

Marketing authorisation transfer to a mutual recognition procedure for a veterinary product

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Keywords

Co-Ordination Group for Mutual Recognition and Decentralised Procedures veterinary (CMDv); Committee for Veterinary Medicinal Products (CVMP); Summary of product characteristics (SmPC); Harmonisation; Referral; Mutual recognition procedure (MRP), Reference member state (RMS); Concerned member state (CMS).

Abstract

This article gives an overview from the CMDv's perspective of the transfer of purely national marketing authorisations to a mutual recognition procedure (MRP) following an Article 34 referral with a positive European Commission decision. The transfer of purely national marketing authorisations to mutual recognition status should be carried out in order to maintain the harmonisation achieved during the referral procedure. An overview on preparatory work and procedural principles is outlined.

In addition, a case study illustrates best practice for transfer to an MRP and its practical implications. The experience gained by a company is provided, discussing both benefits and risks or hurdles stemming from the transfer procedure.

Introduction

A referral, also called an arbitration, is a unique procedure by which the Committee for Veterinary Medicinal Products (CVMP) is requested to conduct an assessment of a particular (class of) veterinary medicinal product(s). European veterinary legislation (Directive 2001/82/EC, as amended¹) provides for the legal framework and the procedural elements of such procedure. The CVMP's scientific evaluation leads to an opinion that provides the basis on which the European Commission issues a binding decision. This decision applies to all member states – including Iceland, Liechtenstein and Norway – and is enforced on the marketing authorisation holder (MAH). The Commission has published a guidance document on this topic under the Notice to Applicants, Volume 6A.²

Article 34 – Harmonisation referral

If EU member states have adopted divergent decisions on the authorisation of a particular product, the matter may be referred under Article 34 of Directive 2001/82/EC, as amended. In essence,

the products have been authorised nationally in two or more member states with different summaries of product characteristics (SmPCs). The CVMP is called on to issue an opinion which aims to resolve the divergences between the national decisions, and therefore the referral leads to a full harmonisation of the SmPC, labelling and package leaflet. This Article 34 referral is usually referred to as the “divergent decision” or “harmonisation” referral.

Following a positive outcome, member states affected by the referral have an obligation to comply with the Commission decision by varying the terms of the marketing authorisation of the product, and implement the harmonised SmPC and product information. Moreover, the marketing authorisation must enter into a procedure which allows future development of the product in a harmonised manner. It is the responsibility of the MAH and the member states to keep the level of harmonisation reached by the referral procedure. As mentioned in the Notice to Applicants,² MRP must be followed in order to maintain the achieved harmonisation.

In light of this, the Coordination Group for Mutual Recognition and Decentralised Procedure (CMDv) has developed a pragmatic way to transfer purely national marketing authorisations to a mutual recognition status.

CMDv procedure for transfer to MRP

The CMDv has established a procedure describing the actions and consequences for national competent authorities and MAHs in cases of a positive decision following a harmonisation referral.³

