CMDv/GUI/034

GUIDANCE

Recommendations for Management of Post-Authorisation Procedures and Pharmacovigilance Activities after Partial Marketing Authorisation Transfer at National Level Following Mutual Recognition or Decentralized Procedure (so-called Partial MAH Transfer)

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1. INTRODUCTION:

A Mutual Recognition (MRP) or Decentralised (DCP) procedure for a new marketing authorisation (MA) for a veterinary medicinal product (VMP) leads to:

- One product
- One MA in each involved member state (MS)
- One holder or holders belonging to the same mother company in all involved member states, including Reference Member State (RMS) and Concerned Member States (CMSs).

Subsequently, the Marketing Authorisation Holder (MAH) may decide to transfer its authorisation to a new MAH only in some MSs amongst those in which the product was authorised. When this case occurs, the administrative procedure to be followed is a transfer of MA, which is a national variation falling outside the scope of the Variation Regulation 1234/2008/EC as amended.

This national transfer is, consequently, a PARTIAL transfer since the MA is transferred only in, at least, one MS without being transferred in all CMSs.

Consequently to this national partial transfer the following situation occurs:

- One product
- One MA in each involved MS
- Several MAHs: the originator MAH in some MSs and one or several new MAH in some other MSs (those in which the transfer(s) occurred).

The product however remains under the Mutual Recognition regimen. A new VMP is not created by the transfer. In other words, the MAHs (old and new) share the same authorisation for 1 VMP.

If this situation may arise, the harmonisation has to be maintained by ensuring harmonisation of the follow-up procedures and of the surveillance, including the pharmacovigilance activities.

2. SCOPE:

This guidance is written for use by the National Competent Authorities (NCA) and the MAHs. It addresses the key steps for handling situations as described above to ensure that MAHs take appropriate measures to maintain the achieved harmonisation of the products in Europe.

The guidance is intended for products authorised via MRP or DCP for which a national transfer of MA occurred in one or more MS.

TOTAL transfer of the MA of 1 VMP from the original MAH to a new one in all MSs is outside the scope of this recommendation paper.

3. PRELIMINARY NOTES:

- The old MAH or the originator is the one to whom has been granted first the MA and who still holds the MA in one or several MSs.
- The new MAH is the holder to whom the MA is transferred at national level in one or several but not all MSs.

The MAHs are reminded that following the transfer of a MA, the legal requirements regarding the authorisation must still be fulfilled by all holders. It is the duty of each MAH to make all efforts to ensure that the product documentation and information remain identical in each MS whoever the MAH is, and to ensure that NCA are informed without any delay of any pharmacovigilance or post authorisation events having a safety impact, as prescribed in legal texts.

4. TRANSFER OF A MA AND SUBSEQUENT STEPS

4.1 Step 1 = National transfer of the MA

4.1.1 National requirements

This step is handled at national level. MAHs are expected to follow the requirements laid down by NCAs with regard to the transfer of a MA. The CMDv has published on its website the list of all national requirements for national procedure of transfer.

The national transfer may not require scientific assessment depending on the national requirements. According to the national law, the NCA may require any type of variation or notification and defined documents.

The transfer of MA may not be approved in some MSs until the change of Detailed Description of the Pharmacovigilance System (DDPS) is approved (see step 3 for the change in DDPS).

The expecting change in European Union (EU) surveillance of the VMP after the national transfer should be explained in a Product-Specific Addendum of the DDPS where the relationship between MAHs with respect to the fulfilment of the Pharmacovigilance duties and contractual arrangement (see below) should be detailed.

4.1.2 Maintenance of the harmonisation

The following information may be required by NCAs to ensure that the product will continue to be harmonised across the EU:

- Cover letter specifying in which MS the MA is transferred to a new MAH and detailing the name(s) of the product(s) intended to be transferred + authorisation number + date of authorisation
- Effective date of the transfer
- Legal details of the new MAH (proof of establishment, local representative...)
- Proposed SPC, labelling and package leaflet and statement that the SPC, labelling and package leaflet will remain unchanged except for the respective section with MAH’s details
- Information concerning the person authorised for communication, recall and quality defects
- Statement from the new MAH who accepts the transfer and takes all the rights and the duties linked to the current MA
- Declaration that all complete and up to date files, including previous variations, have been transferred or made available to the new MAH by the old MAH

- Statement that no other change than the transfer is proposed to the product (no change in the manufacturing process linked to the transfer).

4.1.3 Documented contractual arrangement

To ensure that both MAHs will make all efforts to maintain product harmonisation and will be able to ensure the continuity of the European surveillance of the product, detailed and clear documented contractual arrangement between the MAHs is recommended to fulfil these obligations.

The arrangement should be provided during the national transfer as part of the transfer documentation.

