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Patient Health Protection

Practical questions and answers to support the implementation of the variations guidelines¹ in the centralised procedure

1. Introduction

This question and answer (Q&A) document provides practical considerations concerning the implementation of the Guidelines 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 (hereafter called 'variations guidelines').

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
- revised classification category C.I.8
- new classification category A.8

¹ Guidelines 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 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



2. General considerations

The variations guidelines 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.

For queries marketing authorisation holders (MAHs) are advised to raise these with their Procedure Manager (PM) or if these arise during the pre-submission phase before a PM has been appointed to submit them to the dedicated pre-submission query service (either IAquery@ema.europa.eu, IBquery@ema.europa.eu, IIquery@ema.europa.eu).

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:

- changes to the conditions to the MA as described in Annex II D and E not mentioned under section 3.2.1 below (type IB category) proposed by the MAH;

Changes to RMP:

- introduction of a new RMP outside another regulatory procedure;
- addition or deletion of safety concerns (identified risks, potential risks, missing information) not previously assessed or requested by a competent authority.
- changes to agreed category 3² post-authorisation studies if there is an impact on section III.4.3 of the RMP excluding changes to due dates

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](#)).

Information on category 4 studies listed in the RMP can be updated in the context of any other RMP update as it is not expected that this information is presented in a variation on its own.

² Category 1 or 2 studies (Specific Obligations or Conditions) are already covered by the first bullet point

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

3.2.1. Type IB category

The following changes would be considered as type IB variations:

- Updates of 'stand-alone' RMPs³ not mentioned under 3.1 are type IB variations.
- addition of a safety concern assessed and requested by the competent authority in a previous procedure.
- changes to due dates for category 1, 2 or 3 studies in the RMP and/or the Annex II, as relevant.

3.2.2. Type IA_{IN} category

The following changes would be considered as type IA_{IN} variation

- implementation of changes to the conditions based on an agreed wording without any further changes, provided that no linguistic review of translations is required (e.g. removal of information, changes to timelines).
- update of the RMP core document in response to a request following signal detection, provided an agreed wording is implemented without further changes.
- update of the RMP in response to a request following assessment of a protocol of a category 3 study if no additional information and/or further assessment is needed.

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. 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.

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

³ 'stand-alone' RMPs are variations where the update of the RMP is not consequential to another change such as update of the PI and therefore the only scope of the procedure.

3.4. How will my RMP update be handled if submitted at the same time as a PSUR single assessment (PSUSA)?

As an interim measure, submission of RMP updates cannot be accepted together with the PSURs of medicinal products (centrally and/or nationally authorised) subject to a PSUR EU single assessment (PSUSA). MAHs should update their RMP through another upcoming procedure affecting the RMP. Alternatively MAHs should submit a separate variation to update their RMP, after finalisation of the PSUR single assessment procedure.

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 or listed below in section 4.2. 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.

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. What kind of studies DO NOT fall within this category?

Excluded from the scope of category C.1.13 are

- results of imposed non-interventional safety studies covered by the Art. 107q of the Directive 2001/83/EC
- 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.
- submission of study results related to paediatric population in line with Article 46 of Regulation 1901/2006. Submissions pursuant to Article 46 should continue to follow the procedure for post-authorisation measures, unless the MAH concludes that changes to the PI are warranted based on the data submitted. In such cases, the relevant variation should be submitted.
- studies in the context of an environmental risk assessment (ERA). These are expected to be assessed during the initial marketing authorisation or relevant post-marketing procedures (e.g. extension of indication, extension applications). In the exceptional case that ERA study results are provided stand-alone, they should be submitted as a type IB C.1.z variation.

- 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.

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

Applications for C.1.13 variations must not include proposals by the MAH 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.

4.4. 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.

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](#) by providing advice on the RMP to the CHMP.

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.1.11 variation applications.
- additional Pharmacovigilance (PhV) activity in the RMP [MEA (category 3 studies)], if concerning the submission of a final study report, should be submitted via a C.1.13 variation application OR, if only concerning an update to the RMP via a C.1.11 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.

7. Revised classification category C.1.8: introduction of, or changes to, a summary of pharmacovigilance system for medicinal products for human use

As of 1 February 2016, changes to the summary of the pharmacovigilance system – changes in QPPV (including contact details) and/or changes in the Pharmacovigilance Master File (PSMF) location are to be notified to the authorities through the [Art 57 database](#) only without the need for any further variation. From that date MAHs are not required to notify EMA or national competent authorities (as applicable) of changes to the QPPV or PSMF data by submitting a type IA_{IN} variation.

Upon a change in the QPPV or location of the PSMF, the Art 57 database should be updated by the MAH immediately to allow continuous supervision by the Competent Authorities.

References

- [News Item: Regulatory information – Green light for reliance on Article 57 database for key pharmacovigilance information on medicines for human use in Europe](#)
- Art 57 [Reporting requirements for Marketing Authorisation Holders](#)

8. New classification category A.8: changes to date of the audit to verify GMP compliance of the manufacturer of the active substance

According to the variations guidelines, this variation does not apply when the information has been otherwise transmitted to the authorities (e.g. through the so-called “QP declaration”). What is meant by “otherwise transmitted”? Otherwise transmitted means that the information has been provided to

the competent authorities within any formal regulatory procedure e.g. renewals, variations. In these cases, no separate variation application for the change in the audit date has to be submitted. However, the change has to be mentioned in the scope of the application form as well as under "present/proposed" but not in the section "variations included in this application."

8.1. What is meant by manufacturer of the finished product under documentation requirement 1?

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 B.II.b.1.

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