based on a proposal by the applicant. However, the reference authority has to be a MS concerned in at least one of the procedures. In case all procedures are in MRP/DCP and have the same RMS, this is automatically also the reference authority, see also Chapter 6 of the BPG (http://www.hma.eu/96.html) or the CMDv/BPG/018 for Worksharing http://www.hma.eu/578.html.

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 (Human):

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.

(Please also consider Q/A on naming of generics http://www.hma.eu/20.html).

Answer (Veterinary):

See CMDv RfR 3-4/2016 http://www.hma.eu/557.html.

The name of a generic product authorised through MRP/DCP should be the same in all MSs if the reference product has been authorised through a centralized procedure (Regulation 726/2004). Therefore a variation to change the name in some MSs is not possible for that product.

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}) 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 (Human & Veterinary):

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.

4.10. If the addition of a new manufacturing site requires substantial changes in the manufacturing process, how should these changes be submitted?

Answer (Human & Veterinary):

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.

(Please also consider the examples for acceptable and not acceptable groupings, http://www.hma.eu/96.html).

4.11. Must all changes in a grouped application according to article 7 of the Regulation (EC) 1234/2008 apply to all strengths and pharmaceutical forms that have been included in this group?

Answer (Human & Veterinary):

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.

4.12. If it is intended to update a dossier in preparation of a RUP/MRP/duplicate application in order to conform to the current legislation, how can this update of the dossier be submitted?

Answer (Human & Veterinary):

When updating a dossier for a RUP/MRP/duplicate application in order to conform to the current legislation all changes for the update of the dossier, including changes or addition of Braille, User Test, Environmental Risk Assessment, summary of pharmacovigilance system, RMP, QPs declaration, updated confirmatory stability data, updated Clinical and Non-clinical overviews and summaries or Expert reports based on already submitted and approved clinical and preclinical data, may be submitted as one single variation of type II under category C.I.z, rather than a grouped application.

In case new data are submitted, for example the addition of literature references, separate variations for Modules 4 and 5/Part III and IV should be submitted. A grouped variation might be feasible if justifiable and agreed by the competent authority.

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

Answer (Human):

Please see the document 'Examples for acceptable and not acceptable groupings for MRP/DCP products'.

4.14. How can MAs be adapted to the most current version of the SmPC, if the results of several procedures, e.g. PRAC recommendations and PSUR worksharing or single PSUR assessment (PSUSA), have to be considered?

Answer (Human & Veterinary):

The applicant has to submit one variation application according to the correct category of the classification guideline 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 for generics to wait for the originator to have implemented all these changes and subsequently submit a single variation C.I.2.a in order to adapt to the originator. Nor is it possible for any MA to include all the changes in a Company Core Data Sheet (CCDS) and to submit a single variation of type II under category C.I.4.

4.15. Question deleted in December 2013

4.16. Under which category can I submit a variation or worksharing application for a harmonisation of the quality dossier when the products concerned were not part of an Article 30 (human) or Article 34 (veterinary) referral?

Answer (Human & Veterinary):

Applications for the harmonisation of the quality dossier for the same purely national products and/or the same products approved in MR/DC procedures which are owned by the same MAH not participating in a former referral procedure for product harmonisation may also be submitted as type II variations under category B.V.b.I.z in a worksharing procedure. In case there is an updated dossier, it can be included in the worksharing to adapt all products in the worksharing to that version, leading to no changes on the already updated products. In such cases it is strongly recommended to propose the NCA of the updated dossier as the preferred Reference Authority for the worksharing procedure.

Other adaptions of Module 3/Part II to different marketing authorisations are not applicable to this procedure and should instead be submitted as grouped applications indicating every single change in the dossier as single variation according to the classification guideline.

4.17. How can I submit variations when several changes are falling under the same category in the classification guideline?

Answer (Human & Veterinary):

Generally, each trigger in a variation application results in a single variation which may be submitted in a grouped application. 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.

4.18. How should proposed safety variations, such as the addition of a contraindication or a restriction in an indication or in the posology of a product, be submitted to the authorities when the same MAH has several purely national marketing authorisations in the EU?

Answer (Human & Veterinary):

The protection of public health is one of the major roles of the Competent Authorities of the European Union. Therefore in relation to safety information it is highly recommended that MAHs in their responsibility for the safe use of medicinal products make use of the variation work-sharing procedure to ensure that safety related information is introduced simultaneously to the product information of MAs within the European Union. Where such variations are not submitted by way of the work-sharing procedure and rather by way of single purely national variations within single member states, the applicant is requested to submit a table with the status of the MAs in all member states of the European Union. This table is essential for a short and effective discussion of the case at CMDh/CMDv level. Based on the differences seen in the table the CMDh/CMDv will determine whether any further regulatory action is required by the MAH, the MS, the Agency or the European Commission.

To avoid this unnecessary complication the MAH is strongly recommended to use the variation work-sharing procedure for the introduction of safety related changes to the product information.

4.19. How can generic MAs be adapted to the most current version of the SmPC of the reference medicinal product, if the results of several procedures, e.g. type II variations have to be considered?

Answer (Human & Veterinary):

The applicant has to submit one variation application according to C.I.2 a, b or z 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.

(Human: For implementing PRAC recommendation or PSUR worksharing see Question 4.14, which is applicable for all MAs).

