EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Practical Questions and Answers to support the implementation of the Variations Guidelines[1] in the centralised procedure

1. Introduction

This Question and Answer (Q&A) document provides practical considerations concerning the implementation of the Guidelines of 16.5.2013 on the details of the various categories of variations, on the operation of the procedures laid down in Chapters II, IIa, III and IV of Commission Regulation (EC) No 1234/2008 and on the documentation to be submitted pursuant to those procedures (hereafter called 'Variations Guidelines'). The Q&A applies to all medicinal products for human use that apply for a variation or submit post-authorisation measure (PAM) data as of the 4th of August 2013.

The Q&A document should be read in conjunction with the Variations Guidelines and Commission Regulation (EC) No 1234/2008, as amended by Commission Regulation (EU) No 712/2012. The questions and answers in this document represent the view of the EMA. In case of doubt reference is given to the above-mentioned Guidelines and the Commission Regulation (EC) No 1234/2008.

This document provides a series of questions and answers to clarify procedural elements in relation to the implementation of the revised Guidelines. The questions are organised into the following themes:

- General Considerations
- New Classification Category C.1.11
- New Classification Category C.1.13
- Impact on post-authorisation measure (PAM) submissions

[1] Guidelines of 16.5.2013 on the details of the various categories of variations, on the operation of the procedures laid down in Chapters II, IIa, III and IV of Commission Regulation (EC) No 1234/2008 of 24 November 2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products and on the documentation to be submitted pursuant to those procedures

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2. General Considerations

The Variations Guidelines will apply as of 4th August 2013 coinciding with the entry into force of all changes introduced to the Variations Regulation (EC) No 1234/2008 by Commission Regulation (EU) No 712/2012. Therefore any submission as of the 4th of August 2013 will have to comply with the revised rules as set out in the Variations Guidelines and in this Q&A document.

For queries in relation to a specific centrally authorised product, Marketing Authorisation Holders (MAHs) are advised to raise these with their Product Team Leader (PTL).

For queries in relation to a specific medicinal product authorised through the MRP/DCP, applicants/MAHs are advised to liaise with the Reference Member State. For purely nationally authorised medicinal products, the applicants/MAHs are advised to contact the relevant national competent authority.

3. New Classification Category C.1.11: Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the risk management plan

3.1. What changes to my Marketing Authorisation Dossier are considered to fall within this category as a type II variation, C.I.11.b)?

The following changes are considered type II variations under category C.I.11.b):

Changes to conditions and obligations:

- Any changes to the Annex II D and E (including changes to timelines) proposed by the MAH;

Changes to RMP:

- Introductions of a new RMP outside another regulatory procedure;
- Addition or deletion of safety concerns (identified risks, potential risks, missing information), if submitted outside another regulatory procedure.
- Changes to agreed PASS Interventional and non-interventional protocols. For Category 3 post-authorisation studies, this applies only if there is an impact on section III.4.3 of the RMP (table containing objectives and timelines).

However, initial assessments of PASS protocols are considered to be covered by the procedure from which they originate and therefore fall outside of this category.

The procedure for review and agreement of non-interventional imposed PASS acc. to Art. 107n remains unaffected (see also Q&A on PASS).

3.2. When should I submit my RMP/RMP update as a type IA or type IB variation within the category C.1.11?

If changes to the conditions are implemented based on an agreed wording without any further changes, they can be submitted as a type IA, provided that no linguistic review of translations is required (e.g. removal of information, changes to timelines).If an update of the RMP core document is submitted in response to a request following signal detection, this would be a type IA variation if an agreed wording is implemented without further changes. Similarly, an update of the RMP in response

to a request following assessment of a protocol of a category 3 study is a Type IA variation if no additional information and/or further assessment is needed.

Updates of 'stand-alone' RMPs not mentioned under 2.1 or in the above paragraph are type IB variations.

3.3. Can I still submit an update of the RMP with other post-authorisation procedures?

A RMP update can be submitted as part of a procedure involving a change to an existing marketing authorisation (e.g. extension of indication, extension applications, new manufacturing process of a biotechnologically-derived product). Also, if a change to the RMP is necessary based on a renewal or a safety variation to update the Summary of Product Characteristics, Labelling or Package Leaflet, the RMP can be submitted within that procedure.

If final study results are submitted for assessment through a variation, and the outcome of the study leads to the need to update the RMP, this RMP update should be submitted as part of that variation.

A RMP update can be submitted together with a PSUR only when the changes to the RMP are a direct result of data presented in the PSUR.

The possibility to submit a RMP update together with a PSUR in the context of the EU single assessment of PSURs could only be envisaged where it concerns the same marketing authorisation holder and the same change(s) affect all RMPs. The principles for such update remain as described above.

In case an MAH wishes to include a RMP update together with a PSUR in the context of the EU single assessment, you are advised to contact the Agency in advance of the submission.

3.4. How will my RMP update be handled if submitted at the same time as a PSUR?

A RMP update can be submitted together with a PSUR only if the changes to the RMP are a direct result of data presented in the PSUR. In this case no stand-alone RMP variation is necessary.
Should the timing for submission of both documents coincide in a situation where the changes to the RMP are not a direct result of the PSUR, then the RMP update should be submitted as a stand-alone variation, under category C.I.11.

The possibility to submit a RMP update together with a PSUR in the context of the EU single assessment of PSURs could only be envisaged where it concerns the same marketing authorisation holder and the same change(s) affect all RMPs. The principles for such update remain as described above.

In case an MAH wishes to include a RMP update together with a PSUR in the context of the EU single assessment, you are advised to contact the Agency in advance of the submission.

