



PERF III Acquis Working Group

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This document sets out discussions held in the PERF III Acquis Group. It intends to facilitate preparation and implementation of the relevant EC legislation. The document is of an informal character only and does not bind the parties.

Phasing-in EU procedures: MRP and referrals

September 23, 2003

PERF Acquis Implementation Priority Action Area

Reflection Paper

Having regard to the

- expected date of the Enlargement (1.5.2004),
- need
 - to comply with the Acquis Communautaire and to ensure basic principles of medicinal products legislation, i.e. protecting public health and completing the single market,
 - not to jeopardise the functioning of EU marketing authorisation procedures and to prepare both Acceding Countries and existing Member States for the new situation after Enlargement,
 - to create a reasonable basis for future regulation,
 - to provide guidance to the industry and other stakeholders,
- discussions within PERF II - Acquis Implementation Priority Area meetings and reflection papers arising from these discussions¹,

the following conclusions have been agreed.

A. Dealing with applications for marketing authorisation pending in the Acceding Countries before the day of accession

I. Legal situation and options possible as of the day of accession

As discussed within PERF II, all applications received by the Competent Authorities of Acceding Countries (ACs) before the day of accession are considered national applications. As of the day of accession Articles 17 (2) and 18 of the Directive 2001/83 (Articles 21 (2) and 22 of Directive 2001/82²) due to the broad wording apply to all pending applications irrespective of when the application was submitted.

“Article 17 (2)

Where a Member State notes that an application for authorization is already under active examination in another Member State in respect of that medicinal product, the Member State concerned may decide to suspend the detailed examination of the application in order to await the assessment report prepared by the other Member State in accordance with Article 21 (4).

The Member State concerned shall inform the other Member State and the applicant of its decision to suspend detailed examination of the application in question. As soon as it has completed the examination of the application and reached a decision, the other Member State shall forward a copy of its assessment report to the Member State concerned.”

¹ <http://perf.eudra.org/perf2/IndexA.htm>.

² In order to enhance readability of the document the corresponding references of the Veterinary legislation will only be quoted the first time reference is made to an Articles of the Human legislation.

“Article 18

Where a Member State is informed in accordance with Article 8 (3) (l) that another Member State has authorized a medicinal product which is the subject of an application for authorization in the Member State concerned, that Member State shall forthwith request the authorities of the Member State which has granted the authorization to forward to it the assessment report referred to in Article 21 (4).

Within 90 days of the receipt of the assessment report, the Member State concerned shall either recognize the decision of the first Member State and the summary of the product characteristics as approved by it or, if it considers that there are grounds for supposing that the authorization of the medicinal product concerned may present a risk to public health, it shall apply the procedures set out in Articles 29 to 34.

EEA countries should be regarded as Member States for the application of these Articles.

With regard to the application of these Articles³ it is important to clarify when a medicinal product is considered to be the same as the product under active examination or already authorised. In view of sections E.5 and E.6 of Commission Communication on the Community marketing authorisation procedures for medicinal products of 1998 (OJ C 229 of 22.7.1998, p. 4), two aspects have to be taken into account: the applicant/MA holder on the one side and the characteristics of the product on the other side:

- With regard to the applicant/MA holder:
Articles 17(2), 18 of Directive 2001/83 apply to
 - medicinal products from the same company or from applicants belonging to the same mother company or group of companies or
 - a medicinal product from applicants which, without belonging to the same mother companies, have concluded agreements (for examples “licensees”) or which exercise concerted practices concerning the placing on the market of the relevant medicinal product in different Member States (i.e. the current EU MS, other EEA countries and 10 Acceding Countries).
- With regard to the product:
Articles 17(2), 18 of Directive 2001/83 clearly apply to identical medicinal products. Its objective is to secure an efficient implementation of Community law provisions dealing with the mutual recognition of national marketing authorisations. For this reason, certain differences do not automatically prevent the application of Articles 17(2), 18. If the products have the same qualitative and quantitative composition in active substance(s) (i.e. the same strength) and the same pharmaceutical form, they have to be considered as being the same. There may be the differences in excipients provided that there is no impact on safety and efficacy.

Moreover, the legal basis on which the MA was granted must be identical in case of “same medicinal products”.

Even if MRP started to be mandatory as of 1998, the Articles 17 and 18 are to be applied, irrespective of the date of the MA application/authorisation. Therefore, no difference is being made if the application is submitted or the authorisation is granted before or after 1998.

