

<p style="text-align: center;">National type II variations to module 3 Clarification of the assessment strategy 15.12.2010</p>
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1. Introduction

National type II variations currently require an important part of the evaluation time of the quality assessors. This is caused by the considerable number of applications (about 250 per year) but also by the assessment time attributed to each application.

The total evaluation time of these national type II variations to module 3 has already been reduced by other initiatives:

- The implementation of the classification system of the revised European Regulation EC/1234/2008 in the national legislation on 01/01/2010 has significantly reduced the number of type II variations.
- The MRP-like procedure for type II quality variations facilitates easy approval of national applications that have already been approved in other Member States. It is a purely national initiative and is only applicable when the variation has already been approved in another Member State.

The worksharing procedure, as described in article 20 of Regulation EC/1234/2008, can also contribute to the evaluation time needed for national type II variations. This procedure requires that the variation is simultaneously submitted to the authorities of the different concerned Member States. A reference authority performs the evaluation and informs the other authorities on the outcome.

The strategy that is described in this document provides an additional contribution to the rationalisation framework. Its objective is to optimise the procedure for the type II variations to module 3 for which a national assessment remains necessary.

The optimised strategy will be implemented on 15/12/2010.

2. Clarification of the strategy

Assessment of the documentation presented in support of analytical type II variations often leads to an important number of questions, part of which are not related to the changes proposed in the variation application. This may significantly delay the approval of the variations. Moreover, evaluation of the responses contributes in a significant way to the workload of the assessors.

Questions not related to the proposed changes are partially caused by insufficient transparency in the application form on the scope of the variation or the changes proposed. On the other hand, assessors consider type II variation procedures as an opportunity to give recommendations on compliance of the quality dossier with the current standards.

This document proposes a strategy to avoid delays in the approval of variations due to questions not related to the proposed changes, without eliminating the advisory role of the

assessor on the general status of the quality dossier. Implementation of the strategy will be beneficial for both industry and FAMHP if both parties follow the recommendations.

A difference is made between:

- (a) type II variations with a specific and clearly defined scope,
- (b) general updates of the quality dossier, and
- (c) changes from part II format to module 3 format without changes in content.

The variation application form should be clear on the category that is applicable.

a) Type II variations with specific scope

To allow assessors to focus their evaluation on the changes, the application form for the variation should be fully transparent on the scope of the variation, the changes proposed and the consequences for the supportive documentation.

A focussed assessment is only possible when the proposed changes are clearly related to the scope of the variation. For example, where the scope of the variation is to introduce in module 3.2.P a new test method for impurities, it is clear that there are potential changes in the specifications, analytical methods, validation reports of those methods, discussion on the impurities and stability reports.

However, it is not considered appropriate to introduce a list of unrelated changes in a single type II variation. In that case, a combination of different type I and/or type II variations should be introduced (each with a clear scope and list of changes). Where applicable, the variations can be grouped as foreseen in Article 7 of Commission Regulation 1234/2008.

Where comparison between the current and proposed situation becomes too complex an application for a general update of module 3 can be considered (see point b).

The supportive documentation should contain only the adapted versions of all module 3 sections that are affected by the proposed changes. Presentation of an annotated and a clean version where changes in each section can be identified immediately, facilitates the efficient handling of the dossier. Additional sections of module 3 or a complete module 3 can also be included in the supportive documentation, for example when the applicant uses the opportunity of the type II variation to change the format of the quality dossier from the of NTA format (part II) to the CTD format (module 3). However, in this case the application form should clearly indicate that no other changes to the content are introduced than those described in the application form.

Validation at the FAMHP:

Where the application form of a type II variation is insufficiently clear on the scope, the proposed changes and the sections of which the content is affected, the application will be considered as invalid (at the division marketing authorisation POST, after uploading of the dossier).

The applicant is then requested to present, within 15 working days (as foreseen in Art 10 of RD 14/12/2006):

- a) an appropriate application form for a type II variation, or
- b) an application for a general update of module 3 (see point b) as well as an amended payment form, corresponding to a general update of module 3 (see website FAMHP for fee update module module 3).

Quality Assessment at FAMHP:

Where the application form and the supportive documentation comply with what is described above, the assessment will be focused only on the proposed changes. Questions (for which a response is required during the procedure) will only be raised on issues related to the proposed changes.

Although it is not the intention to perform a complete evaluation of supportive documentation not directly related to the proposed changes, other points of concern may be arising from the assessment. Assessor's concerns that are not related to the proposed changes will be included in a separate list that should be considered as a recommendation to the applicant. Those concerns should not be cleared during the variation procedure. It is the applicant's responsibility to investigate how those recommendations can be used in the maintenance programme of module 3 (autocontrol). This gives the applicant flexibility, for example to combine those recommendations with requests from other member states where the product is marketed.

During the assessment of subsequent variations or updates, the FAMHP assessor can ask feedback on the follow up that was given on the recommendations. However, it is not the intention that the FAMHP organises a systematic follow-up of those recommendations. This is considered within the responsibility of the MA holder (autocontrol).

In exceptional cases and where there is a potential serious risk to public health, the FAGG can request that issues that are not necessarily immediately related to the proposed changes are cleared during the procedure or that a clear commitment is given during the procedure

b) General update module 3

Where changes through the complete module 3 are introduced or where a comparison between the current and the proposed situation becomes too complex, a general update of module 3 can be introduced.

Updates of module 3 in the revision-validation procedure are also considered as general updates of module 3.

Validation at the FAMHP:

In the section of the application form that describes the "scope", it should be clearly indicated that a general update of module 3 is proposed.

Quality Assessment at FAMHP:

In this case, the dossier will be fully assessed. Questions raised are to be addressed during the procedure.

c) Changes from part II to module 3 without changing the content

A third possibility is an application where the applicant presents a module 3 for which the content fully corresponds to a previously approved part II.

Validation at the FAMHP:

In this case the application form (sections "scope") should clearly confirm that the content of the quality dossier is not affected.

Quality Assessment at FAMHP:

In this case, no assessment is required.

3. Recommendations to the applicants

In the application form ("scope" section), it should be clearly indicated whether the application is:

- (a) a type II variation (with a specific and clearly defined scope),
- (b) a general update of the quality dossier
- (c) a change from the part II format to the module 3 format without changes in content

If the category is not clear, this can delay the validation of the application.

The level of assessment is dependent on the category.