



EUROPEAN MEDICINES AGENCY  
SCIENCE MEDICINES HEALTH

30 March 2012  
EMA/CHMP/CVMP/QWP/586330/2010  
Committee for Medicinal Products for Human Use (CHMP)

## Questions and answers on post approval change management protocols

Draft agreed by CHMP / CVMP Quality Working Party	9 September 2010
Adopted by CHMP for release for consultation	23 September 2010
Adopted by CVMP for release for consultation	14 October 2010
End of consultation (deadline for comments)	28 February 2011
Agreed by CHMP / CVMP Quality Working Party	2 February 2012
Adopted by CVMP	8 March 2012
Adopted by CHMP	15 March 2012
Date for coming into effect	1 October 2012

Keywords	Post approval change management protocol; Variation; Control strategy
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# Use of Post Approval Change Management Protocols

## 1. Introduction:

The concept of post approval change management protocols has been introduced in the EU through the Commission's 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) that supports the Variations Regulation (Commission Regulation (EC) No 1234/2008).

This Questions and Answers document sets some general principles about the content and future use of these protocols and will be updated in the light of more experience, particularly for biological products.

## 2. Scope:

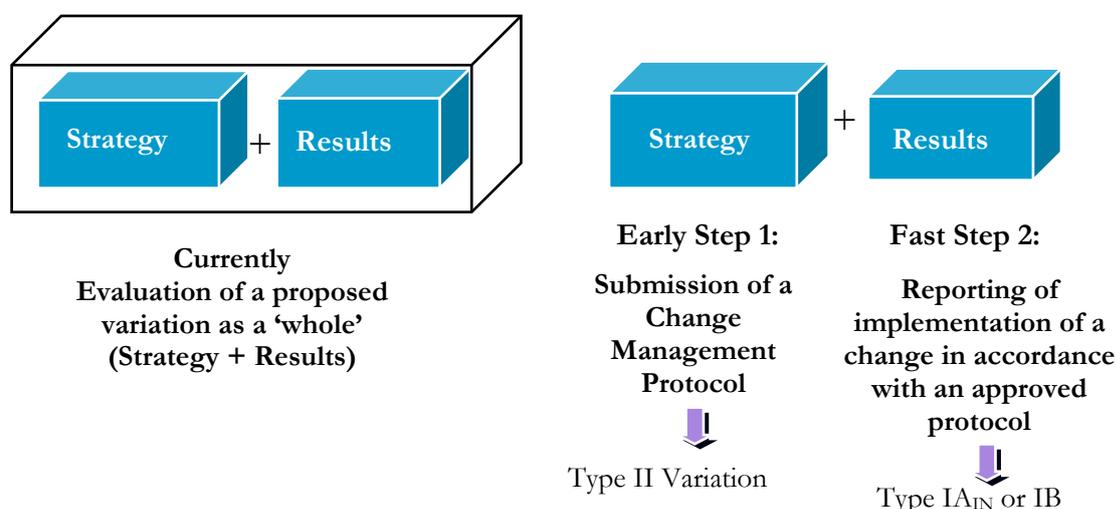
This Questions and Answers document is intended to apply to all medicinal products for human and veterinary use including biotechnological or biological products. It applies to all types of products, irrespective of whether a traditional or enhanced Quality by Design (QbD) approach has been used for product development. The use of Post Approval Change Management Protocols is optional.

## 3. What is a Post Approval Change Management Protocol?

A post-approval change management protocol describes specific changes that a company would like to implement during the lifecycle of the product and how these would be prepared and verified. It is a step-wise approach in the assessment of changes, which allows an early evaluation of the strategy for the change and a later separate evaluation of the data produced based on the agreed strategy (Figure 1). Such a stepwise approach is expected to lead to faster and more predictable implementation of changes post-approval, since the MAH will have obtained agreement from the Regulatory Authorities about the proposed strategy and tests to verify the effect of the change on product quality.

Typically the variation category designated for reporting changes under an approved post approval change management protocol is at least one category lower than would normally be the case.

**Figure 1: Post Approval Change Management Protocols**



## 4. What should be in the content of a post approval change management protocol?

In general, in order to support the proposed change, the company should submit all relevant information that can demonstrate that it has acquired adequate knowledge to prepare and manage the impact of the change.