By this contractual arrangement, the holders should arrange a harmonised surveillance EU level and designate only one Qualified Person for Pharmacovigilance (EU-QPPV) for this product, in charge of EU surveillance. This should be described in the specific addendum.

By this contractual arrangement:

- both MAHs should commit themselves to ensure communication between them to share all information concerning pharmacovigilance notifications, any other post-authorisation issues, such as quality defects or non-compliant batches and future variations. When the issues are considered as having an impact on the safety of the products, the agreement should be as such that NCAs are informed without delay.

- the distribution of pharmacovigilance tasks between old and new MAHs should be described.

Two cases should be considered that would ensure that Pharmacovigilance activities will be handled by only one MAH with respect to signal detection and Periodic Safety Update Report(s) (PSUR):

- either the new MAH (i.e. the principal) subcontracts the global EU surveillance to the old MAH (subcontractor), i.e. signal detection, PSURs. In this case, the tasks of the new MAH consist of the receipt of cases and transmission to the EU QPPV (old MAH’s QPPV) in the appropriate defined period.

- or the old MAH (i.e. the principal) subcontracts the global surveillance to the new MAH (subcontractor). In this case, both MAHs should confirm and detail the transfer of existing Pharmacovigilance data from the old to the new MAH.

In both cases, the following activities are distributed as such:

- To the principal: MAH giving orders, whose role is limited to the receipt and transmission of initial cases and their follow-up to the subcontractor.

- To the subcontractor: MAH receiving orders, in charge of the global surveillance at EU level.
In PART I ‘Guidelines for Marketing Authorisation Holders’ (1.3 Contractual Arrangements) of volume 9B of the Rules Governing Medicinal Products in the European Union it is specified that:

“A MAH may transfer any or all of the pharmacovigilance tasks and functions, including the role of the QPPV, to (an)other person(s) or organisation, but the ultimate responsibility for the fulfilment of all pharmacovigilance obligations and the quality and integrity of this always resides with the MAH. In such cases, it is the responsibility of the MAH to ensure that detailed and clear documented contractual arrangements for meeting pharmacovigilance obligations are in place between MAHs and persons or organisations involved in the fulfilment of pharmacovigilance obligations and to provide the CAs and, if applicable the Agency, with information on such arrangements in line with the requirements set out in Part I Chapter 2. Requirements for Pharmacovigilance Systems, Monitoring of Compliance and Pharmacovigilance Inspections. The contracted person(s) or organisation should implement quality assurance and quality control and accept to be audited by or behalf of the MAH. In cases of contractual arrangements between MAHs in relation to co-marketing of separately authorised VMPs, which are identical in all aspects apart from their invented names, these arrangements should include measures to avoid the duplicate submission of adverse events to EVMet.”

The requirements set in Volume 9B need to be met. Therefore the written arrangements should be in place for meeting pharmacovigilance obligations and reflect the distribution of tasks between old and new MAH. Each MAH remains responsible for the fulfilment of all pharmacovigilance obligations and the quality and integrity of this always resides with the MAH in the territory where they are MAH.

At least the following issues needs to be detailed and documented between the MAHs:
- Commitment of both parties to communicate about pharmacovigilance issues (outcome of signal detection and PSURs, requests from NCA) and other post-authorisation issues such as quality defects, non-compliant batches as well as variations
- Potential procedures of the contracting company to be respected
- Obligations of both parties and method of exchanges between both parties
- List of contact persons and contact information details for each party
- The future of pharmacovigilance data and the responsibilities of both parties at the end of the contract

Contractual Agreements between the parts would also be made available to the NCAs for inspection at any point during the product life.

4.2 Step 2 = informing of the MS that a national transfer has occurred

On completion of the national procedure, the NCAs should inform, via eudra mailbox, the RMS that the MAH has changed. CTS should also been updated in the “comments section” accordingly to reflect the new situation.

It is at the discretion of the RMS to store the information for future applications or reference.

The MSs in which the transfer occurred should give the necessary order that a variation procedure will be required to change the DDPS to add the specific addendum explaining the contractual arrangement. The RMS should be informed.
4.3 Step 3 = MR procedure to change the DDPS

After a transfer, and in accordance with the contractual arrangement mentioned in step 4.1.3:

- in MSs where the transfers occurred, the new MAH should submit the DDPS including a product specific addendum specifying that, for this product, the main pharmacovigilance tasks, in particular signal detection and PSURs at EU level are subcontracted to the old MAH or that the new MAH is in charge of EU surveillance, including MSs where the MAH is the old one. A variation is needed.

- in MSs where the MAH remains unchanged, a product specific addendum of the DDPS should be provided stating that, for this product, the old MAH is in charge of EU surveillance, including countries where the MAH is the new one or that the main pharmacovigilance tasks, in particular signal detection and PSURs at EU level are subcontracted to the new MAH. For this change, in such MSs, either a variation or a notification is needed according to the national requirements.

