Veterinary medicinal products:

**CMDv recommendations for reducing administrative burden**

Veterinary medicinal products are recognised as having a disproportionately high administrative burden, which is felt most strongly by industry for those products approved on a national basis or through the MRP or DCP. This supplement reviews CMDv advice intended to reduce the burden and help applicants avoid unnecessary delays during regulatory procedures.

KEYWORDS: Co-Ordination Group for Mutual Recognition and Decentralised Procedures veterinary (CMDv); Committee for Veterinary Medicinal Products (CVMP); Harmonisation; Referral; Workshare variation; Reference authority; National competent authority (NCA); Marketing authorisation holder / application (MAH/A); Decentralised procedure (DCP); Mutual recognition procedure (MRP); Summary of product characteristics (SmPC); Reference member state (RMS); Concerned member state (CMS).

**Pre-submission planning**

Prior to submission of a MAA through the DCP and particularly prior to commencing a MRP, where the reference product may have been originally authorised many years ago, the CMDv has provided some simple recommendations which can help the Applicant avoid common pitfalls (see Box below).

**Product name and standard terms**

The name of a veterinary medicinal product (VMP) is subject to close scrutiny during the assessment procedure and a rejection of the name by the regulators can result in a last-minute panic and delays to the final issue of a MA. It should be clarified what we mean by the “product name”.

According to Directive 2001/82/EC as amended, the name of a VMP may be either an invented name not liable to confusion with the common name, or a common or scientific name accompanied by a trademark or the name of the marketing authorisation holder. It is also stated in the Directive that a common name is the “international non-proprietary name recommended by the World Health Organisation, or, if one does not exist, the usual common name.”

The invented or common name by itself is not sufficient to identify the VMP unambiguously. For identification purposes the strength, pharmaceutical form and possibly the target species would be required. The combination of the product name with these qualifiers is referred to as the “full (information) name”. However, the term “full name” is not provided in any legislation but is understood to mean the name of the product, followed by the strength, pharmaceutical form and the target species. In some cases the strength is not relevant, eg, for vaccines.

It should be noted that the “full name” is not the actual name of the product, unless this has been specifically applied for and approved during the procedure. In such cases, the product name is not to be translated and the strength, pharmaceutical form and target species must still be stated in the national language, following the product name, even if the product name contains information such as the pharmaceutical form or target species.

Reaching agreement on the product name is a national issue and there is the possibility to have different invented names in different member states. As such, the final approval of a product name during a MRP or DCP only happens during the national phase of the procedure. However, to avoid critical delays in the issue of a MA, it is permitted and recommended to bring forward as much of the discussion on product name as possible, to the clock-stop period of the procedure.

Aside from the product name, there are other standard terms, some of which may or may not be included in the full name. As with the product name, ensuring that you use the correct standard terms to describe your product can help avoid unnecessary delays later in the procedure and minimise amendments to be made to the packaging artwork. Important considerations for these standard terms are summarised in Table 1.

**Worksharing variations for VMPs**

Article 20 of Regulation 1234/2008/EC, as amended by Regulation 712/2012/EC introduces variation worksharing, which provides an opportunity for a significant reduction in administrative burden. The largest benefit is that there is a single assessment, following an agreed and predictable timetable, leading to a single outcome. The same data package is prepared and submitted to those competent authorities involved, with no need to submit national applications or to wait for separate national decisions running on different national timeframes. Also, once approved, the change(s) may help in other aspects, eg, benefits in manufacturing processes resulting from greater harmonisation in Part II of the respective dossiers, or uniform withdrawal periods approved across product ranges.

Before submitting a workshare application, first liaise with your preferred reference authority to seek agreement, as illustrated in the process summary (see Figure 1). It can also advise on timings and the proposed classifications.

