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# Questions and answers on post approval change management protocols for veterinary medicinal products

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For veterinary medicines this Questions and Answers document replaces the Questions and answers on post approval change management protocols (EMA/CHMP/CVMP/QWP/586330/2010).

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# Questions and answers on post approval change management protocols for veterinary medicinal products

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# 1. Introduction

The concept of post approval change management protocols (PACMPs) was 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).

The requirements for variations to veterinary medicinal products were amended via Regulation (EU) 2019/6 and Commission Implementing Regulation (EU) 2021/17, and the associated Variations Guidelines (EMA/CMDv/7381/2021) were revised in 2021.

This Questions and Answers document describes general principles regarding the use and content of PACMPs for veterinary medicinal products.

# 2. Scope

This Questions and Answers document is intended to apply to all medicinal products for veterinary use, irrespective of whether a traditional or enhanced Quality by Design (QbD) approach has been used for product development. The use of a PACMP is optional. A PACMP can only be submitted for a quality change which does not require clinical and/or non-clinical data assessment.

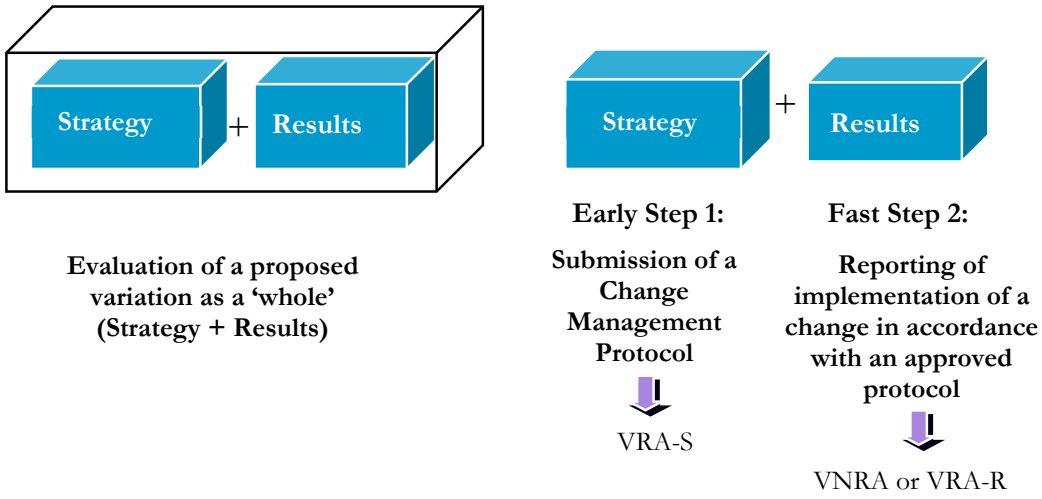
# 3. What is a PACMP?

A PACMP describes specific changes that a company would like to implement during the lifecycle of the product and how these would be prepared and verified. A PACMP is a protocol to which the future implementation of the concerned change(s) and data package has to comply. 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.

A PACMP may be included in an initial marketing authorisation application (MAA) and should be clearly defined in the MAA as such or may be submitted subsequently as a stand-alone variation requiring assessment (VRA). The Guidance on the details of the classification of variations requiring assessment (EMA/CMDv/7381/2021) includes specific scopes for the introduction of a PACMP (F.I.e.2.a, F.II.g.2.a), changes to an approved PACMP (F.I.e.2.b, F.II.g.2.b) and implementation of changes foreseen in a PACMP (F.I.e.2.c, F.II.g.2.c) for the active substance and the finished product.

Typically, the variation category designated for reporting changes under an approved PACMP is one category lower than would normally be the case. The Commission Implementing Regulation (EU) 2021/17 establishing a list of variations not requiring assessment (VNRA) includes variation category B.3.h) that is intended for the deletion of an approved PACMP for the active substance and the finished product. It also includes specific scopes for the implementation of changes foreseen in an approved PACMP for the active substance (VNRA B.8) or finished product (VNRA B.42) when implementation requires no further supporting data, as well as for minor changes to an approved PACMP of the active substance that do not change the strategy defined in the PACMP (VNRA B.12.g).

**Figure 1: Post Approval Change Management Protocols (PACMPs)**




## 4. What should be in the content of a PACMP?

In general, to support the proposed change(s), the applicant should submit all relevant information that can demonstrate that adequate knowledge to manage the implementation of the change(s) has been acquired. Consequently, the PACMP should unequivocally define which changes will be made, which studies will be performed, which supporting data will be provided, and when studies and data will be considered acceptable.