As of day of accession, the application of Articles 17(2) and 18 means a complex exercise in practice. For practical reasons, the applications for MA pending in a Member State (both existing and new MSs) on the day of accession should be differentiated according to the following groups and dealt with accordingly:

1. The “same” medicinal product either is *authorised* in existing Member State(s) by MRP or by national procedure or is authorised in new Member State(s) by national procedure.

If a medicinal product, for which an application is pending in a Member State, has already obtained a marketing authorisation in another existing or new Member State, there are two ways to proceed in compliance with the Community law. These ways are the same, whether the existing national marketing authorisation has been granted by mutual recognition or by a purely national procedure:

³ The wording of Articles 21 (2) and 22 of Directive 2001/82 is identical.

- Article 18 of Directive 2001/83 lays down specific rules for such situation. It creates an obligation on Member States to initiate, each time it is applicable, a mutual recognition procedure independently of the course of action chosen by the applicant. The Member State that is informed that another Member State has already authorised the product shall suspend the assessment and shall request this other Member State to forward its assessment report. Within 90 days of the receipt of the assessment report, the Member State concerned shall either recognise marketing authorisation of the other Member State or, if it considers that there are grounds for supposing that the authorisation may present a risk to public health, shall apply Articles 29 to 34 of Directive 2001/83 (Articles 33 to 38 of Directive 2001/82).
- The applicant chooses the Reference Member State amongst existing or new EU Member States, requests the assessment report, which according to Art. 28 (Art. 32 of Directive 2001/82) the Reference Member State shall prepare or update within 90 days. For a given product only that new EU Member State may become Reference Member State, which authorised or “updated” the product according to EU standards. After the applicant withdraws his application in the other Member State(s) he can resubmit an application in the Member State(s) concerned, this time under the mutual recognition procedure of Article 28.

For further details see:

- [Triggering of Mutual Recognition by Member States \(Article 18 of Directive 2001/83/EC\) Member States' Standard Operating Procedure](#)
- [MRFG Position paper on repeat use of MRP](#)
- [VMRFG - Repeat Use of the MRP](#)
- [Procedure for Automatic Validation of MR Procedures for New Applications](#)
- [Best Practice Guide for Mutual Recognition](#)
- [VMRFG Best Practice Guide](#)
- [MRFG Best Practice Guide for the Reference Member State in the Mutual Recognition Procedure](#)
- [Applications under Annex II of Regulation \(EC\) No 541/95 in Mutual Recognition Procedures – Member States Recommendation](#)
- [Notice to Applicants, Volume 2A, Chapter 2 - Mutual Recognition](#)
- [Notice to Applicants, Volume 6A, Chapter 2 - Mutual Recognition](#)

2. The “same” medicinal product is not authorised in any of the existing or new Member State/s but an application for authorisation is under *active examination* in any of them

In this case, there are three possibilities to proceed:

- The Member States in which an application has been filed could continue to proceed with the examination of the applications independently. This option however is unsatisfactory in various ways, as it would mean unnecessary duplication of work for the competent authorities and the companies. However, this possibility is only theoretical, because as soon as one of the Member States actually grants a marketing authorisation, Article 18 becomes applicable and the Member State that has not yet granted the authorisation must start a mutual recognition procedure in accordance with that Article.
- On proposal by the applicant, one Member State where the application is already under active examination acts as future Reference Member State. The other Member States, in which an application has been filed, suspend the authorisation procedure in agreement with the applicant and await the assessment report by the Reference Member State.
- The applicant chooses the Reference Member State and withdraws his application in the other Member States. After accession, he resubmits an application in the Member States concerned, this time under the mutual recognition procedure of Article 28.

For further details see:

- [Simultaneous applications \(Article 17 paragraph 2 of Directive 65/65/EEC\) Member States Standard Operating Procedure](#)

3. The “same” medicinal product neither authorised in any of the existing or new Member State/s nor is any MA application pending in any of them

In such a case assessment in the only Member State that has an application pending continues on a purely national basis and national decision is issued.