Once you have discussed your workshare application with your preferred reference authority, you are ready to submit the workshare variation request to the CMDv...
Secretariat. There is guidance on worksharing and a letter of intent template available on the CMDv webpages of the HMA website, but in short, the letter of intent will include the following information, as stated in the CMDv Best Practice Guide for Worksharing:

- List of marketing authorisations concerned: name and respective MR/DC procedure numbers and/or MA number for purely nationally authorised products
- Description of the changes and proposed classification of those changes according to the European Commission variation classification guideline

Table 1: Standard terms that may or may not be included in the full VMP name.

<table>
<thead>
<tr>
<th>Standard term</th>
<th>Included in the full product name?</th>
<th>Important considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pharmaceutical form</td>
<td>Yes</td>
<td>• Use Ph Eur full standard terms, as maintained by the EDQM and available in the Referentials Management Services (<a href="https://spor.ema.europa.eu/sporwi/">https://spor.ema.europa.eu/sporwi/</a>)</td>
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<td></td>
<td></td>
<td>• If no appropriate Ph Eur term, a new term may be constructed from a combination of standard terms or a new term can be created, subject to agreement by the RMS and CMS and update of the EDQM Standard Terms database.</td>
</tr>
<tr>
<td>Active substance</td>
<td>Sometimes</td>
<td>• Can be accompanied by a trademark or the name of the MAH to form the product name</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• NTA Vol 6C defines a hierarchy in nomenclature for the qualitative composition, with the first choice being the INN, accompanied by its salt, derivative or hydrate form if relevant</td>
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<td></td>
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<td>• Where an active is presented as a salt form, the correct presentation of the quantitative form is, eg, “Amoxicillin x mg equivalent to y mg amoxicillin trihydrate”.</td>
</tr>
<tr>
<td>Target species</td>
<td>Sometimes</td>
<td>• Only required if there are different presentations of the VMP (eg, the same active substance and invented name) in different formulations for different target species</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Refer to the list species or target species in RMS (<a href="https://spor.ema.europa.eu/sporwi/">https://spor.ema.europa.eu/sporwi/</a>). Always include the species, not just any sub-categories, eg, “Pigs (piglets at age of 3–5 days)” not “Piglets (at age of 3–5 days)”.</td>
</tr>
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Key facts for workshare procedures:

- It is optional for MAHs
- Applies to products authorised under the CP, DCP, MRP and NP; a workshare request can include a combination of products authorised under these routes
- Should a workshare request involve at least one centrally authorised product then the EMA will automatically become the reference authority
- Workshares can only include Type IB and Type II variations, unless these variations result in consequential changes in which case any required Type IA notifications may be included
- Workshares can include several changes to one product which is authorised in several EU member states or the same change(s) to a range of products
- The product(s) concerned by the workshare must belong to the same MAH
- The same data package must apply to all the authorisations included within the application
- Workshares cannot include MAs where only some of the data apply to some of the authorisations
- Assessment of workshares follows a Type II variation timetable.

Preferred reference authority

Justification as to why the MAH believes that a worksharing procedure is suitable

Planned submission date

Confirmation that all marketing authorisations included belong to the same MA holder

If applicable, details of submission/approval/rejection of the same variation(s) in any Member State(s)

If applicable, details of any marketing authorisations (MR/DC or purely national) that have been excluded from the proposed worksharing procedure, with reasons.

Following the completion of a workshare variation procedure, if changes to the SmPC are made, it should be noted that any subsequent changes to that section of the SmPC must be submitted to all the member states involved in the original workshare application in order to maintain the achieved harmonisation.

MA transfer to MRP for a VMP

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, prior to the introduction of the legal basis for MRP and DCP, in two or more member states with different 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 sometimes referred to as the “harmonisation” referral.

Following a positive outcome in a harmonisation referral, the CSMs has developed a pragmatic way to transfer purely national marketing authorisations to a mutual recognition status, so that the MAH and the member states can maintain the level of harmonisation reached by the referral procedure.