The content of the PACMP should include the following, depending on the nature of the change:

- Justification that there is a recognised future need for the proposed change(s), that it is feasible to implement within the planned 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(s) which is clear, sufficiently detailed, and complete, presenting in a granular way all changes that are in scope of the PACMP.
- The differences compared to what is already approved should be clearly highlighted (preferably in a tabular format). This description of the proposed change(s) should facilitate cross-reference to the present/proposed table in the future implementing variation.
- The planned approach to demonstrate the comparability of the pre- and post-change product should be described in detail;
    - A risk assessment of the impact of the change on product quality should be provided. This should include identification of the potential risks and detailed strategy of how these risks will be mitigated or managed. Based on the risk assessment, 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 and acceptance criteria proposed to assess the impact of the proposed change.

- The PACMP should define the strategy and criteria for demonstrating comparability of the pre- and post-change product. In every case, the planned approach to demonstrate comparability is expected to include comparison of quality control (QC) batch release data. Where relevant, comparability testing should also include extended physicochemical characterisation and/or additional biological characterisation via functionality and/or potency assays. The actual comparability data would normally be provided in the implementing variation.
- Where relevant, a process validation protocol should be provided. Supportive data (e.g. from development, pilot or commercial scale studies) may be required to provide assurance about the relevance and adequacy of the validation protocol and/or the proposed type and scope of the implementing variation.
- A plan for stability studies should be included, if appropriate. In addition to real time studies, accelerated or forced degradation studies may be included.

- In case that the PACMP describes several changes, a justification should be provided showing how the changes are related, and that a simultaneous review under a single PACMP is meaningful.
- Where a PACMP proposes addition of a manufacturing or testing site, demonstration of GMP compliance is required prior to implementation of the change, i.e. with the implementing variation. Respective GMP related documentation is not a requirement for initial approval of a PACMP.
- The precise type and scope of the planned implementing variation should be defined. A proposal of how the implementation of the change will be reported to the relevant competent authorities using a VNRA or VRA should be provided;
  - If a VNRA variation has been chosen, then the conditions that need to be fulfilled by the 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 VRA-R variation has been selected, then a description of the amount and level of detail of the data to be provided should be included. In exceptional cases, the implementation of a PACMP could require submission of a VRA-S variation. This should be discussed and agreed during the initial assessment.

# 5. When and how can a PACMP be updated?

Minor changes to an approved PACMP (e.g. implementation/replacement of an analytical procedure by an orthogonal method in a comparability approach) that do not change the strategy defined in the PACMP should be submitted as a VNRA B.12.g) or VRA-R F.II.g.2.b).1 prior to implementation of changes foreseen in the PACMP.

Major changes to an approved PACMP, (e.g. removal/addition of tests and studies or changes to specifications and pre-defined acceptance criteria), should be submitted as a VRA-S variation under F.I.e.2.b) or F.II.g.2.b.1).

Where deviations from the approved PACMP occur during execution of the PACMP (e.g. minor deviations during process validation, reduced finished product batch size compared to what was originally foreseen), a justification that the deviations do not change the overall strategy defined in the PACMP should be included in the documentation submitted to implement the change(s) foreseen in the

PACMP. In this case implementation via a VNRA is not possible and the variation should be submitted as a VRA.

## 6. How will the change(s) described in the PACMP be implemented?

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

The type of implementing variation is proposed as part of the PACMP and approved during the initial assessment. The procedure number of the application that led to the approval of the PACMP should be provided.

If a VNRA has been agreed during the evaluation of the PACMP, then the applicant may implement the change without any further regulatory evaluation prior to its notification.

If a VRA has been agreed during the evaluation of the PACMP, the variation needs to be notified to the Competent Authority prior to implementation of the change(s). If the same PACMP has been submitted for several products, and no product specific assessment is needed to support the implementation of the change, the implementing variation can be submitted via a worksharing procedure. See also Q10.

## 7. Can applicants submit a PACMP for any type of change?

The types of changes that would benefit from, and consequently could be included in a PACMP, depend on the complexity of the product and its manufacturing process, as well as the understanding that the company has gained about them.

A PACMP can only be accepted if the proposed change(s) allow for all the necessary studies and criteria to be defined beforehand in a manner sufficient to support implementation via the proposed variation category. If this is not possible, the PACMP may be refused or implementation via a variation of the applicable category without a PACMP may be requested. Furthermore, a PACMP cannot be used when non-clinical and/or clinical data are required.

For submission and acceptance of a change as part of a PACMP, the applicant should demonstrate suitable scientific knowledge and understanding of the active substance and of the finished product and their respective manufacturing process. It is strongly recommended that companies submit PACMPs only for those changes that they are highly likely to implement within the planned timeframe and whose feasibility has already been investigated and is supported by relevant data.

## 8. Can a PACMP cover multiple changes?

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

Unless changes are clearly interrelated and simultaneous implementation with one supporting data package is appropriate, separate PACMPs for each change should be submitted, since unrelated multiple changes covered in a single PACMP would unnecessarily increase complexity of assessment and implementation of the respective changes.

## 9. Can a PACMP be used multiple times?

Depending upon the specific nature of the change(s), a PACMP could also be designed to be used repeatedly, applying the same principles ('multi-use PACMP'). A prerequisite is that the conditions and acceptance criteria for such a multi-use PACMP are sufficiently specific. If needed, the feasibility of the intended multi-use approach should be demonstrated.