4. Specific handling of Well Established Use applications and line extensions

In those cases where the application is

- a bibliographic application based on Well Established Use supported by data referring to an existing group of products with different SPCs in the Member States (as far as no Community harmonisation of the use of the constituent(s) of the said product exists); such an application should meet all the requirements on full self-standing dossier and all the aspects of assessment should be covered, or
- a line-extension of a “purely” national independent MA (i.e. neither involved in MRP nor a referral procedure is related to it),

a national procedure can continue even if the product is already authorised in more than one Member State (i.e. the current EU MS, other EEA countries and 10 Acceding Countries).

In the case of “mixed data” applications where literature data replacing tests and trials are submitted together with original results of test and trials, the legal basis for the application is bibliographic and well established use has to be demonstrated. Where the literature data are merely supportive of a complete, independent dossier there is no need to demonstrate a well established use.

A line-extension is defined as a significant change to an authorised product. In the case of line extension, the applicant of the present application must be the same as the MAH of the existing MA and an application for a line extension should be made under the same legal basis as the existing MA of the product line or where appropriate under the Article 10(1)(a)(iii) second subparagraph (either a complete application or an abridged one, as appropriate).

It should be emphasised that for the product which underwent a referral procedure the follow-up (e.g. variations, line extensions) must go through MRP. However, as the ACs were not involved before the accession either in MRPs or in referral procedures, this obligation is not relevant to them.

II. Recommendations to be taken into account before the day of accession

To prevent that applicants and Competent Authorities of ACs invest resources and workload into the assessment of applications, which finally cannot be finished as a national procedure because of Article 18, there should be established;

- co-operation amongst applicants and regulatory authorities,
- co-operation amongst regulatory authorities both in existing MSs and ACs,
- careful planning and monitoring of processing of individual applications.

It is important to identify as early as possible, before the day of accession, all the situations described above and to adopt the necessary preparatory measures. As the processing time for MA applications before the accession in ACs might exceed the EU limit of 210 days active time, it is important to identify in each AC, which applications will be finalised before the accession and which will not. It is realistic that some applications submitted now will not be finished before the day of accession and therefore they can be subject to EU procedures.

1. Recommendations to the applicants

The applicants should take account of the regulatory situation in the EU at the day of accession with regard to the medicinal product in question, and they should in particular take into account:

- the intention to submit the application in an AC or MS, including the expected date of granting a MA or the intention to start a MRP,
- the submission of an application in the AC or MS, including the expected date of granting a MA or the intention to start a MRP,

- the granted MA in the AC or MS or the intention to start MRP,
- the pending or completed MRP,
- the status of line extensions and bibliographic applications for products with non-harmonised SPCs if the product is already authorised in more than one Member State (both existing and new MSs).

It should be noted that there is little experience with regard to the procedures set out in Articles 17 (2) and 18. In addition, no deadlines are fixed in which the assessment report should be provided to the requesting national authority. It is therefore recommended that applicants, for practical reasons, use the “normal” Mutual Recognition or Repeat Use Procedure as laid down in Chapter 4 of the Directive 2001/83/EC. Having in mind the expected authorisation times in the individual AC and foreseeing the situation at the day of accession, the applicants are thus advised the following:

- When the product is not authorised either in an EU MS or in an AC, it is recommended to submit the application in only one existing EU MS or AC and to start the “normal” MRP after the enlargement. The aim of such instruction is to prevent a situation where the MA application is pending in more than one existing or future EU Member States. However, if there are already more applications pending close to the day of accession, the “Reference Member State” should be chosen and negotiated amongst existing or new EU MSs. If that MS commits to fulfil this role the other pending applications should be withdrawn. New applications are then to be resubmitted after accession under the regular mutual recognition procedure according to Article 28 of Directive 2001/83.
- When the product is already authorised in an existing EU or an AC, and when there is no reasonable chance that the application will be finished in the AC before the day of accession, it is recommended to withdraw the application and to reapply under the MRP according to Article 28 of Directive 2001/83 after accession. In the meantime, the RMS can be selected and the availability of the assessment report negotiated. If however, the product has already been authorised through MRP, the Repeat Use MRP should be initiated after accession.
- When there is pending or completed MRP in the EU it is highly recommended not to submit the application in an AC and use the Repeat Use MRP after the accession.

The applicants are recommended to voluntarily withdraw applications, which might lead to conflicting situations as described above, especially to ensure that only the RMS selected by them will finish the application.