The content of the protocol could include the following, depending on the nature of the change:

- Justification that there is a recognised future need for the specific change within a reasonable timeframe and that adequate knowledge has been acquired to define criteria to appropriately evaluate and manage the change for the specific product concerned;
- A detailed description of the proposed change. The differences with what is already approved should be clearly highlighted (preferably in a tabular format). Depending upon the nature of the change, it should be demonstrated, preferably with data from development or pilot scale studies, that the proposed approach is feasible. If only lab-scale data are provided the potential scale up effect should be discussed;
- Risk assessment of the impact of the change on product quality. This should include identification of the potential risks and detailed strategy of how these risks will be mitigated or managed;
- Discussion on the appropriateness of the approved control strategy to identify and manage these risks and, if required, description of the additional controls that might be needed to be put in place. This should take into consideration the extent of the change and therefore the potential impact on the quality of the active substance and/or finished product, as appropriate;
- Description of the studies to be performed, and the test methods and acceptance criteria that will be used to fully assess the effect of the proposed change on product quality<sup>1</sup>. The applicant should justify the appropriateness of the methods proposed to assess the impact of the proposed change. Data from development or pilot scale studies can provide assurance about the relevance and adequacy of the proposed tests;
- For biologics, the approach to be used to demonstrate the comparability of the pre- and post-change product;
- A plan for stability studies should be included, if appropriate;
- Commitment to update the approved protocol, if this becomes invalid, due to significant changes to the proposed test methods/acceptance criteria or a significant body of new knowledge or new regulatory requirements;
- In case that the protocol describes several changes, a justification showing that how the changes are related, and that a simultaneous review under a single protocol is meaningful;
- For chemical medicinal products, a proposal of how the implementation of the change will be reported to the relevant competent authorities using the existing variation procedures, e.g., as a Type IA / IAIN variation (implemented prior to notification) or Type IB variation (requires approval before implementation);

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<sup>1</sup> Whenever a particular change is investigated it should be evaluated against the specified acceptance criteria in terms of the relevant registered specification(s) and analytical methods at that point in time. It is recognised that these tests and limits may have changed since the original protocol was presented and accepted. However, the protocol will still remain valid provided the changes to the tests and limits are minor in nature and therefore do not fundamentally impact the basis for the original protocol and have already been formally registered and, where relevant, assessed and approved.

- If a Type IA/ IAIN variation has been chosen, then the conditions that need to be fulfilled by the marketing authorisation holder (MAH) prior to the implementation of the change, as well as a description of the amount and level of detail of the data to be provided, need to be clearly stated;
  - If a Type IB variation has been selected, then a description of the amount and level of detail of the data to be provided should be included;
- For biological medicinal products, in accordance with the Variations Classification Guideline, the reporting will always be made as a Type IB variation.

If this is not the case, or if there are other fundamental changes to the protocol, they will need to be separately updated as part of a Type IB variation before the change can be notified. However, in the event that there are minor changes to an approved protocol that has already been agreed to be notified as a Type IA (annual or immediate), where necessary, it will be possible to include the minor changes to the protocol at the same time as the submission to implement the change.

These will need to be notified as Type IB variations and the change cannot be implemented prior to approval.

## **5. What is the mechanism for the submission and evaluation of a Post approval Change Management Protocol?**

A post approval change management protocol may be included in an original marketing authorisation application or (line) extension application, or may be submitted subsequently as a stand alone variation. The Variations Classifications Guideline includes specific scopes for the introduction (Change no. B.1e.2) or deletion (Change no. B.1e.3) of a protocol for the active substance and the finished product (introduction B.2.g.2) (deletion B.2.g.3).

When submitted as part of the original marketing authorisation or a (line) extension application, the evaluation of a post approval change management protocol will follow the rules of procedure applicable to the actual marketing authorisation or extension application.

When submitted post approval, the evaluation of a post approval change management protocol will follow the rules of procedure applicable for all Quality Type II variations with a 60 days timetable.

A change to an already approved protocol will be processed as a Type IB variation, unless it fundamentally changes the content of the protocol. In the later case, the submission of a new protocol would be required. This is very relevant for biological/biotech products where comparability principles apply.

## **6. How will the change be implemented after all the studies described in the approved protocol have been performed?**

A prerequisite for the implementation of a change described in an approved protocol is that all studies described in the protocol have been performed, and the results of the studies comply with the predefined criteria set out in the protocol.

