

**Recommendation for Mutual Recognition Procedure after finalisation of an article 34
referral procedure with a positive decision by the EC**

1. Introduction

Community pharmaceutical legislation has created a binding Community referral mechanism which may be invoked on the basis of an article 34 of Directive 2001/82/EC as amended ('Divergent Decision Referral').

Whenever this referral mechanism is being invoked, scientific evaluation of the matter will be undertaken by the EMA's Committee for Medicinal Products for Veterinary Use (CVMP) leading to an opinion from which the Commission issues a single decision binding the Member States (MSs) and applicant(s)/Marketing Authorisation Holder(s) (MAH).

The procedural elements of the referral procedure are laid down in Article 36, 37 and 38 of Directive 2001/82/EC as amended. All referral procedures will end with a final opinion given by the CVMP.

After submission of the final opinion to the Commission, the Commission will start the Community decision making procedure. Details, including the timetable, are given in Chapter 6 of Volume 6A of the Notice to Applicants (NtA).

Community decisions taken following a Community referral require MSs to take action. The Member States concerned by the referral shall either grant, suspend or withdraw the Marketing Authorisation (MA), or vary the terms of a MA as necessary to comply with the decision within 30 days of its notification and it has to inform the Commission and the Agency thereof.

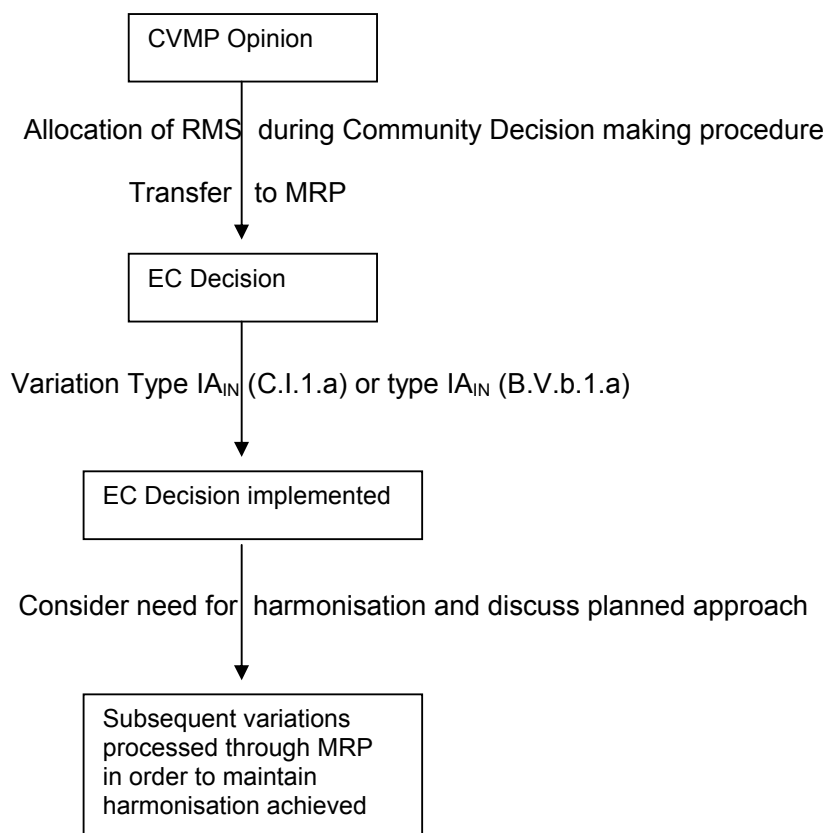
2. Aim and scope

After finalisation of a referral, subsequent applications must be submitted under European procedures in order to maintain the harmonisation achieved following the referral. However where the referral procedure was limited to certain specific parts of the authorisation, there is no obligation to follow a mutual recognition or decentralised procedure for subsequent applications. In that case, the MAs granted through "purely" national procedures stay national (Chapter 3 of Volume 6A, section 9.3 of the NtA).

This is also reflected in article 1 of Commission Regulation (EC) No 1234/2008, which describes the scope of the Variations Regulation and includes MAs granted following a referral *which has led to complete harmonisation*.

This Guidance will only cover the consequences for the applicant/MAH and MS in the case of a positive Commission decision (granting a MA or varying it) following an article 34 referral which has led to complete harmonisation of the Summary of Product Characteristics (SPC). Products not subject to the referral (not mentioned in Annex I of the Opinion/Decision) will not be dealt with in this document.

This document aims to elaborate recommendations on steps to be taken before and after the implementation of positive Commission decisions.



In addition examples of some relevant aspects around the transfer of purely national authorisations into MR-products are given in order to guide industry and authorities in the process. See annex I.