The Guidelines on the details of the various categories of variations C(2013)2804\(^1\) classifies a change in DDPS as C.II.7 : Introduction of a new Pharmacovigilance system. Depending on whether the DDPS of the new MAH has already been assessed or not, the new MAH should apply for a type IB or II variation application respectively. The change of DDPS is handled as a MR variation.

Both DDPSs should adequately reflect the contractual arrangements and lead to only one EU-QPPV and one surveillance for the product at European level.

For old products having no DDPS, it is reminded to the applicant that any change in the Pharmacovigilance system implies that a DDPS should be submitted.

In summary: a first variation is necessary for MSs in which the DDPS is changed and a second variation (or notification) is also necessary at MR level for MSs in which the DDPS is not changed but to include the subcontract/product-specific addendum.

5. SUBSEQUENT VARIATIONS, EXTENSIONS OR RENEWALS

After the transfer, if the MAHs wish to vary the product, it is necessary that an identical application (application forms and documentation) is submitted simultaneously in RMS and CMSs. For that purpose, it is recommended that one MAH takes the lead in the procedure and submits the application to the RMS and CMSs together with agreements of the respective national MAHs to act on their behalf which is signed by the respective national MAHs. Alternatively each MAH submits an application in the member state(s) where he acts as MAH for that product. The MAH holding the MA in the RMS and in the CMSs where he acts as MAH submits the application form to the RMS whereas the different MAHs holding the MA in the CMS where the transfer occurred submits the application form in those CMS.

The RMS is requested to check the letter of dispatch as prescribed in the corresponding BPGs for post-authorisation procedure (variations, extensions, renewals) in order to ensure that each CMS has received the application. However, it is the duty of the MAHs to act

\(^1\) Guidelines of 16.05.2013 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.
together to submit the unique letter of dispatch according to the actual situation and to submit the variation in all CMSs. The procedure is followed as prescribed in the corresponding BPGs for procedures. The RMS sent the request for supplementary information (RSI) to the corresponding MAH. It is the duty of the applicant to forward this RSI to the others MAHs. It is expected that the old and new MAHs would take the opportunity to liaise with each other to reach a common position during the procedure. It is mandatory that the outcome of the procedure and decision is identical in each MS. The associated product literature should remain harmonised in RMS and CMSs. The product remains within the MR regimen. The only case where the decision can differ accordingly to the MAH in each MS is if the change impacts the MAH details (address, name of the holder...).

To note: it is not possible for the new MAH in one MS to develop its own data and to claim for them. If such new data are developed, the new MAH should follow the duplicate application procedure in order to be granted a new MA and to benefit of the new data in a subsequent step.

6. POST-AUTHORISATION SURVEILLANCE

The Pharmacovigilance duties should be performed according to the relevant guidance documents and the contractual arrangements cited in step 4.1.3. In particular, the requirements prescribed by the Volume 9B should be fulfilled by both the NCA and the MAH. Even if the new MAH subcontracts all pharmacovigilance activities to the old MAH, he remains responsible for pharmacovigilance in the territory where he is MAH: good communication and cooperation with old MAH is essential. The new MAH can monitor and review the performance of the subcontracted activities and the identification and implementation of any needed improvement through, for example, compliance data or audits. Outcome of the surveillance by the EU QPPV should be communicated regularly to the new MAH as well as requests made by NCAs. The new MAH should be involved in decision-making concerning pharmacovigilance issues. The same is true in the reverse situation when the old MAH subcontracts all pharmacovigilance activities to the new MAH. The RMS is in charge of the post-MA surveillance and ensures a harmonised position of all MSs concerning pharmacovigilance issues and related regulatory actions. Variations submitted following assessment of pharmacovigilance data should follow the procedure described in section 5. Regarding quality defects and other post-authorisations events, the transfer should not affect the procedure to inform the NCAs. The MAHs are expected to liaise together to share the available information relating to the use of the product in order to safeguard animal and human health.
ANNEX 1

EXAMPLES OF COMMUNICATION BETWEEN MS

I/ Example of e-mail to inform the RMS and CMSs of the transfer

E-Mail header:
DE/V/1234/001 – DUPONTOL – MAH transfer

Text:
Dear colleagues,
Please be informed that the MA of DUPONTOL product has been nationally transferred in [name of the country].
Old MAH: DUPONT
New MAH: DURAND – Adresse

II/ Example of type II procedure running:

1- Reception of the application by the RMS which should identify that different MAHs are acting in different MSs. MAHs are expected to facilitate this identification when submitting the procedure.
2 – Announcement of the procedure by the RMS to the CMSs via mrve mailboxes.

