EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

27 October 2010
EMA/CHMP/CVMP/QWP/586330/2010

Questions and answers on post approval change management protocols

Draft

Draft Agreed by QWP	September 2010
Adoption by CHMP for release for consultation	23 September 2010
Adoption by CVMP for release for consultation	14 October 2010
End of consultation (deadline for comments)	28 February 2011

Comments should be provided using this template. The completed comments form should be sent to QWP@ema.europa.eu

Keywords	*Post approval change management protocols; Variation; Control strategy*

7 Westferry Circus ● Canary Wharf ● London E14 4HB ● United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7418 8595
E-mail info@ema.europa.eu **Website** www.ema.europa.eu

Introduction

The concept of post approval change management protocols has been introduced in EU through the 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 that supports Variations Regulation EC (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.

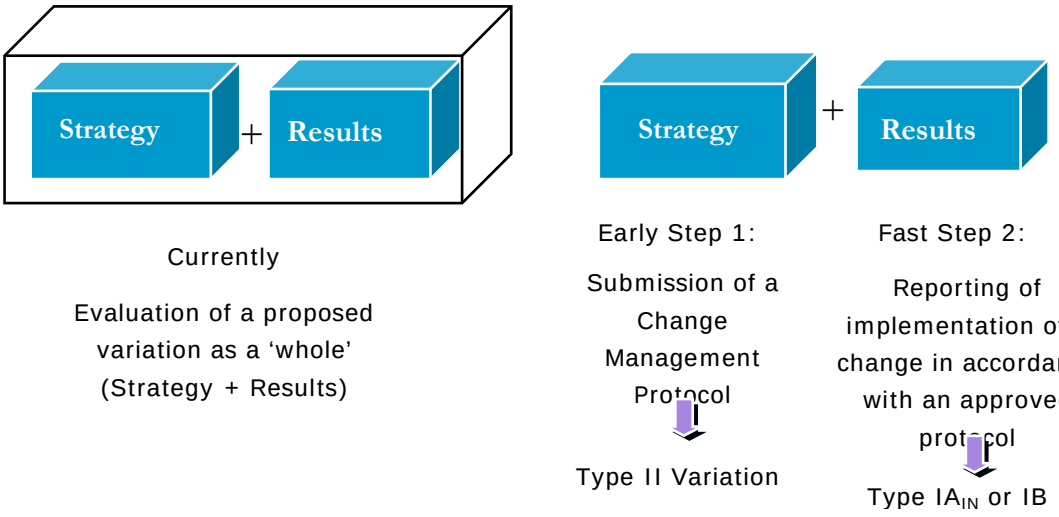
Question 1. What is a Post Approval Change Management Protocol?

Answer:

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 step wise 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.

Such a protocol would include a description of the proposed change, risk assessment of the impact of the change on product quality, safety and clinical performance, description of the methods used to evaluate the effect of the change, description of the studies to be carried out and the acceptance criteria based on which the effect of the proposed change will be evaluated. The protocol should also include how the changes will be reported to the Regulatory Authorities post approval using the existing variation procedures e.g. as Type IAIN or IB variations.

Figure 1: Post Approval Change Management Protocols



Question 2. Content of a post approval change management protocol?

Answer:

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 depending on the nature of the change:

- Justification that there is a definite recognised future need for the specific change, within a reasonable timeframe, and that adequate knowledge has been acquired to appropriately evaluate and manage the change for the specific product concerned. Justification should also be provided for the proposed evaluation strategy.
- 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 identified, 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.
- 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. 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.
- Commitment to update the approved protocol, if needed, in the light of changes to the proposed test methods/acceptance criteria or any new knowledge acquired during the manufacture of the product, or new scientific developments or new regulatory requirements.
- In case that the protocol describes several changes, a justification showing that they are directly linked and interrelated.

- 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_{IN} (implemented prior to notification) or Type IB variation (require approval before implementation).
  - If a Type IA_{IN} variation has been chosen then the conditions that need to be fulfilled by the manufacturer (MAH) prior to the implementation of the change on site 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.

Question 3. Submission and evaluation of a Post approval Change Management Protocol

Answer:

A post approval change management protocol may be included in an original Marketing Authorisation Application, or may be submitted subsequently as a stand alone variation. The 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).

The evaluation of a post approval change management protocol will follow the rules of procedure applicable for all Quality Type II variations, while a change to an already approved protocol will be processed as a Type IB variation, B.I.e.z (active substance) and B.II.g.z (finished product) respectively.

Question 4. How will the change be implemented after the protocol is approved? Will deadlines for implementation be set by the CxMP?

Answer:

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.

The implementation of a change in accordance with an already approved protocol could be done via a Type IA_{IN} 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 IA_{IN} variation has been agreed during the evaluation of the protocol, then the applicant may implement the change without any further regulatory evaluation prior 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, 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

It is also possible that the results of the studies show that the studies approved in the protocol need to be redesigned. In this case the protocol needs to be amended and a revised protocol needs to be submitted to the Authorities for approval (Type IB variation).

Question 5. Can the applicants submit post approval change management protocols for any type of change?

Answer:

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 be worded in a generic way for different products. 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 substance/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.

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.

Question 6. Can a post approval change management protocol cover multiple changes?

Answer:

It is only possible to cover more than one change in a single protocol if all the changes are directly related and interdependent. A justification should be provided in the protocol. Separate protocols should be submitted in all other cases.

Question 7. Where should the requested documents (description of change/change management protocol) be placed in the application dossier?

Answer:

The protocol should be included in the original marketing authorisation application as part of Module 3 in the relevant section of the CTD affected by the proposed change.

A summary of the agreed protocols should also be provided in Module 3.2.R. 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 CTD section.

For Veterinary applications in the Notice To Applicants format the information should be included in the relevant section of Part 2.

Question 8. Are post approval change management protocols applicable to all types of applications?

Answer:

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.