3. Allocation of Reference Member State (RMS)

- For products concerned by the article 34 referral the MAH(s) could submit a recommendation for choice of the RMS for the Mutual Recognition Procedure (MRP) if there is no RMS already in place. This recommendation should be sent to the CMDv secretariat (CMDv@ema.europa.eu).
- The choice of the RMS shall be made after the CVMP-opinion is adopted and before the Commission decision is forwarded to the MSs concerned.
- The RMS has to be chosen by the MSs at the level of the CMDv. Any recommendation submitted by the MAH(s) shall be taken into account as well as the

fact that one or more MSs have already reached a specific knowledge regarding the medicinal product involved in the referral.

- A list of products concerned (including pharmaceutical form, strengths, animal species, route of administration, MAHs in the MSs) will be circulated by the CMDv secretary to the MSs. The MSs will be allowed to inform their interest in acting as RMS for products concerned. In case there is already an RMS it is advisable that the RMS continues its responsibility.
- Information concerning the RMS appointed by the CMDv will be forwarded to the concerned MAHs and published on the CMDv website (however bearing in mind confidential aspects).
- If different strengths and/or pharmaceutical forms and/or duplicates of the product are not all authorised in the chosen RMS, different RMSs will be needed to cover the entire range of strengths and forms. The different RMSs will need to co-operate in the handling of future applications, to ensure where applicable continued harmonisation of the SPC, PL and labelling.
One common renewal date for all products would enhance the opportunity for sharing assessment and contribute to maintenance of harmonisation.

Two options are available for the MAH:

- i. The MAH may decide to obtain MAs for all strengths, forms and duplicates of the product in one of the RMSs, by repeat-use procedures using the MAs in the other RMSs. The latter RMSs should then transfer the role of RMS to the chosen, sole RMS, in accordance with the proposed strategy of the MAH. In order to facilitate this harmonisation process, the 'old' and 'new' RMS are encouraged to aim for short timelines of the repeat-use procedure(s). An administrative procedure could be applied if the RMS and future RMS both agree to.
- ii. Alternatively, the MAH may use the worksharing procedure as described in Commission Regulation (EC) No 1234/2008 to keep the SPCs harmonised.

4. Transfer to MRP

- All purely national authorisations will be included in a newly created MRP or will be enclosed in an existing MR/DC procedure for the same product, provided that the national authorisations do have the same legal base as the products of the existing MRP/DCP.
- The appointed RMS will create and finalise the same day a procedure in CTS and include the MSs involved. These MSs have been informed beforehand by the RMS. The RMS and CMSs have already received a dossier and corresponding fee in the past, therefore no dossier will be submitted again. From then on the product has been transferred to MRP status and is to be regarded as an MR-product.
- Ongoing procedures started under the national status of the product can still be finalised at the national level. It is preferred that such applications are finalised as soon as possible.
- If needed, the RMS, in consultation with the CMSs, should agree on a common renewal date with the MAH. This date should whenever possible be defined as the

earliest renewal date in a Member State that allows for a submission date within 6 months after implementation of the decision from the Commission.

- A list of 10 Critical Pharmaceutical Characteristics (CPCs) detailing the differences should be provided by the MAH as soon as possible as this would be of help to get a picture of the level of harmonisation of Part II. See annex II for the '10 points' check.

5. Implementation of the Commission Decision

- Member States concerned by the referral have an obligation to implement the Commission decision within 30 days by granting the MA or varying the terms of an existing MA and to implement the harmonised SPC, PL and labelling of the Commission decision, if applicable.
- Therefore the RMS will request the MAH to submit a type IA_{IN} (C.I.1.a) mutual recognition variation. The documentation includes the revised Product Information (PI) in accordance with the Commission decision.
- While the PI is annexed to the EC decision (in all languages) and has already been dealt with in the EMA linguistic review procedure, this is not the case for the mock-ups. In order to comply with the 30 days time frame to vary the terms of a MA including mock-ups, the MAH is recommended to submit the mock-ups during the type IA variation in the MSs (if applicable) and to discuss them with the NCA during the variation procedure.
- In case the PI is not impacted by the referral but only Part II of the dossier, the MAH will be requested to submit a type IA_{IN} (B.V.b.1.a).