To facilitate the smooth running, it is recommended that the MAH provides this table that can be reused by the RMS.
RMS: UK
CMSs: BE, DK, FR, DE, IE, LU, SE
Procedure number: UK/V/1234/001

Table 1: Example for a multi-MAH case as per the following table:

<table>
<thead>
<tr>
<th>Product name</th>
<th>MS</th>
<th>License number</th>
<th>MA holder</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dupontol</td>
<td>UK</td>
<td>111111</td>
<td>Dupont</td>
</tr>
<tr>
<td>Dupontol</td>
<td>IE</td>
<td>222222</td>
<td>Dupont</td>
</tr>
<tr>
<td>Durandol</td>
<td>FR</td>
<td>333333</td>
<td>Durand</td>
</tr>
<tr>
<td>Durandol</td>
<td>DK</td>
<td>444444</td>
<td>Durand</td>
</tr>
<tr>
<td>Durandol</td>
<td>BE</td>
<td>555555</td>
<td>Durand</td>
</tr>
<tr>
<td>Durandol</td>
<td>LUX</td>
<td>666666</td>
<td>Durand</td>
</tr>
<tr>
<td>Martinol</td>
<td>DE</td>
<td>777777</td>
<td>Martin</td>
</tr>
</tbody>
</table>

Procedure number: UK/V/1234/001/II/001
Subject of the variation: xxxxxxxxxxx
Proposed Timetable: DO/D40/D54/D59
Short text to explain the situation.

3- Running of the procedure as detailed above and in accordance with the relevant BPG. It is recommended that at least at the beginning and the end of procedure, the RMS reminds all the CMSs that there are different MAHs for the same product in the MSs ("Multi MA holder").
4- Finalisation of the procedure: in the final email, the table summarising the situation can be repeated.
ANNEX 2

Request for transfer of the marketing authorisation holder

Pharmacovigilance for Product Name (Registration No)

From the Transfer implementation date, the DDPS governing EU Pharmacovigilance Surveillance activities would be that of the Transferor / Transferee [delete as applicable].

Contractual Agreements between the Transferor and Transferee can be made available to the NCAs for inspection at any point during the product life.

(Transferee) has the services of the QPPV stated below, and has the necessary means for the collection and notification of any adverse event occurring either in the Community or in a third country.

Qualified Person responsible for pharmacovigilance:

Name:
Company name:
Address:
Country:
Telephone:
Mobile:
Telefax:
E-mail:

Requested date of transfer of MA holder responsibility to the transferee:
The implementation date of the transfer of the MA holder responsibility to the transferee will be the DATE.

CV of the EUQPPV is provided in Annex.

<table>
<thead>
<tr>
<th>Transferee</th>
<th>QPPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Name</td>
<td>Name</td>
</tr>
<tr>
<td>Title</td>
<td>Title</td>
</tr>
<tr>
<td>Transferee Legal Entity</td>
<td>Company</td>
</tr>
<tr>
<td>Address</td>
<td>Address</td>
</tr>
</tbody>
</table>

name.surname@transferee.com  name.surname@company.com
Date : .................................... Date : .................................
ANNEX 3

LIST OF USED ABBREVIATIONS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>BPG</td>
<td>Best Practice Guide</td>
</tr>
<tr>
<td>CMDv</td>
<td>Co-ordination Group for Mutual Recognition and Decentralised Procedures - veterinary</td>
</tr>
<tr>
<td>CMS</td>
<td>Concerned Member State</td>
</tr>
<tr>
<td>DCP</td>
<td>Decentralised Procedure</td>
</tr>
<tr>
<td>DDPS</td>
<td>Detailed Description of the Pharmacovigilance System</td>
</tr>
<tr>
<td>EU</td>
<td>European Union</td>
</tr>
<tr>
<td>MA</td>
<td>Marketing Authorisation</td>
</tr>
<tr>
<td>MAH</td>
<td>Marketing Authorisation Holder</td>
</tr>
<tr>
<td>MRP</td>
<td>Mutual Recognition Procedure</td>
</tr>
<tr>
<td>MS</td>
<td>Member State</td>
</tr>
<tr>
<td>NCA</td>
<td>National Competent Authority</td>
</tr>
<tr>
<td>PIL</td>
<td>Package Information leaflet</td>
</tr>
<tr>
<td>PSUR</td>
<td>Periodic Safety Update Report</td>
</tr>
<tr>
<td>QPPV</td>
<td>Qualified Person for Pharmacovigilance</td>
</tr>
<tr>
<td>RMS</td>
<td>Reference Member State</td>
</tr>
<tr>
<td>RSI</td>
<td>Request for supplementary information</td>
</tr>
<tr>
<td>SPC</td>
<td>Summary of Product Characteristics</td>
</tr>
</tbody>
</table>