It is not acceptable for generics to wait for the originator to have implemented all these changes and subsequently submit a single variation C.I.2.a in order to adapt to the originator. Nor is it possible for any MA to include all the changes in a Company Core Data Sheet (CCDS) and to submit a single variation of type II under category C.I.4.

4.20. When a new or updated CEP is submitted under B.III.1.a and condition No. 2 (additional impurity) is not fulfilled a type IB variation is to be submitted. Is it possible to include this additional impurity within the same variation or is a separate variation necessary?

Answer (Human & Veterinary):

As the impurity is the reason for the upgrade of this variation to a type IB variation it will be assessed within the same variation and no separate variation is necessary.

4.21. Is it possible to use the worksharing procedure to harmonise different nationally approved stand-alone ("originators") product informations and if so how should they be submitted?

Answer (Human):

The CMDh has introduced the promotion of the worksharing procedure for the harmonisation of medicinal products in its workplan 2020. It is therefore encouraging applicants to make use of the worksharing procedure in these cases.

The member states (MS) have already agreed to accept worksharing in the situation where the intention is to harmonise different nationally approved, stand alone, SmPCs of the same MAH. The main prerequisite for these procedures is a harmonised product information as the outcome of the worksharing procedures.

Changes that are so far not approved in any of the member states are not accepted in these worksharing procedures for harmonization of the product information. They should be submitted as separate variations or worksharing applications including the respective documentation to support these changes and regular handling as possible grouped variation would be applicable (see Q&A 4.14 and 4.17).

To be able to handle these types of worksharing applications the CMDh has agreed the following set of conditions to be fulfilled:

To the Applicant:

- Choice of the Reference Authority: If the worksharing is based partly on MRP/DCP procedure and partly on nationally approved products, it is highly recommended that the RMS in the MRP/DCP is chosen as the Reference Authority for the worksharing. If only nationally approved products are involved the applicant may choose a preferred Reference Authority in the letter of intent. The CMDh will discuss these cases and select a Reference Authority for this procedure.
- Referring to eAF: "TYPE(S) of CHANGE(S)": The worksharing applications should be submitted as a single type II variation under the scope C.I.4.
- In the eAF: "PRECISE SCOPE AND BACKGROUND FOR CHANGE ": This section should include a clear statement that the variation applied for is a worksharing application for harmonisation of national product information and include an explanation and justification for this procedure.
- In the eAF "Present" and "proposed":
  - Present: The approved product information in the Reference Authority is sufficient (See also next bullet point on "(non)clinical overview";

  - Proposed: This would equal the proposed final, harmonised product information.

- Product Information: All changes compared to the approved product information in the Reference Authority are highlighted as tracked changes.
- (Non)Clinical overview: The (non)clinical overview should explain all changes to the content of the approved Product Information in the different member states (both additions and deletions) with regard to different information in SmPC sections 4.1, 4.2, 4.3, 4.4, 4.6, 4.8 and 5.1.
- The major changes – also applicable only for single MS - applied must be accompanied by the relevant documentation package, or justification.
- An inclusion of information in the SmPC of one MS, even if it is already approved in another MS, is still considered a variation and must be justified/ documented.

To the Reference Authority:

- The Reference Authority should evaluate and address all the proposed changes mentioned in the overview.
- These variation applications will follow the extended 120-day timetable.

Maintenance after the worksharing:

We also remind the MAHs of the Article 20 of Commission Regulation (EC) No 1234/2008 p 10:

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

4.22. How should I submit several changes to the pack size?

Answer (human and veterinary):

The introduction of a new pack size (i.e. additional to currently approved pack sizes) should be submitted as a variation under subindent B.II.e.5.a) according to the variations classification guidelines.

Range is defined from the smallest to the biggest approved pack size (not from '0') for the same pharmaceutical form and strength. The pack size equals to the number of units of the pharmaceutical form (e.g. tablets, sachets, ampoules, etc) contained per outer packaging. Pack sizes not included within this range are considered to be outside of the range.

For the addition of a new pack size where the number of units of the pack is **within the range** of the currently approved pack sizes for the strength and pharmaceutical form, applicants should submit a variation B.II.e.5.a).1 (IAIN).

For the addition of a new pack size where the number of units of the pack is **outside the range** of the currently approved pack sizes for the strength and pharmaceutical form, applicants should submit a variation B.II.e.5.a).2 (IB).

Several changes to the pack sizes always have to be submitted as grouped applications with a single change for each pack size classified according to the relevant sections of the classification guideline (see above).

5. Questions regarding the approval and implementation of variations

5.1. Is there a possibility for an appeal by the MAH in case of rejection of type IB or type II variations?

Answer (Human & Veterinary):

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/CVMP.

5.2. What is meant by "implementation" for Type IA variations?

Answer (Human & Veterinary):

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 IA_{IN} 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 (veterinary) 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 should normally be used in the next packaging run.

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 (Human & Veterinary):

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.

[1] For example the type IA_{IN} 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.

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

Answer (Human & Veterinary):

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 may be implemented by the applicant.

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' (human) or 'Date on which the package leaflet was last approved' (veterinary) be detailed in the printed version of the package leaflet?

Answer (Human & Veterinary):

For Type IA and IA_{IN} variations the "Date of revision of the text" (human) or "Date on which the package leaflet was last approved" (*veterinary*) will correspond to the implementation date (i.e. when the Company internally approves the revised product information) (see also Question 5.2).