The applicants should also take account of the provisions concerning the Common Technical Document (CTD) format for dossiers⁴. New MA applications submitted in the EU MS after November 2003 have to follow the CTD format. With regard to existing MA, for triggering the MRP or the Repeat Use MRP, the old EU dossier format is accepted until December 2004; after December 2004 the CTD format is mandatory also in the “normal” MRP or the Repeat Use MRP (http://pharmacos.eudra.org/F2/eudralex/vol-2/B/ctdqa_032003.pdf - Question 10). For the ACs, the CTD format is mandatory, at the latest, as of the day of accession. Before the day of accession the implementation of the CTD and its binding nature depends on the national legislation in ACs. However, applicants should be aware that if future MRP is intended the above-mentioned deadlines apply regardless of the fact if the MA application was submitted in an existing EU MS or AC.

2. Recommendations to the ACs Competent Authorities

In a number of situations, pending applications will not be concluded by a final decision before accession. In order to avoid duplication of work, the competent authorities should work closely together with the applicants to determine the best way forward. If the AC Competent Authority expects that the MA will not be granted before the day of accession and that there is a reasonable chance that on the day of accession one of the following scenarios occurs:

- the product is authorised in another MS (old or new) ⇒ the assessment should not be started (Art. 18 situation presumed),
- an application is simultaneously pending in an existing EU MS ⇒ the assessment should not be started or should be suspended until the assessment report from the existing EU MS (RMS) is available (Art. 17 situation presumed),

⁴ Not applicable for medicinal products for veterinary use.

- an application is simultaneously pending in another AC \Rightarrow it is to be clarified with the applicant, which authority will carry out the assessment of the application and this authority should give a strong commitment to fulfil the role of future RMS. Other authorities should not start or should suspend the assessment until the assessment report from the new EU MS (RMS) is available (Art. 17 situation presumed).

In general, it is recommended to suspend the assessment in the Acceding Country, based on relevant national provisions or/and an agreement with the applicant.

To be able to differentiate the above-mentioned situations, the ACs Competent Authorities have to collect in the pre-accession period the necessary information and keep it up-to-date till the day of accession.

The EU application form could, in particular, facilitate the provision of such relevant information, namely by requesting:

- information on the legal basis of the application according to the Acquis,
- information on the existing authorisation and/or the submitted application in an AC or an existing EU MS, including information on the question if a Centralised or Mutual Recognition procedure has been/is being used, and
- information on which authority has been identified as current/future RMS.

Using the EU application form could also facilitate the exchange of information on the regulatory status, not only between applicants and Competent Authorities in all ACs, but also amongst ACs Competent Authorities, if required.

Applications to be submitted

In order to obtain all relevant information for applications to be submitted, the new version of EU application form should be introduced in ACs as soon as possible (http://pharmacos.eudra.org/F2/eudralex/vol-2/B/PartIA_032003.pdf for human medicinal products, http://pharmacos.eudra.org/F2/eudralex/vol-6/newdoc/v6b_part1a_122002.pdf for veterinary medicinal products).

Pending applications

In case of pending applications, updated information on the regulatory status of the product in the ACs and the existing EU MSs should be requested from the applicants using the form “*Additional information to applications pending in ACs*”. This form consists of relevant parts of the EU application form and is slightly modified to reflect the information needed in the pre-accession period in the ACs (see Annex 1).

Management of collected information

After the evaluation of the collected information and after consideration of the situation on the day of accession, the applications eligible for “purely” national independent procedure may be selected, i.e.:

- the bibliographic applications based on Well Established Use for products with non-harmonised SPCs,
- the applications for line extensions of purely nationally authorised products,
- the applications neither pending nor authorised in any of the EU MS on the day of accession,
- the applications for MA of those products, for which the respective Competent Authority in the AC is identified by the applicant as RMS after the accession.

These selected applications should be processed and finalised through the national procedure. In addition, particular attention should be given to the drafting of the assessment reports in the required EU format for those products which are intended to be included into the MRP after accession,

It is advisable for the ACs Competent Authorities to communicate amongst themselves the information obtained from the applicants with the aim to preventing duplication of efforts. To achieve functional communication amongst the ACs and the existing MS Competent Authorities in the pre-accession period, available tools for information management are essential (EUDRAtrack/CTS). It is advisable to intensify the communication with applicants, as well.