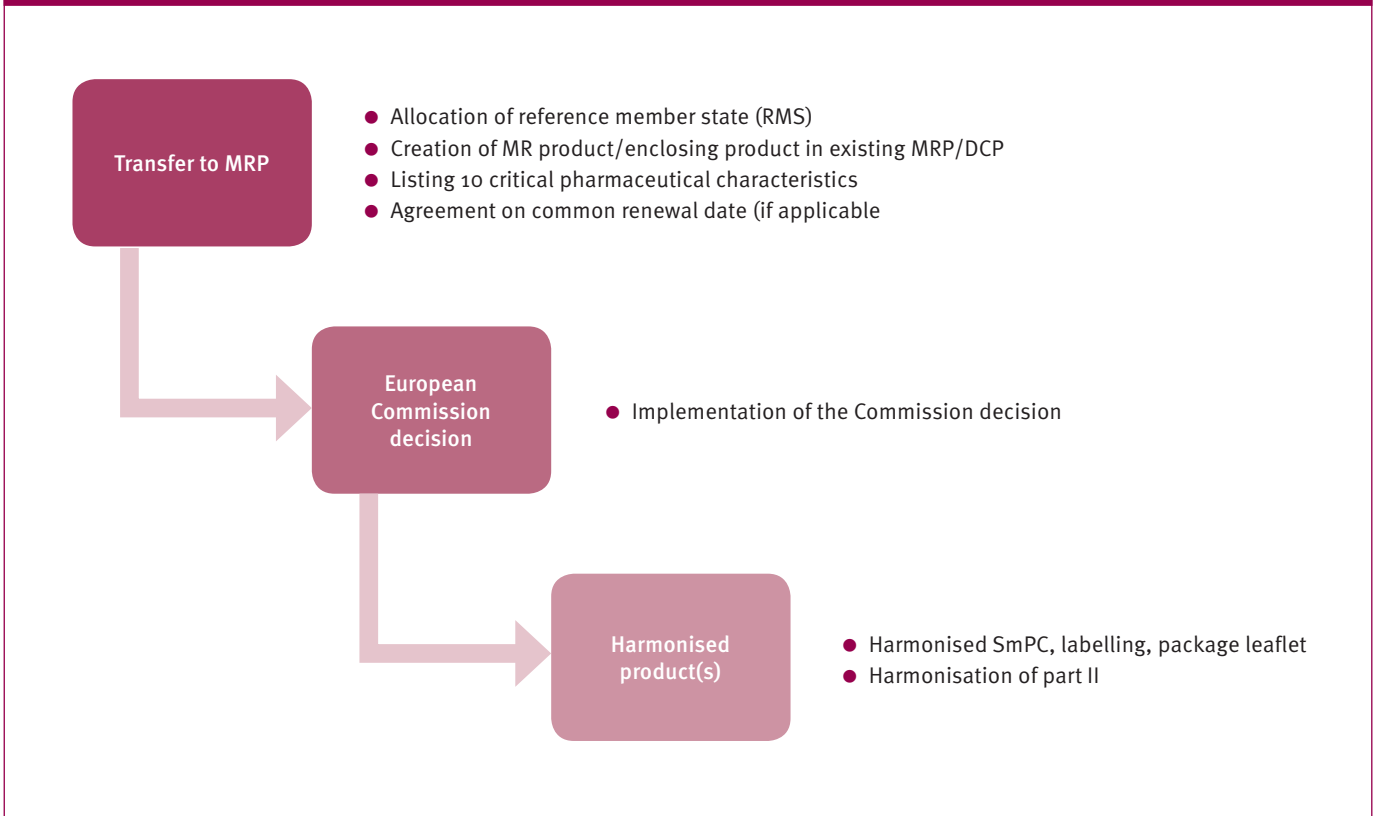
The CMDv strongly encourages that products involved in a referral pursuant to Article 34 and originally granted a marketing authorisation via a purely national procedure in the member states are transferred to an MRP immediately after the conclusion of the referral. This is the only transparent and reliable way to ensure the maintenance of the harmonisation achieved across the EU.

To get a general idea of how to handle a transfer to an MRP, a brief overview of preparatory work and procedural principles is detailed in Figure 1. The procedure can be initiated once the MAH has contacted the CMDv and committed to transfer the purely nationally authorised products concerned by the referral to MRP.

The timing is straightforward: since the member states affected by the referral have a legal obligation to implement the Commission decision within 30 days, the transfer should be completed during the decision-making procedure, resulting in the adoption of the Commission decision. The following steps to be taken are:

- **Allocation of a reference member state.** Allocation of the reference member state (RMS) is done by the CMDv. The fact that a member state has specific knowledge or has gained experience regarding the products involved should be taken into account. In cases where the products concerned have been authorised following MRP or decentralised procedure (DCP), it is advisable that the member state acting as RMS continues its duties. When the products concerned have all been initially granted a marketing

Figure 1: Overview of preparatory work and procedural principles for handling a transfer to an MRP.



authorisation following a purely national procedure, a new RMS should be appointed. The MAH may put forward a proposal to CMDv for a member state to take the lead and act as RMS.

- **Transfer to MRP.** When all the products concerned by the referral have purely national authorisations, these will be transferred to a newly created MRP. In case some but not all products were authorised following MRP or DCP, the purely national authorisations can be enclosed in an existing MRP/DCP for the same product, on the condition that the legal basis on which the initial application for marketing authorisation was made is identical.

The transfer to MRP is of a purely administrative nature. There is no need for the MAH to submit to the national authorities the documentation presented to the CVMP during the arbitration procedure. Furthermore, it has been agreed by the CMDv that the transfer in itself should be free of charge in the concerned member states (CMS).

The MAH should provide the CMS with a list of ten critical pharmaceutical characteristics (CPCs), as mentioned in the annex to the CMDv’s recommendation document.³ Based on this, a picture of the level of harmonisation of the quality part of the purely national dossiers can be drawn. In cases where part II of the dossier of an individual product is not fully harmonised within the concerned member states, the MAH and the RMS should consider how to proceed and plan an approach.

It might be necessary, although it is not mandatory, to agree on a common renewal date in close liaison with the RMS, CMS and the MAH.

- **Implementation of the Commission decision.** Once transferred,

the first variation to be handled by MRP is the implementation of the Commission decision. The appropriate variation, as listed in the Commission guideline on the classification of variations⁴ is categorised type IA_N under C.I.1: “Change(s) in the Summary of Product Characteristics, Labelling or Package Leaflet intended to implement the outcome of a Union referral procedure, (a) The medicinal product is covered by the defined scope of the procedure”. The sole condition to be fulfilled is that the variation implements the wording requested by the authority and it does not require the submission of additional information and/or further assessment. Corresponding documents which should be presented are:

- Application form making reference to the Commission decision concerned with the annexed product information
- A declaration that the proposed SmPC, labelling and package leaflet is identical for the concerned sections to that annexed to the Commission decision
- Revised product information in track-changed and clean versions in editable format.