In addition, the possibility for repeated use of a PACMP will need to be transparent and should therefore, if applicable, be clearly stated in the protocol itself. The strategy, acceptance criteria and data requirements for establishing comparability should remain relevant over the planned multi-use timeframe.

If product or site-specific adaptations are required in the PACMP, the proposed multi-use of the PACMP might be rejected. In such a case, the PACMP should either be withdrawn or amended as a more specific 'single-use' PACMP.

Alternatively, it could be acceptable to keep the multi-use PACMP without amendment, if the reporting category of the implementing variation is not lowered. In the latter case, applicants and regulators would still benefit from increased predictability regarding the implementation of respective change(s).

## 10. Can a PACMP cover multiple products?

Typically, a PACMP refers to one product; however, a PACMP can include multiple products where the PACMP and the change(s) proposed are applicable to all products in scope. Where a PACMP includes multiple products, the required information for implementing the change(s) for each product, and the type of implementing variation, should be clearly defined.

Multi-product PACMPs can only be submitted via a VRA via a worksharing procedure, i.e. they should not be included in an initial MAA. All products covered by the PACMP should be in scope of the VRA, i.e. listed in the application form.

## 11. What information should the implementing variation contain?

A reference to the approved PACMP and the precise scope of the change(s) applied should be included in the application form for the implementing variation under the section "scope". This reference should include the procedure number(s) of the application(s) through which the initial PACMP and any subsequent modifications were agreed.

A variation overview with high level description of the proposed change and supporting data should be provided. The information should be clear, sufficiently detailed, complete and presented in a granular way in line with the information in the present/proposed table.

The documents in Part 2 in the implementing variation should be self-standing, i.e. it should be possible to assess the documentation without cross-reference to the PACMP. For ease of reference, in the supporting documentation all data should be presented together with the acceptance criteria pre-defined in the PACMP (e.g. in tabular format). In case of deviations from the approved PACMP, a description and justification for the deviation(s) should be provided (see also question 5).

## 12. Can an implementing variation be grouped with other variations, that are not included in the PACMP?

Additional VRAs (not covered by the PACMP) can be grouped with the implementing variation. VNRAs can only be included in the group if they are directly consequential to the main change. In all cases, such additional changes need to be submitted as a separate variation scope, classified as VNRA and/or VRA as appropriate.

## 13. Where should the PACMP be placed in the application?

The PACMP should be included in the marketing authorisation application in Part 2.G. The relevant section(s) of Part 2 affected by the proposed PACMP, should cross refer to the PACMP.

When submitting the implementing variation, the respective sections of Part 2 have to be updated.

## 14. How is oversight of all PACMPs maintained?

A listing (table of contents) of the relevant PACMPs should be provided at the time of the submission of the first PACMP and maintained in Part 2.G.

This listing should detail for all PACMPs in the dossier

- the unique PACMP identifier/name
- the procedure number in which the PACMP was submitted,
- a brief description of the change(s) covered by the PACMP,
- the proposed reporting category for the implementing variation and an overview of the Part 2 section(s) that are expected to be impacted by the implementing variation. The status of the PACMP (pending implementation, implemented) and, if already implemented, the procedure number of the implementing variation.

In case of deletion of a PACMP from the dossier (via VNRA B.3.h)) reference to that PACMP should be deleted from the list.

## 15. In which situations is the submission of a PACMP not recommended?

Submission of a PACMP as part of an initial MAA should be carefully considered. Product and process complexity, knowledge and understanding influence the timepoint when the submission of a PACMP is appropriate. It is noted that PACMPs submitted as part of an initial MAA may need extensive revision if the assessment of the initial MAA results in amendments to the manufacturing process and the control strategy. Therefore, the PACMP may be better submitted post-authorisation via variation when more knowledge on the product and manufacturing process has been gained from commercial manufacturing.

Furthermore, experience indicates that for certain changes (e.g. a complete redesign of the manufacturing process for active substance, reformulation of the finished product) it can be challenging to completely define all necessary studies and acceptance criteria beforehand in a way that would support implementation through a VNRA or VRA-R. In such situations, implementation of the changes via a VRA-S should be considered.

The submission of a PACMP is discouraged if there are no concrete plans to implement the change in the foreseeable future (e.g. an initial MAA containing a PACMP for a new manufacturing site to be added post-authorisation). Especially, if no specific site has yet been identified, it would be more appropriate to submit a PACMP as a separate variation post-authorisation and when there is clear intention to add a specific site.

## 16. When will a PACMP be refused?

A PACMP will be refused if it is considered incomplete, especially if it is not sufficiently detailed and specific enough. Furthermore, multi-use PACMPs may be refused if multiple implementations are not feasible without first amending the PACMP to assure a sufficient level of detail and specificity.