The procedure can be initiated once the MAH has contacted the CMDv and committed to transfer the purely nationally authorised

Figure 1: Summary of the process for submitting a workshare variation request
products concerned by the referral to MRP. Since the member states affected by the referral have a legal obligation to implement the Commission’s decision within 30 days, the transfer should preferably be completed after adoption of the CVMP opinion, during the Commission decision-making procedure.

Step 1: Transfer to MRP
Following the allocation of a reference member state for the MRP, 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 referral. Furthermore, it has been agreed by the CMDv that the transfer in itself should be free of charge in the concerned member states (CMSs).

The MAH should provide the CMS with a list of 10 critical pharmaceutical characteristics (CPCs), based on which 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. A variation according to the classification guideline will be required anyway, together with the appropriate fees for the variation, to harmonise the 10 CPCs based on a common denominator of what has been authorised in the member states.

Step 2: Implementation of the referral outcome
Once transferred, the first variation to be handled by MRP is the implementation of the Commission’s decision. The appropriate variation is categorised as type IA1, and it does not require the submission of additional information and/or further assessment. The fees applicable for this variation remain governed by national conditions.

Although changes to the SmPC will be addressed by this variation, this is not the case for mock-ups, so the MAH is recommended to submit the mock-ups during the type IA variation in the CMSs (if applicable) and to discuss them with the NCA during the variation procedure.

Step 3: Maintenance of the harmonisation
The harmonisation of the SmPC, labelling and package leaflet that has been reached by implementing the Commission’s decision should be maintained throughout the lifecycle of the product. All post-referral variations, renewals, repeat-use procedures and periodic safety update reports (PSURs) should now be submitted by MRP.

For any future variation applications, the list of CPCs 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.

Case study:
**MA transfer to MRP**

This is an example of the experience gained by one company, detailing product information, benefits, risks and hurdles.

The VMP concerned was an antimicrobial product initially authorised through the national procedure in 25 member states across Europe, in the 1970s, and used in multiple food producing species. As a result, every member state had its 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 MA 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 quickly and easily. The first variation submitted via MRP was a grouped variation, including:

- The implementation of the Commission’s decision, amending the SmPC, labelling and package leaflet – variation IA1
- The harmonisation of the 10 critical pharmaceutical characteristics by appropriate variation
- An extension of shelf-life of the finished product – variation IB

To complete the harmonisation of the leaflet an additional type IA1N 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 SPC, 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 period in the vast majority of the member states, the product still needed to be renewed in a couple of countries. However, as the product was almost completely reassessed from a safety and efficacy point of view by the CVMP, all CMSs could agree 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 can be sent to all CMSs. Another advantage is that in the 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, rather it will be the timelines for an MRP. This also increases 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. Since countries had 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 because the product had already been on the market for decades.

**Conclusions**
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 CAs. The transfer in itself is administrative, and carried out by the leading member state which will become the RMS. Implementation of the Commission decision and amendment of the SPC, labelling and package leaflet are straightforward, but the implementation time for compliance of the batches on the CMSs’ markets was subject to national requirements.

The content of this supplement is drawn from Regulatory Rapporteur, in particular:


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1. Which of the following information is mandatory for inclusion in the full product name for a VMP?
   a) The pharmaceutical form
   b) An invented name
   c) The target species.

2. Which of the following statements regarding workshare applications are true?
   a) Workshares which include only Type IB variations follow the timetable for Type IB variations
   b) A workshare request can involve a combination of products approved through the CP, MRP, DCP as well as product authorised on a purely national basis
   c) Type IA notifications cannot ever be included in a workshare procedure.

3. Following the completion of an Article 34 harmonisation referral, a number of changes are required to allow future development of the product in a harmonised manner. For which of the following changes are fees not payable to the competent authorities?
   a) Transfer of the products to MRP
   b) Harmonisation of the critical pharmaceutical characteristics
   c) Updates to the SPC, labelling and package leaflet required by the implementation the Commission decision.

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TOPRA – for instance as a member of a workshare group or as a participant in a CPD event – is a valuable step on the road to ‘registered’ member status.