The fees applicable for this variation remain governed by national conditions.

- **Maintenance of the harmonisation.** The harmonisation of the SmPC, labelling and package leaflet that has been reached by implementing the Commission decision should be maintained throughout the lifecycle of the product. However, new information, gained via pharmacovigilance data or, for example, on the development of antimicrobial resistance, needs to be taken into consideration. All post-referral variations, renewals, repeat-use procedures and periodic safety update reports (PSURs) should

be submitted by MRP. Industry would benefit from predictable timelines, simultaneous assessment by all CMS and a single procedure outcome.

For any future variation applications, the list of critical pharmaceutical characteristics should be checked, and used to decide whether the upcoming variation could be processed without prior harmonisation of certain parts of the dossier. The application form should in any event reflect the differences.

A case study

Below is an example of experience gained by one company, detailing product information, benefits, risks and hurdles:

- **Product information.** The veterinary medicinal product concerned was an antimicrobial product initially authorised through the national procedure in 25 member states across Europe, in the seventies, and used in multiple food producing species. As a result, every member state had their own country-specific terms of authorisation characterised by SmPC divergences. In addition to this, the release specifications were also different in almost all countries, which resulted in higher logistic complexity.

Since the product information was so diverse across the CMS, an Article 34 referral procedure was initiated by a member state. In order to justify the authorised target species, indications and withdrawal period, the MAH generated new data. Even so, the CVMP restricted the indications to those that were adequately substantiated by efficacy data. The outcome of the Article 34 referral procedure was positive, requesting the amendment of the terms of the marketing authorisation and resulting in the full harmonisation of SmPC, labelling and package leaflet. The MAH wanted to transfer the product from the national procedure to an MRP, provided that the quality part of all the national dossiers could be harmonised smoothly. The member state that had referred the matter to CVMP took the lead and acted as the RMS. The transfer in itself was finalised in a quickly and easily. The first variation submitted via MRP was a grouped type IB variation, including:

- The implementation of the Commission decision, amending the SmPC, labelling and package leaflet – variation IA_{IN}
- The harmonisation of the 10 Critical Pharmaceutical Characteristics – variation IB by default
- An extension of shelf-life of the finished product after first opening, supported by real time data – variation IB.

To complete the harmonisation of the leaflet an additional type IA_{IN} variation was submitted in the RMS and CMS in order to harmonise the batch release site. As a result, the concerned dossier and the product's SmPC, labelling and package leaflet are fully harmonised across the member states wherein it is authorised.

Although the marketing authorisation of the product was already renewed for an indefinite time period in the vast majority of the member states, the product still needed to be renewed in a couple of countries. However, since the product was almost completely reassessed from a safety and efficacy point of view by the CVMP, all involved member states could agree on an administrative renewal procedure.

- **Benefits.** The procedure went smoothly. The transition to MRP and the harmonisation of the quality part was quick, taking around three months. At the end of the grouped variation, the product information and the quality part were harmonised, resulting in

one set of specifications throughout all countries. Additionally, this lowered manufacturing costs and increased compliance.

Furthermore, for future variations, line extensions or renewals, the same documentation package will be sent to all CMS. Another advantage is that in future, in cases of questions for any other applications, this will result in one single list of questions.

Moreover, the timelines of national procedures will no longer be applied, instead of which it will be the timelines for an MRP. This also increases the predictability on future timelines for implementation of any upcoming variations.

- **Risks and hurdles.** As a result of the referral, the labelling needed to be amended concomitantly. As countries did have different standards for transition periods, the MAH was faced in some countries with batch recalls from the market and supply constraints, although there were no safety concerns as the product had already been on the market for decades.

Conclusion

In summary, the procedure established by the CMDv to transfer nationally authorised products to MRPs following a positive outcome in an Article 34 referral is considered a quick win for both industry and national competent authorities. The transfer in itself is administrative, and carried out by the leading member state who will become the RMS. Implementation of the Commission decision and amendment of the SmPC, labelling and package leaflet are straightforward, but the implementation time for compliance of the batches on the member state's markets was subject to national requirements.

A critical issue remains the degree of (dis)harmonisation of part II of the dossier for purely nationally authorised products. A first pragmatic approach set up by the CMDv is the default type IB variation to harmonise the 10 critical pharmaceutical characteristics based on a common denominator of what has been authorised in the member state.

Further information relating to the CMDv, its activities, Best Practice Guides and guidance can be found on its webpages at the HMA website (www.hma.eu/159.html). The CMDv would also encourage use of the RSS feed option to ensure companies receive alerts to newly posted documents. ■

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