6. Maintenance of harmonisation

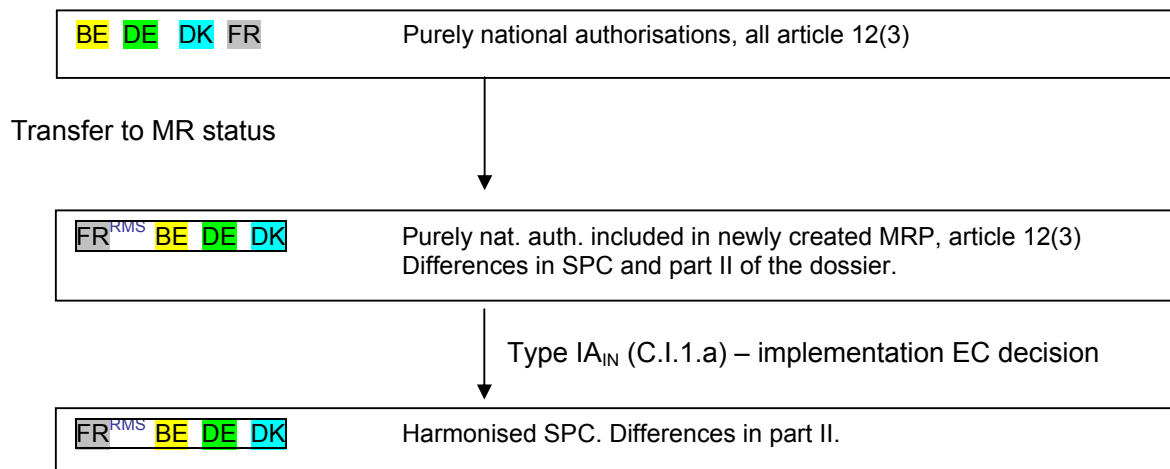
- The harmonised SPC, PL and labelling adopted by the referral and annexed to the Commission decision shall be maintained through future procedures, but will take into account new information gained during the life cycle of the medicinal product.
- For future procedures (e.g. variations, renewals, PSUR) the RMS should be the same as that appointed by CMDv.
- In case Part II of the dossier of an individual medicinal product is not fully harmonised within the EU and it was not harmonised during the referral process itself, it is an obligation of the MAH and RMS to consider how to proceed and to discuss the planned approach with the CMSs. The list of CPCs detailing the differences would be of help to get a picture of the level of harmonisation.
- In case Part II of the dossier is not yet harmonised at the time of submission of the application for renewal, any differences regarding the dossier as far as they concern the renewal application form and/or PI have to be specified. The application form should reflect these differences.

7. MR procedure numbers / CTS

The MR procedure numbers should be allocated to products transferring into MR i.e. when the RMS is appointed. A specific procedure sheet for these products following a referral procedure will be created in CTS if applicable.

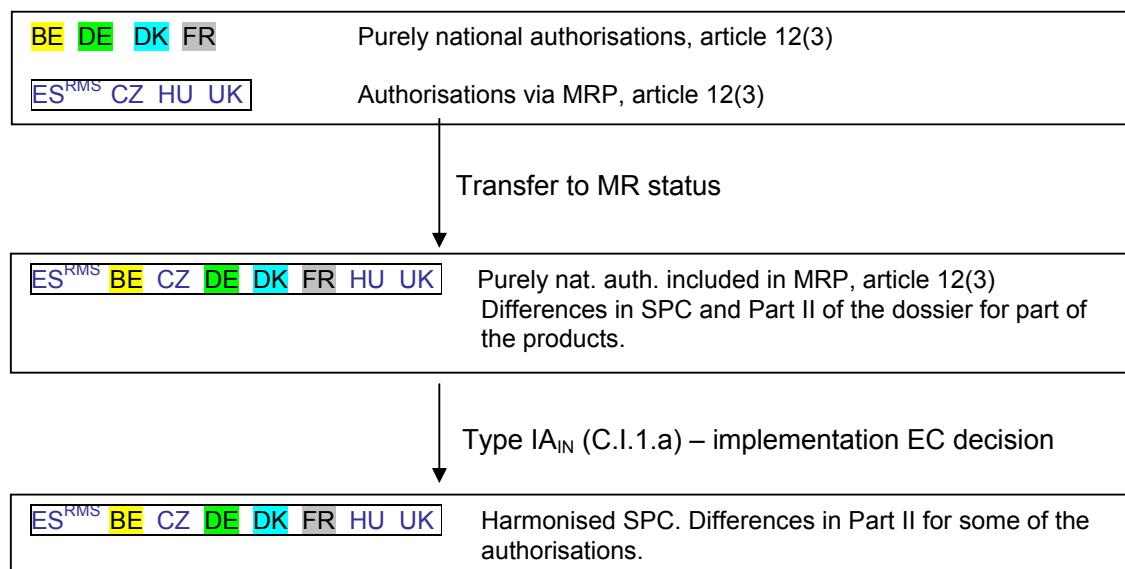
Annex I

A. Products covered by the article 34 referral – purely national authorisations – same legal base



Based on the '10 points' check (10 Critical Pharmaceutical Characteristics) the RMS, CMSs and MAH will decide whether harmonisation is needed or not. In case differences are minor, a list detailing the differences could be sufficient. For future variation applications the list should be checked and used to decide whether an upcoming variation could be processed without prior harmonisation of certain parts of the dossier.

