

<p style="text-align: center;">RECOMMENDATION FOR MUTUAL RECOGNITION PROCEDURE AFTER FINALISATION OF A REFERRAL PROCEDURE WITH A POSITIVE DECISION BY THE EC</p>

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Introduction

Community pharmaceutical legislation has created a binding Community arbitration mechanism which may be invoked on the basis of the following Articles:

- Article 29 (4) of Directive 2001/83/EC as amended ('Mutual Recognition Referral');
- Article 30 of Directive 2001/83/EC as amended ('Divergent Decision Referral');
- Article 31 of Directive 2001/83/EC as amended ('Community Interest Referral');
- Articles 35 and 36 of Directive 2001/83/EC (Follow up - referrals).

Whenever this referral mechanism is being invoked, scientific evaluation of the matter will be undertaken by the EMA's Scientific Committee for Human Medicinal Products (CHMP) or in specific cases by the Committee for Herbal Medicinal Products (HMPC), leading to an opinion from which the Commission issues a single decision binding the Member States and Applicant(s)/Marketing Authorisation Holder(s) (MAH).¹

The procedural elements of the referral procedure are laid down in Article 32, 33 and 34 of Directive 2001/83/EC as amended. All referral procedures will end with a final opinion given by the CHMP or HMPC.

After submission of the final opinion to the Commission, the Commission will start the Community decision making procedure. This procedure is, in most aspects, the same as the procedure applicable in the Centralised Procedure. Details including timetable are given in Chapter 6 of Volume 2A of the Notice to Applicants (NtA).

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

This Guidance will however only cover the consequences for the applicant/MAH and MS in the case of a positive Commission Decision.

Depending on the status of the MA involved in the community referral in the Member States different action has to be taken by the MAH to receive a MA in all Member States concerned after finalisation of a referral procedure with a positive Commission Decision. Further information is given in sections 1. to 6.

¹ Note the judgement ECJ- C- 39/03 P ("Anorectic case")

The requirements to receive or to vary a MA after finalisation of the referral with a positive Commission Decision are described in the following sections and, in particular, what type of documentation and information is required by the Member States from the applicant/MAH or from the Reference Member State depending on the status of the MA. This recommendation of the Member States should be read together with Chapter 3 of Volume 2 of the NtA.

Moreover, after finalisation of a referral the MA shall enter into a procedure which allows the MAH to improve and/or develop the product further in a **harmonised manner**, as foreseen in Article 1 of Commission Regulation (EC) No 1234/2008.

Therefore the MA has to be handled in a Mutual Recognition Procedure for MA after a referral procedure following either Article 29(4)² or 30 or 31(1).

For a MAH involved in Article 31(2) procedures specific information is given in the corresponding section.

A Commission Decision as result of an application according to Article 29 of Commission Regulation (EC) No 1901/2006 as amended ('Paediatric Regulation') is outside the scope of this Recommendation. Specific guidance is available on the CMDh website – see: [‘Recommendations for Implementing Commission Decisions following an Article 29 application under the Paediatric Regulation’](#).

- **Implementation of the Commission Decision following Article 30 or 31(1)**

- Member States concerned by the referral have an obligation to implement the Commission decision within 30 days by granting a marketing authorisation or varying the terms of a marketing authorisation and to implement the harmonised SmPC, PL and labelling of the Commission decision, if applicable. This will be achieved by the applicant/MAH with the submission of a variation according to Commission Regulation (EC) No 1234/2008.
- If the applicant has fulfilled its obligations, the applicant has the possibility after Day 30 has passed to submit variations, repeat-use procedures, extension applications or renewal and RMS can start the procedure accordingly.

- **Allocation of Reference Member State (RMS)**

- With the exception of referrals based on Article 31(2) of Directive 2001/83/EC, as amended the MAH has to choose the RMS for the Mutual Recognition Procedure (MRP) if there is no RMS already in place.
- **The choice of the RMS shall be made after the CHMP/HMPC-opinion is adopted and before the Commission decision is forwarded to the MS concerned.**
- The Member State of the Rapporteur for the referral procedure will have initial responsibility to oversee the transfer of national marketing authorisations into mutual recognition following completion of Article 30/31(1). This Member State will liaise directly with the MAH.
- If the MAH does not use his right to choose the RMS, the Rapporteur will refer the matter to the CMDh which will contact the MAH and appoint the RMS. It may be taken into account that one or more Member States could have acquired specific knowledge regarding the medicinal product involved in the referral and therefore should preferably act as RMS.
- If the Article 30/31(1) referral concerns more than one medicinal product/applicant(s)/MAH(s) and more than one RMS, the Rapporteur will refer the matter to CMDh who will appoint a Member State coordinator. The coordinator will take over responsibility from the Rapporteur for liaison with the MAHs and other member states about appointment of RMSs for the medicinal products concerned.

