

## PROCEDURAL ADVICE ON REPEAT-USE

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### **1. INTRODUCTION**

A Marketing Authorisation Holder (MAH) can use the Mutual Recognition Procedure (MRP) for the same authorisation more than once after completion of a first MRP or a Decentralised Procedure (DCP) for the recognition of a marketing authorisation by other Member States (MS). This procedure is known as “Repeat Use”.

This procedure can be used in the following situations:

- either by application to new Concerned Member States (CMS) not involved in the first MRP or DCP
- or by reapplication to CMS withdrawn from the first procedure.

In the case the applicant withdraws its application for marketing authorisation during a MRP or DCP, this does not prevent an MAH initiating a Repeat Use procedure for that/those MSs at a later stage. For MRP, if withdrawal was on an issue relating to potential serious risk to public health (PSRPH), this issue would already have been referred to CMDh and, if necessary, CHMP for a decision. In the case of DCP, if the application is withdrawn before the Draft Assessment Report is distributed, i.e. before Assessment Step II, in a CMS which raised a PSRPH earlier in the procedure, then a CMDh referral will not be initiated (unless another MS raised the same PSRPH either earlier in the procedure or during Assessment Step II).

It should be noted that any concerns raised and dealt with in a previous MRP or DCP should not be raised again in any subsequent repeat use procedure except for justified reasons.

There is no limit to the number of Repeat Use procedure(s) until all Member States are involved in the procedure.

This document describes the procedure to be adopted for “Repeat Use”.

### **2. PRIOR TO THE REPEAT USE PROCEDURE**

#### **2.1 The MAH should finalise all ongoing procedures and update the dossier.**

##### **2.1.1 *Changes in Reference Member State (RMS) post-MRP***

Amendments to the original authorisation, Summary of Product Characteristics (SmPC), product leaflet (PL) and labelling (the RMS product) in accordance with agreements made in the first procedure must be completed before the start of a Repeat Use procedure. The RMS in liaison with the applicant will introduce such amendments using the appropriate (national) procedures. (Ref. – Notice to Applicants Vol. 2A Chapter 2 section 6.1).

### **2.1.2 Case of withdrawal of the application during an earlier procedure**

When a CMS application was withdrawn during the first or an earlier Repeat Use procedure, a PSRPH may sometimes be solved by providing additional data before reapplication in the Repeat Use. It is not acceptable to provide additional data during a Repeat Use Procedure. However, the MAH can submit documentation for addition to its dossier after completion of a previous MRP or DCP in preparation for a Repeat Use procedure.

A variation application to add any new data/documentation to formally update the dossier will be required in the RMS and existing CMS before the commencement of the Repeat Use procedure.

### **2.1.3 Variations**

Any additional changes to an application requiring a Mutual Recognition variation should be completed before the start of the Repeat Use procedure. The first MRP or DCP needs to be completed before submitting such a variation.

The CMDh has agreed that :

- in a case where all MSs have granted the marketing authorisation, the MAH may submit variations regardless of the number of days after finalisation of the procedure.
- in situations where not all MSs involved in a MRP or DCP have granted a Marketing Authorisation within the 30 day after finalisation of the procedure, MAHs can submit variations after this date, provided that high quality translations of the agreed SmPC, labelling and package leaflet reflecting the final MRP/DCP agreement have been submitted in all involved MSs.

### **2.1.4 Harmonisation of the labelling and package leaflet**

In order to initiate a Repeat Use procedure of a previous MRP approved before the requirement for harmonisation of the product particulars, harmonisation of the labelling and package leaflet must be achieved in the “old CMS” before the start of the Repeat Use procedure.

### **2.1.5 Renewals**

Any renewal procedure should be completed before undertaking a Repeat Use procedure as some changes of the marketing authorisation are allowed during the renewal process.

### **2.1.6 Updating of the dossier**

Updates to the dossier must be completed prior to a Repeat Use procedure. This updating would include:

- Any additional information/data submitted in response to the questions asked by the CMS in the previous procedure(s) in order that the new CMS are aware of the procedure history.
- Documentation relating to variations and renewals that have taken place following completion of the MRP/DCP
- Commitments that have been fulfilled without a variation procedure
- Provision of additional data to ensure compliance with current regulatory requirements, e.g. provision of details of the Pharmacovigilance System, Risk Management Plan, Environmental Risk Assessment. Additional data should be added to the dossier by variation. The applicant should discuss the exact variation procedure(s) to be followed with the RMS.

If the original dossier is structured according to the “old” EU format, when starting a Repeat Use procedure it is a requirement to submit Modules 1, 2 and 3 in the CTD structure. There is no need to reformat non-clinical and clinical data submitted with the original dossier to CTD structure. It should be stated however that Part III corresponds to Module 4 and Part IV to Module 5. Overviews and summaries of non-clinical and clinical data in Module 2 can be replaced by expert statements with reference to the corresponding expert reports in the “old” EU format. Any new preclinical or clinical data submitted to update the dossier e.g. in support of a variation, must be submitted using the CTD format. It is also necessary to provide new CTD-format summaries and overviews to cover any new information or data provided in support of the application.

Although the first MRP/DCP needs to be completed and the dossier to be updated prior to a Repeat Use procedure, the Repeat Use procedure can start 30 days after finalisation of the procedure even if that is before all marketing authorisations are granted in old CMS. However the national marketing authorisation after a DCP must have been granted in the RMS.

### **2.1.7 Repeat Use of “old dossiers”**

The MAH is responsible for ensuring that the dossier for a medicinal product is kept up to date throughout the life of the product. This should take account of any technical and scientific progress. The MAH should submit any new information which may require a variation or may influence the evaluation of the risk-benefit of the product.