B. Products covered by the article 34 referral – mix of purely national authorisations and MR-products – same legal base



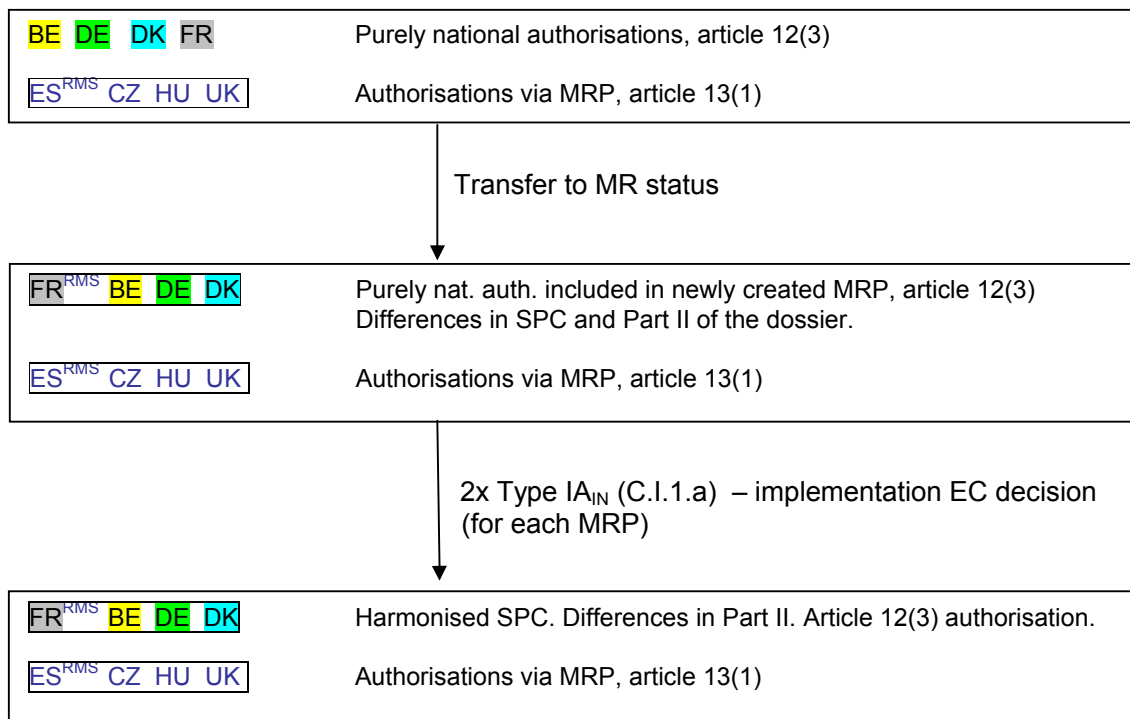
The purely national authorisations might be added to the existing MRP. As there is a harmonised Part II available in ES, CZ, HU and UK, it would be desired to replace Part II of the purely national authorisations with the one already assessed in the MRP.

Variation B.V.b.1 could be applied – Update of the quality dossier following a Commission Decision following the procedure of articles 30 or 31 of Directive 2001/83/EC or articles 34 or 35 of Directive 2001/82/EC (referral procedure):

- z) The harmonisation of the quality dossier was not part of the referral, but a harmonised quality part is available which has been assessed in a previous MR/DC procedure.

This would be per default a type IB variation.

C. Products covered by the article 34 referral – mix of purely national authorisations and MR-products – *different* legal base



With regard to the newly created MRP, the RMS and MAH (in consultation with the CMSs) will decide whether harmonisation of the quality part is needed based on the ‘10 points’ check (10 CPCs).

In case of future variations the worksharing procedure could be used. Harmonisation of the complete initial dossier is not a prerequisite for a worksharing procedure as long as there is no or limited need for assessment of a potential product-specific impact.

Annex II – Critical Pharmaceutical Characteristics

‘10 point’ check:

1. Full qualitative and quantitative composition of the product.
2. Packaging description; qualitative & quantitative composition and specification of the packaging.
3. Active substance specifications and methods of analysis (not the validation of the methods).
4. Name/address of active(s) substance(s) manufacturer(s), including some means of reference to the data, such as CEP or DMF number.
5. Active ingredient retest-period (not the stability data).
6. Specifications of excipient(s) not described in a Pharmacopoeia and test methods (not validation of the methods).
7. For excipient(s) described in a Pharmacopoeia, any tests additional to those of the monograph.
8. Finished product specifications (release and shelf-life) and methods of analysis (not the validation of the methods).
9. Name/address of finished product manufacturer(s).
10. Method of manufacture of the product and in-process controls (not process validation).