² In the case of Article 29(4) the medicinal product has been handled via the MRP/DCP for the granting of the marketing authorisation
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- Information concerning the Member State coordinator or the RMS appointed by the CMDh will be published on the CMDh website.
- 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 continued harmonisation of the SmPC, PL and labelling.

Two options are available for the MAH:

- o 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. This course of action is recommended as it will simplify the processing of all future applications and improve the harmonisation of the products involved. In order to facilitate this harmonisation process, the 'old' and 'new' RMS is encouraged to aim for short timelines of the repeat-use procedure(s).
- o Alternatively, the MAH may use the worksharing process as described in Commission Regulation (EC) No 1234/2008 to keep the dossier harmonised in all RMS appointed.

- **Maintenance of harmonisation**

- The harmonised SmPC, 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 informations 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 following referral.
- The maintenance of harmonisation may vary if multiple MAH/product/RMSs are concerned.
- If the Quality dossier is not yet harmonised at the time of submission of the application for Renewal, any differences regarding the dossier (e.g. composition and/or manufacturer(s)) as far as they concern the Renewal application form and/or product information have to be specified. The application form should reflect these differences.
- If the Quality dossier was not harmonised during the referral process itself, it is an obligation of the MAH to harmonise the Quality dossier after the Commission Decision. This has always be done by variation procedure according to Commission Regulation (EC) No 1234/2008. It is recommended to perform the quality harmonisation as soon as possible.

After Article 30 and Article 31(1) procedure

If the referral concerned only **one MAH/product/RMS**, the maintenance of harmonisation is straightforward through MR procedures.

If the quality dossier of an individual medicinal product is not fully harmonised within the EU in particular Module 3, it is an obligation of the MAH to decide on a single quality dossier which will then be used for the Mutual Recognition Procedure and all following variations.

The harmonisation can be done in a one step procedure addressing the whole Module 3, in this case the MAH may submit a single (composite) Type II variation to harmonise the quality dossier. In exceptional cases and as agreed by RMS and CMS, the harmonisation can be done in several steps (to be defined). In both cases, the CTD format in consistence with the Module 3 CTD granularity is applicable.

Such and any other variations may be submitted 30 days after granting of the Commission Decision, if the applicant has fulfilled the requirements as described in Commission Regulation (EC) No 1234/2008.

The RMS, taking into consideration the agreed harmonized birth date, 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. If in the majority of MS no further renewal is necessary and in case a complete harmonisation of the dossier (including Module 3) has taken place, the possibility of a pure administrative renewal in these MS based on the Commission Decision can be the better alternative in order to save resources. The RMS should in such a case raise the item at the CMDh Meeting for discussion and agreement of an administrative renewal for the product in question

After Article 31 procedure

If the referral concerned **multiple MAH/product/RMS(s)**, the coordinator MS appointed by CMDh will have a continuing role to oversee development of the clinical aspects of the dossier:

- (a) to ensure that harmonisation of the key issues between all concerned marketing authorisations is maintained
- (b) to maintain a record of major differences between the marketing authorisations as may arise during the evolution of a product over time e.g. addition of new indications supported by data. Such information would be available to the Commission in case of any further referral deemed necessary.

The quality dossier has to be harmonised for each individual product aligned into a MRP for which the RMS is responsible, by variation as described above. This is necessary to facilitate future MR quality variations to be processed as one procedure for individual products. It will not be necessary to harmonise the Quality dossier between the dossiers of the different RMS.

- **MRP numbers / CTS**

The MRP 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. This is also the case of the MRP consists of the RMS only.

- **Fees**

Fees in the MR remain under whichever national conditions apply.

1. Article 29(4) procedure (MR and DC referral)

1.1 After finalisation of an Article 29(4) procedure

- **Actions to be taken by RMS and CMS**

In general there is no need for the applicant/MAH to submit to the national authorities the documentation presented to the CHMP/HMPC during the referral procedure. In case of an exception from this rule, the respective MS will provide this information in the Notice to Applicants Volume 2A Chapter 7 (*National procedure after a commission decision on a referral*)

The (original) RMS will circulate the final product information to all CMS without delay.

