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EMA/CHMP/QWP/505156/2023
Committee for Medicinal Products for Human use (CHMP)

Q & A on implementation of Ph.Eur. Medicinal Product Monographs

A) Demonstration of compliance with Ph. Eur. Medicinal Product Monographs (MPM).

1. Should a finished product for which a Ph.Eur. Medicinal Product Monograph (MPM) is official comply with the requirements of that Monograph?

In principle, finished products for which a Ph.Eur. Medicinal Product Monograph (MPM) is official should comply with the requirements described in the Monograph, unless otherwise prescribed in General Notices of the Ph.Eur.

Different scenarios exist:

In case the MPM is official before the medicinal product is approved, the finished product has to comply with the requirements described in the Monograph. In this case the applicants have possibility and time to take the MPM specifications and analytical methods into account when setting specifications and developing suitable analytical methods for the specific medicinal product.

In case the medicinal product is approved before the MPM is developed, the MPM should have been developed to embrace the quality of all approved medicinal products. If this has not been the case and the finished product specification is wider than the range described in the MPM, this should be communicated to the NPA (National Pharmacopoeia Authority) and EDQM (European Directorate for the Quality of Medicines & HealthCare) to be considered for inclusion in a revised monograph.

See also questions below for more details.

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2. How can the compliance with the Ph.Eur. monograph for a medicinal product be demonstrated during a MA procedure, when alternative methods are proposed in the MA dossier?

In order to demonstrate compliance with the Ph. Eur. MPM, the applied finished product should be tested against the Ph. Eur. MPM using same analytical methods (except for dissolution, see Question 3 below).

It should be demonstrated whether the Ph. Eur. analytical methods are suitable for controlling the specific product in question (composition, manufacturing method and container closure system etc.). It should be demonstrated (preferably in CTD Module 3.2.P.5), whether the MPM actually controls the entire impurity profile of the finished product (i.e. all relevant impurities, degradation products, nitrosamines) or not.

According to the General Notices of the Ph. Eur., alternative methods (i.e: in-house methods) may be used for control purposes, provided that the methods used enable an unequivocal decision to be made as to whether compliance with the standards of the monographs would be achieved if the official methods were used. The methods of analysis confirm compliance with corresponding Ph.Eur. criteria, if tested. (see also Question 4 and 5).

"It is acknowledged that additional controls may be required to monitor degradation products other than those controlled by the monograph (e.g. degradation products related to different excipients or containers used, or from a different manufacturing process)." (Ph. Eur. General Notices 1.5.3.1.)

3. Is it necessary to demonstrate the compliance with the dissolution test and requirements recommended in the Ph.Eur. MPM?

Test and requirements for dissolution in MPMs are minimum requirements and not mandatory per se (see Ph. Eur. General Notices). For dissolution test, the specification should be derived from the dissolution results of the biobatch(es) in the individual marketing authorization procedure and the dissolution method should be discriminatory for the specific product (manufacturing process/product formulation).

Broadening the Q-value can only be justified by in-vivo data. It is important to note that the dissolution test described in the respective Ph. Eur. Medicinal Product Monographs can only be used if the applicant has demonstrated the suitability (including discriminatory power) of the test for the given product to the satisfaction of the competent authority. In any case, the dissolution test proposed should be approved by the competent authority in the context of the marketing authorization procedure.

Demonstration of compliance with the monograph dissolution test is not required as part of a MAA or MAV. However, when tested, the medicinal product has to comply with the monograph dissolution test, unless otherwise justified by the applicant.

Further guidance on the dissolution test can be found in the Ph. Eur. General Notices (1.5.3.2).

4. Should the already approved in-house specification be changed to the one described in the MPM?

For medicinal products already on the market with a valid marketing authorization licence, in case the approved shelf life specification limits are in line with or stricter than the Medicinal Product monograph there is no need to change the specification(s) limits and methods.

Alternative methods (i.e: the already approved in-house methods) may be used for control purposes, provided that the methods used enable an unequivocal decision to be made as to whether compliance with the standards of the monographs would be achieved if the official methods were used. The methods of analysis confirm compliance with corresponding Ph.Eur. criteria, if-tested.

If higher/wider limits than indicated in the Medicinal Product Monograph (limits compared using the same analytical method) have been approved for a product, and these are justified in line with current ICH/EU requirements and actual batch data, these should be communicated to the NPA and EDQM to be considered for inclusion in a revised monograph (see also Question 6 below).

However, in case the higher/wider limits of the product are not fully justified by batch data, tightening the limits to the MPM's requirements is needed by submission of a variation application.

'It should be noted that the specification limit is specific for the respective analytical method and therefore, limits cannot be compared across different analytical methods'.

5. Should the in-house developed methods be changed to the methods described in the MPM?

No. The product should comply with the requirements of the Medicinal Product Monograph (MPM) see Question 1, but it does not mean that it is mandatory for the manufacturer to use the monograph methods.