As a result, the requirement at the time of the first approval in one or more Member States may no longer be in accordance with the current standards for granting a new MA in another MS. This may lead to a “new” MS raising a PSRPH during the Repeat Use procedure, and a subsequent referral to CMDh and CHMP.

In the case of “old dossiers” that may no longer be in accordance with current standards or where the risk-benefit evaluation may have changed, the MAH should consider whether there is a need to conduct new studies according to the current standards required or to provide an updated evaluation of the risk-benefit. In these cases, the MAH should discuss the issues with the RMS before submission of the Repeat Use procedure.

## **2.2 Updating of the assessment report**

The MAH should submit the updated dossier to the RMS and request the update of the assessment report (AR). A comprehensive list of variations or changes made in updating the dossier should be provided.

When the Repeat Use procedure is following an MRP (either first wave or another Repeat Use), the RMS should write an addendum to the original assessment report commenting on the changes made subsequently. Variations assessment reports or reports on other changes made to the original dossier can be appended to the original assessment report. Other relevant assessments, e.g. assessments of PSURs, or the AR within the framework of an Article 30 referral procedure, can be appended to the end of the assessment report.

When the Repeat Use procedure is following a DCP, it is recommended that the RMS prepares an updated assessment report which is representative of the outcome of the procedure, especially regarding issues raised during the DCP and an indication of how these were resolved. Variations assessment reports or reports on other changes made to the original dossier can be appended to the original assessment report. Other relevant assessments, e.g. assessments of PSURs, or the AR within the framework of an Article 30 referral procedure, can be appended to the end of the assessment report.

The RMS should mention the common renewal date (as agreed at the completion of the initial MRP or DCP) in the assessment report or if the MA has already been renewed in the RMS and “old” CMS this renewal date should be stated. In some cases the first procedure may have been concluded more than 5 years before the repeat use and the authorisation may have been granted unlimited validity in the RMS and the ‘old’ CMS. In order to comply with Article 24(1) of Directive 2001/83/EC, which states that an MA shall be valid for 5 years, any new authorisations granted as a result of ‘repeat use’ will be subject to a renewal procedure. ‘New’ MS concerned by the ‘repeat use’ application should clearly state before the end of the procedure if they accept unlimited validity already agreed in some MS and do not require a renewal.

The RMS will confirm whether an additional renewal is required or not in the end of procedure letter. Any subsequent renewal will follow the MR renewal procedure and involve all CMS. For legislative reasons the default is that a renewal will be required.

Where a further renewal is required and unlimited validity has already been agreed in some MS, then the documentation requirements may be reduced for the consolidated file if agreed by all MS concerned. In such cases the RMS should raise an item for discussion and agreement at CMDh that the documentation requirements can be reduced for the product in question.

### **3. SUBMISSION OF THE DOCUMENTATION AND VALIDATION PHASE**

The MAH should submit an application to the “new” CMS(s) according to Article 28(2) of EC Directive 2001/83.

The RMS will send the updated assessment report to the new CMS(s).

The procedure number of the second procedure is an expansion of the number of the first procedure, e.g. UK/H/123/01/E/01.

The new CMS(s) should validate the application according to the CMDh Procedure for Automatic Validation of MR Procedures for new applications.

### **4. MUTUAL RECOGNITION PHASE**

The new CMS(s) must recognise the MA of the product with the same, identical SmPC, labelling and package leaflet that were approved in the earlier MRP or DCP. The package leaflet should however be updated at the end of the Repeat Use procedure to include the product names in the new CMS(s) in section 6. The applicant will inform the ‘old’ CMS(s) of this change at the time of the next variation/notification affecting the package leaflet.

If a new CMS is not able to recognise the product with its current SmPC, labelling and package leaflet because the CMS considers that the product will cause a potential serious risk to public health (PSRPH), the procedure will be referred to CMDh for discussion. If no agreement can be reached at CMDh, the matter may be referred to CHMP for arbitration. According to Article 29 (6) the Member States that have approved the assessment report, the SmPC and the labelling and package leaflet may, at the request of the applicant, grant an authorisation at any point of time after the end of the CMDh referral procedure without waiting for the outcome of the CHMP arbitration procedure laid down in Article 32.

When a ‘new’ CMS suggests some improvements to the SmPC and/or product particulars (without PSRPH concerns), this will not influence the course of the Repeat Use procedure.

The Marketing Authorisation will be issued by the ‘new’ CMS at the end of the Repeat Use procedure with the identical SmPC, labelling and package leaflet approved in the earlier procedure.

Upon request of the new CMS, a variation immediately after the close of the Repeat Use procedure may be submitted by the applicant allowing the evaluation and the discussion of the requested SPC and/or product particular changes by all CMS (‘old’ and ‘new’).

It should be noted that any matter dealt with in a previous MRP or DCP should not be raised again in any subsequent procedure except for justified reasons.

## **5. SPECIAL CASE – SIMPLIFIED CADREAC PROCEDURE**

Although the normal timeframe for the Repeat-Use procedure is 90 days, in the case of existing marketing authorisations for the identical product granted via the ‘simplified CADREAC procedure’ this period may be reduced to 30 days with the agreement of all Member States involved in the procedure. Agreement means that the new Member States can accept the current SmPC, labelling and package leaflet in the Repeat Use procedure without any comments and are therefore prepared to grant a marketing authorisation. If all MSs involved in the Repeat Use procedure will inform the RMS between day 25 and day 29 at the latest, the RMS will finalise the procedure at day 30.