The MA has to be issued/varied by the Member States concerned according to Article 34(3) Dir. 2001/83/EC within 30 days by use of the appropriate national procedure. An additional assessment by MS is deemed not to be necessary.

If a MA was granted already after the CMDh referral according to Article 29(6) by a NCA, the SmPC, PL and labelling has to be harmonised in line with the Commission Decision according to the national procedure of this MS. The Commission Regulation (EC) 1234/2008 is in this case not applicable.

In case of a repeat use procedure, CMS who have granted a MA as result of the involvement in previous wave(s), will have to harmonise the already existing MA with the Commission Decision according to national procedures.

- **Actions to be taken by Member States not involved in the MRP or by Member States where the application was withdrawn during the MRP/DCP**

If the MAH decides to request a MA in these Member States all requirements for the repeat use of MRP shall be taken into account.

The applicant has to submit to the national authorities the complete dossier (including questions and responses) from the MRP/DCP and the documentation presented to the CHMP during the referral procedure as an addendum.

The (original) RMS submits the original AR including the reports provided by the Agency (Rapporteur/Co-Rapporteur referral AR) as an addendum to the original AR in a timeframe agreed between MAH and RMS.

If the repeat use procedure (RUP as MRP) occurs with a significant delay after the Commission Decision, the RMS may be required to write an addendum to the original AR taking into account the reports provided by the Agency (Rapporteur/Co-Rapporteur referral AR) and commenting on the changes subsequently made, e.g. by approved variations).

1.2 Maintenance of the harmonisation after an Article 29(4) procedure

As an Article 29(4) referral will not change the status of the marketing authorisations in question they will stay in Mutual Recognition. The known legal requirements for the life cycle management (e.g. variations, renewal) will apply.

2. Article 30 procedure (“Divergent decision referral”)

2.1 After finalisation of an Article 30 procedure (Article 30 (1) and Article 30 (2))

- **Member State/Marketing Authorisation (Holder) involved in the referral – a national MA is already granted (brand leader or other MA)**

There is no need for the applicant/MAH to submit to the national authorities the documentation presented to the CHMP/HMPC during the referral procedure via a variation. According to the document requirements in the Variation Classification Guideline (B.V.b.1.a) only a reference to the Commission Decision concerned is necessary.

The designated RMS will submit, if available, the original AR including the reports provided by the Agency (Rapporteur/Co-Rapporteur referral AR) as an addendum to the original AR.

If no "original" AR has been prepared or if one or more national AR(s) are existing the designated RMS has to take into account all information available preparing the AR. However, there is no obligation for the RMS to write at this point of time a new AR.

The Commission Decision has to be implemented according to Article 34(3) Dir. 2001/83/EC within 30 days by use of the appropriate variation according to Commission Regulation (EC) No 1234/2008.

The outcome of an Article 30 procedure will be published in the CMDh press release and in tabular form on the CMDh homepage (<http://www.hma.eu/261.html>) for reminding MAHs of generic MPs to submit Variation procedures in order to comply with the outcome of the Article 30 procedure. Depending on the status of the MP in question this has to be done either by a Type IB Notification (MRP/DCP) or for purely national authorised medicinal products in accordance with national requirements.

The next following Variation procedure should not be validated in case the product was not transferred to MRP by the MAH.

- **Member State where no MA has been granted**

If the MAH decide to ask for MA in the above mentioned situation all requirements for the repeat use of MRP should be taken into account regarding the dossier to be submitted by the applicant and the AR by the RMS (see paragraph 1.1). The MRP should be handled in a timeframe agreed between MAH and RMS.

2.2 Maintenance of the harmonisation after an Article 30 procedure

The RMS shall be chosen by the MAH for all up-coming procedure after the CHMP/HMPC-opinion is adopted and before the Commission Decision is forwarded to the MSs concerned.

If the MAH is not using his right to choose the RMS before the Commission Decision is forwarded to MSs the RMS has to be chosen by the Member States at the level of the CMDh. It may be taken into account that one or more Member States have already reached a specific knowledge regarding the medicinal product involved in the referral and therefore should preferably act as RMS.

3. Article 31 procedure (“Community interest referral”)

3.1 After finalisation of an Article 31 procedure

Member State/MAH involved in the referral – **a national MA is already granted** (brand leader or all MA with the same active substance).

In general there is no need for the applicant/MAH to submit to the national authorities the documentation presented to the CHMP/HMPC during the referral procedure. In case of an exception from this rule (Article 31(2) for medicinal products outside the scope of Commission Regulation (EC) No 1234/2008), the respective MS will provide this information in the Notice to Applicants Volume 2A Chapter 7 (*National procedure after a commission decision on a referral*).