According to the Ph. Eur. General Notices, alternative methods (i.e: in-house methods) may be used for control purposes, provided that the methods used enable an unequivocal decision to be made as to whether compliance with the standards of the monographs would be achieved if the official methods were used. The methods of analysis confirm compliance with corresponding Ph.Eur. criteria, if-tested.

According to the Ph. Eur. General Notice, alternative methods can be used:

***"1.1.2.5. Alternative methods**. The tests and assays described are the official methods upon which the standards of the Pharmacopoeia are based. With the agreement of the competent authority, alternative methods of analysis may be used for control purposes, provided that the methods used enable an unequivocal decision to be made as to whether compliance with the standards of the monographs would be achieved if the official methods were used. In the event of doubt or dispute, the methods of analysis of the Pharmacopoeia are alone authoritative." (General Notices of Ph.Eur.)*

For dissolution testing see Question 3 above.

6. Is it possible to authorize a finished product with wider limits than those laid down in the MPM?

A medicinal product with wider limits than those laid down in the monograph could be authorized only in very exceptional cases.

In case the proposed wider limits than those laid down in the monograph (limits compared using the same analytical method) are appropriately justified by the applicant in line with current ICH/EU requirements (by respective preclinical/toxicological studies/references, proper development, excipients, packaging material, actual batch analysis and stability data etc.) the marketing authorisation could be granted.

According to the General Monograph on Pharmaceutical Preparations (2619) section "Related substances": *"In exceptional circumstances and if justified by the applicant to the satisfaction of the competent authority, the latter may approve a wider limit than that described in the monograph. In these rare cases, the competent authority shall bring this to the attention of the Ph. Eur. Commission for review of the monograph and, where appropriate, its revision".*

B) Questions concerning variation submissions

7. Is it necessary to submit variation application in order to demonstrate compliance with the MPM?

If no change is required, a variation application does not need to be submitted, but the supportive data (including suitability of the MPM methods) demonstrating compliance of the existing product with the MPM should be available at the manufacturing/control site. It should be kept in mind that the product should comply with the requirements of the MPM if tested (e.g. by an OMCL).

If any changes are needed, they should be submitted in line with the EC variation classification guideline.

8. Which type of variation should be used for changing the specification and/or analytical methods to those described in the MPM?

The classification of the variation should correspond to the existing sub-categories of the EC Variation Classification Guideline in sections:

B.II.d.1 "Change in the specification parameters and/or limits of the finished product" or
B.II.d.2 "Change in test procedure for the finished product"

According to CMDh Q&A (List for the submission of variations according to Commission Regulation (EC) 1234/2008) point 3.8.:

«Variation B.III.2 only relates to active substances, excipients, immediate packaging materials and active substance starting materials. Changes to comply with Ph.Eur. or with a national pharmacopoeia of a Member States affecting the finished product should be submitted according to the relevant variations listed under B.II. d.»

9. Is it necessary to submit variation application if the approved shelf life limits are in line with or stricter than the MPM?

No. In order to avoid the numerous unnecessary variation applications, it is not recommended to change the already approved specifications and/or the method in case the approved shelf-life limits are in line with or stricter than the MPM. The approved specification has already been evaluated and authorized according to EU/ICH guidelines and the obtained batch/stability data using validated analytical methods.

10. Is it possible to widen the specification limits to be the same as specified in the MPM?

Impurities/related substances: For already authorized products compliance with a monograph does not mean that the limits for impurities/related substances have to be widened. The specification represents process capability/product performance associated with safety and efficacy. Therefore, wider limits than previously approved need sound justification.

Dissolution: No. For dissolution test, the specification should be derived from the dissolution results of the biobatch(es) in the individual marketing authorization procedure and the dissolution method should be discriminatory for the specific product (manufacturing process/product formulation). Broadening the Q-value can only be justified by in-vivo data.

It is important to note that the dissolution test described in the Ph. Eur. MPM can only be used if the applicant has demonstrated the suitability of the test for the given product to the satisfaction of the competent authority. In any case, the dissolution test proposed should be approved by the competent authority in the context of the MAA assessment.

11. Which variation category should be used to widen the specification limits to be the same as specified in the MPM?

Change (widening) the impurity or assay limits of the finished product to the limits in the Ph. Eur. monograph: Type II, B.II.d.1.e (Change outside the approved specifications limits range).

Change (widening) the dissolution limits of the finished product to the limits in the Ph. Eur. monograph: Type II, B.II.d.1.e (Change outside the approved specification limits range). It is important to note that such a change should be justified by new in vivo data (see also Question 10).

References

- 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
- Ph. Eur. General Notices
- Ph.Eur. General Monograph on Pharmaceutical Preparations (2619)