In all cases, a justification that the approved protocol is still valid should be provided, together with the procedure number of the application that led to the approval of the protocol.

In the event that any of the relevant specifications (limits or analytical methods) that are to be used for the evaluation have changed in a minor way since the original protocol was accepted, provided the

changes have in the interim been formally registered, there is no requirement to submit an updated protocol before the change is notified.

However, any changes to the specifications should be clearly highlighted as part of the reporting variation. If this is not the case, or if there are other changes that fundamentally impact the basis of the original protocol, the protocol itself should be formally updated before the change is notified (Type IB variation) or a new protocol should be submitted (Type II variation). Minor deviations to the protocol may be reported and justified in the variation (Type IB) submitted in support of the implementation of the change. However, the change(s) cannot be implemented prior to approval.

The implementation of a change in accordance with an already approved protocol can be made via a Type IAIN or Type IB variation (Change no. B.V.c.1 of the Variations Classification Guideline) depending on whether it requires the evaluation of supportive data.

If a Type IAIN variation has been agreed during the evaluation of the protocol, then the applicant may implement the change without any further regulatory evaluation prior to its approval. A notification of the implementation should immediately be sent to the relevant competent authority.

If a Type IB variation has been agreed during the evaluation of the protocol, or is mandatory, as is the case for biological medicinal products, then the applicant may only implement the change upon receipt of a positive notification from the relevant Competent Authority. In both cases the respective timelines and procedural requirements for Type IA and IB variations apply.

If the same protocol has been submitted for several products changes, the implementation of the change can be made using the existing Grouping and Worksharing procedures.

## **7. Can applicants submit post approval change management protocols for any type of change?**

The types of changes that would benefit from, and consequently could be included in such a protocol, depend on the complexity of the product and its manufacturing process, as well as the understanding that the company has gained about them. It is not possible to set a priori a list of acceptable changes since it depends on the type of the products, and the type of information presented in the dossier. However, protocols should be specific to a product and should therefore not name multiple products, although the proposed change(s) and management strategies may be applicable to other products and processes.

In order for a change to be submitted and accepted as part of a protocol, the company should demonstrate suitable scientific knowledge and understanding of the active/product and the process, coupled with the use of an appropriate quality risk management and an efficient pharmaceutical quality system.

Consequently, it is strongly recommended that companies submit post approval change management protocols only for those changes that they are highly likely to implement and whose feasibility has already been investigated and is supported by relevant data.

For a biological medicinal product where non-clinical/clinical data are needed as part of the comparability exercise, a post approval management protocol will not be feasible.

Changes that should not be submitted in a post approval change management protocol include any change that would result in a (line) extension to the original marketing authorisation.

## **8. Can a post approval change management protocol cover multiple changes?**

It is possible to cover more than one change in a single protocol provided that they are directly related and a simultaneous review under a single protocol is meaningful. A justification should be provided in the protocol.

Depending upon the specific nature of the change(s), it is also possible for the content of a protocol to be applied on more than one occasion, e.g., new manufacturer of active substance starting material. However, this will depend upon successful implementation each time, in line with the protocol. In addition, the possibility will need to be transparent and therefore, if applicable, clearly stated in the protocol itself.

## **9. Where should the requested documents (description of change/change management protocol) be placed in the application?**

The protocol should be included in the marketing authorisation application as part of the Regional Section 3.2.R of Module 3 (or in Part 2.G for veterinary applications). The relevant section(s) of Module 3 (or Part II for veterinary), affected by the proposed change, should cross refer to the protocol.

At the time of submission of the protocol (Type II) only 3.2.R/2.3.R (or Part 2.G for veterinary) is affected. Update of the relevant section(s) of Module 3 (other than 3.2.R) (or Part II for veterinary) is done with the Type I variation to implement the protocol.

A listing of the approved protocols should also be provided and maintained in Module 3.2.R (or Part 2.G for veterinary). This should include a listing of all the protocols with a description of the change, the proposed reporting category and a reference to the relevant section in Module 3 (or Part 2 for veterinary).

## **10. Are post approval change management protocols applicable to all types of applications?**

Change Management protocols are applicable to all types of applications, irrespective of the development approach that has been followed, i.e., traditional or enhanced. However, it is expected that if the applicant has applied Quality by Design principles during product development, then an increased product and process understanding is achieved, thus making it easier to predict the impact of a change on the active substance or finished product quality.