The designated RMS will submit, if available, the original AR including the reports provided by the EMA (Rapporteur/Co-Rapporteur referral AR) as an addendum to the original AR.

If no "original" AR has been prepared or if one or more national AR(s) are existing the designated RMS has to take into account all information available preparing the AR. However, there is no obligation for the RMS to write at this point of time a new AR.

The Commission Decision has to be implemented by the Concerned Member State according to Article 34(3) Dir. 2001/83/EC within 30 days.

- **Member State where no MA has been granted**

If the MAH decides to ask for a MA in the above mentioned situation all requirements for the repeat use of MRP shall be taken into account regarding the dossier to be submitted by the applicant and the Assessment Report by the RMS (see paragraph 1.1). The MRP should be handled in a timeframe agreed between MAH and RMS.

3.2 Maintenance of the harmonisation after an Article 31 procedure

Article 31 (1) – complete SPmC is affected.

1. If only one MAH was/is involved the rules described under the Article 30 procedure shall be followed.
2. If more than one MAH are involved in an Article 31 procedure more than one Member State can act as RMS. For each independent MAH (not in line with the definition of the same MAH) the rules described under the Article 30 procedure shall be followed.

- The RMS should be chosen by the MAH for all up-coming procedures after the CHMP/HMPC-opinion is adopted and before the Commission Decision is forwarded to the MSs concerned.

- If the MAH is not using his right to choose the RMS before the Commission Decision is forwarded to MSs the RMS has to be chosen by the Member States at the level of the CMDh.

Article 31 (2) – specific parts of the SmPC are affected

– The referral concerns a range of MPs or a therapeutic class. In this case the procedure is limited to certain specific parts of the authorisation.

- In an Article 31(2) referral procedure there might be MA included which are issued nationally, that will remain national. In these particular cases - only parts of the SmPC are harmonised, not the full text – the MA stays within the existing legal framework – either as purely national MA or as national MA within the context of mutual recognition.

- For MAs issued via the MRP or DCP, the RMS should circulate to all MSs the full product information, including the specific parts of the authorisation agreed during the referral procedure, for information;
- In case of Mutual Recognition the implementation has to be done according to the Commission Regulation (EC) No 1234/2008 in line with the respective scope of the variation under section C.I.1 for the Classification Guideline.
- Variations regarding changes in the harmonised parts of the SmPC shall be done in a co-ordinated process where all MAH and all (R)MS are involved in order to maintain harmonisation as far as possible.

A “Coordination RMS” should be nominated among the acting RMS. Discussions can be held at the level of the CMDh.

4. Article 35 and 36 procedure (“Follow-up referrals”)

4.1 After finalisation of an Article 35 procedure

Changes in the MA should be done according to the outcome of the referral procedure.

4.2 Maintenance of the harmonisation after an Article 35 or 36 procedure

The RMS is responsible for maintaining the harmonisation.

5. Harmonisation of the national and EU-Market

For MA's with the same active substance (same qualitative and quantitative composition) and having the same pharmaceutical form which were not involved in the Article 30 or Article 31 procedure it is recommended to reach harmonisation with the out-come of the referral procedure via variation procedures. According to the first registration procedure a national variation or a variation through the Mutual Recognition shall be initiated.

If the MAH is not willing to alter the medicinal product in question (SmPC, PL, labelling) in line with the outcome of referral procedure /CHMP/HMPC opinion/Commission Decision a new referral may be triggered either by the Member State or by the EU-Commission.

6. Information on the handling of medicinal products not involved in the referral procedure

6.1 Article 30 and 31 procedures

During an Article 30 or 31 procedures the Member States will validate, start and evaluate all applications with the same active substance (**same qualitative and quantitative composition in active substance and having the same pharmaceutical form**) if they are not involved in the referral procedures in particular generics. A MA will be given depending on the issue raised in the referral. Also variations and renewals will be accepted depending on the issue raised in the referral.

In any case the outcome of the referral procedure has to be implemented afterwards. This is within the responsibility of the respective MS.

6.2 Extension

Extensions of medicinal products involved in referral procedures will be accepted depending on the issue raised in the referral (see also MRFG press release July 2000).

Member States and applicants shall make efforts to reach a harmonisation during the different procedures.

Detailed information on this subject is given in the Notice to Applicants Volume 2A Chapter 3 Section 9.2.