4. New Classification Category C.1.13: Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority

4.1. What changes to my Marketing Authorisation Dossier fall within this Category?

After 4th of August 2013, all submissions of studies to the Agency concerning a marketing authorisation granted under the centralised procedure will have to be submitted as a type II variation application, unless otherwise specifically covered in the Annex to the Guideline on Variations. Studies are considered final reports of studies, including both non-clinical and clinical studies (interventional and non-interventional studies). Examples of such study results include clinical study reports (CSR) of both efficacy and safety studies as well as drug-drug interaction studies, results from toxicology studies, pharmacokinetic/pharmacodynamic studies, meta-analyses, studies to investigate the effectiveness of risk minimisation measures defined in the RMP, drug utilisation studies as well as final registry reports. This includes submission of study results related to paediatric population in line with Article 46 of Regulation 1901/2006.

Excluded from this scope are results of imposed non-interventional safety studies covered by the Art 107q of the Directive 2001/83/EC and submissions of final study results in support of a variation application to update the product information or annex II of the marketing authorisation, which should be done under the respective specific category (e.g. C.1.3, C.1.4, C.1.6 and C.1.11), extension applications, renewals, annual renewals or annual re-assessments.

Likewise, results including reports from bioequivalence studies to support quality changes to the marketing authorisation should be submitted under the applicable variation category for quality changes.

In case of questions whether or not a submission falls under variation category C.1.13, MAHs are advised to contact the Agency in advance of the submission.

4.2. Can I introduce an update to the product information with a C.1.13 variation?

Applications for C.1.13 variations should not include proposals for an update of the product information or annex II of the marketing authorisation. Variation category C.1.13 only applies if the application is not covered elsewhere in the Annex to the Guideline on Variations. Variation applications concerning changes in the Summary of Product Characteristics (SmPC), Labelling or Package Leaflet due to new quality, preclinical, clinical or pharmacovigilance data should continue to be submitted under variation category C.1.4. MAHs should also consider other relevant variation categories covering an update to the Annexes of the marketing authorisation. As no changes to the Annexes are expected under this category, MAHs are also advised that C.1.13 cannot be used to introduce minor administrative updates, such as changes to local representatives or QRD template updates.

However, where the Agency's Committees' assessment of the data submitted as a C.1.13 variation leads to changes of the product information, these changes are covered by this variation category.

4.3. Do I need to group variation applications concerning the submission of final study results to support an update of the product information?

If study results are submitted in support of a proposal to update the product information or annex II of the marketing authorisation, MAHs should file a single variation application under the applicable variation category (e.g. C.1.3, C.1.4, C.1.6 or C.1.11), i.e.in such cases there is no need to group a C.1.13 with any of the mentioned categories.

4.4. How will ongoing/pending assessments of study results submitted before 4th of August 2013 be handled?

Study results submitted before 4th of August 2013 will be assessed according to the respective applicable procedure prior to the implementation of the Variations Guidelines. If the need for changes to the marketing authorisation arises from the assessment of these data, MAHs should submit a variation application in line with the outcome of the assessment using the relevant category.

5. How will the PRAC be involved in my variation assessment?

The PRAC will remain involved in all post-authorisation procedures where an RMP (update) is submitted as already outlined in the pre-authorisation procedural guidance on RMP (insert hyperlink) by providing advice on the RMP to the CHMP.

Similarly, variation submission containing a stand-alone RMP under C.1.11 or non-interventional PASS results only will be assessed by the PRAC. Based on the PRAC assessment, the CHMP will adopt an Opinion or RSI, as applicable, hence the overall time tables for the relevant procedure will not change (same submission dates/start dates as for CHMP).

6. Impact on post-authorisation measure (PAM) submissions

6.1. What will change for my submission in response to a PAM after 4th of August 2013?

MAHs should continue to submit data post-authorisation as requested by the Agency's Committee(s) under the appropriate legal framework. Following the implementation of the amended Guideline on Variations, some of the data so far submitted as PAMs will henceforth be required to be filed as a variation application. MAH should carefully review if their data fall under any of the categories of the Annex to the Guideline on Variations, in particular with a view to the new variation categories C.1.11 and C.1.13.

PAM types concerned include:

- Annex II conditions (ANX) and specific obligations (SOB), if submitted to fulfil or change the condition/obligation as specified in Annex II.D and II.E to the marketing authorisation will need to be submitted as C.I.11 variation applications
- Additional Pharmacovigilance (PhV) activity in the RMP (MEA), if concerning the submission of a final study report and/or update to the RMP, should be submitted via a C.I.11 or C.I.13

variation application (unless submitted in support of a proposal to update the product information of the marketing authorisation, in which case the applicable variation category should be selected (e.g. C.1.3, C.1.4, or C.1.6).

For PAM submissions or in case a procedure such as a variation addresses an outstanding PAM, MAHs should indicate in the cover letter the PAM type and area (clinical, non-clinical , pharmacovigilance, quality). The cover letter should contain the template table to facilitate submission and registration indicating that the PAM submission does not fall into any variation category. In case of doubt, it is advised to contact the Agency in advance of the PAM submission. The Agency will check PAM submissions with respect to the Variations Guidelines and will reject any PAM submission that should be filed as a variation application.

6.2. What will change for my submission in line with Article 46 of Regulation 1901/2006 after 4th of August 2013?

Following the implementation of the amended Variations Guidelines, final study results submitted in line with Article 46 of Regulation 1901/2006 should be filed under C.I.13, unless changes are proposed to the product information or annex II of the marketing authorisation, in which case the specific classification category should be used . However this has no impact on the requirement related to the publication of studies falling under the Article 46.