The following risks should be considered by the ACs Competent Authorities and appropriate remedying steps should be prepared:

- the lack of knowledge with regard to which authorisation applications are already under active assessment in one of the existing EU Member State or in another Acceding Country,

- the difficulties in reaching agreement on the responsibility to elaborate the assessment report according to Art. 17,
- the difficulties in providing the assessment report according to Art. 17 and 18,
- errors in the prediction of the marketing authorisation date done by the applicants,
- the limited use of the CADREAC MRP procedure,
- the reluctance/hesitance to withdraw pending applications, even if it would be better to follow the regular MRP (in particular the repeat-use MRP) under Article 28 after accession than to follow the Art. 17 or 18 procedures,
- frequent objections against the assessment reports of other EU MS or AC (based e.g. on non-compliance with good practices, major public health issues, etc.),
- the late start of the exercise in ACs,
- the lack of resources and trained staff in authorities of ACs, insufficient capacity to fulfil the role of future RMS, if committed,
- the connectivity to EudraTRACK/CTS unavailable,
- increased number of MRPs before December 2004, when CTD format starts to be mandatory for MRP/Repeat use MRP.

B. Repeat Use MRP for products authorised in Acceding Countries before the accession

There is no legal obligation for MA holder after the accession to involve those EU-MRP products authorised in ACs before the accession in MRP. However such an involvement could be advantageous and if it is the choice of MA holder a Repeat Use MRP should be used. The timing of the procedure, its preparation and the individual steps to be followed to involve new CMSs, are described in the [MRFG Position paper on repeat use of MRP](#) for human medicinal products and in the [VMRFG - Repeat Use of the MRP](#) for veterinary medicinal products. It is desirable to use one Repeat Use MRP to involve all new CMSs at once.

1. EU-MRP human medicinal products authorised in ACs via simplified CADREAC procedure

The basic principle of the Repeat Use Procedure is the obligation to recognise, without any change, the Summary of Product Characteristics previously approved in the MRP. Products authorised in ACs via the simplified CADREAC procedure will be the easiest category of products, as their harmonised MRP SPC have already been approved in the ACs and therefore do not require any further assessment in the ACs. No difficulties within Repeat Use MRP are thus to be expected.

On the EU side, the Repeat Use Procedure should follow the procedure set out in the relevant document. As the products are already harmonised with the outcomes of MRP, there is being planned to shorten the duration of procedure. On the side of the new MSs, a simple formal procedure for switching existing authorisations could be applied. Such a procedure could consist of maintaining the name of the already authorised medicinal product, its MA number and other identification codes, if appropriate. In addition, the product should be included in the database of MR products. Such a formal switch would then result in saving resources in the new MSs, in preventing confusion amongst health care professionals and patients, and in preventing irregularities in the supply of these products. In the case that minor differences to the MRP MA were introduced in the ACs or when differences arose during the post-authorisation phase such changes should be rectified before such simple formal procedure is initiated.

Such a simple and fast Repeat Use MRP can be used when no other procedure for the product concerned is pending and when the product concerned is already fully harmonised. It is important therefore to finalise also the pending applications for variation in those ACs, which are potential CMSs. To create sufficient space for Repeat Use Procedure the variations in ACs should be processed within CADREAC simplified procedure either in parallel with EU MRP variation procedure or in an accelerated manner.

2. EU-MRP veterinary medicinal products authorised in ACs via simplified CAVDRI procedure

According to simplified CAVDRI procedure „D1“ approach⁵, Accessing Countries have been involved in the MR procedure as “candidate CMSs” at identical conditions as EU CMSs before the accession. The product authorised is fully harmonised and these “candidate CMSs” are and/or will be involved in all following variation procedures. The formal inclusion of the former “candidate CMS” in the MRP will be subject to an administrative procedure after accession.

In the case that the simplified CAVDRI procedure has been used after completion of EU-MRP, i.e. „D2“ approach has been applied, the same procedure as described above in point B.1 for human medicinal products should be applied.

3. EU-MRP products authorised in ACs nationally without harmonisation of outcome with MRP

For those products, which did not follow the simplified CADREAC procedure, the SPC in the new MS can differ significantly from the outcome of the MRP in the existing EU Member States. Also their dossier is not necessarily identical with the EU MRP dossier. In the case that MAH of such a product intends to use the Repeat Use Procedure it is recommended to harmonise the national MA in the new MS with the outcome of the MRP in the EU15. To achieve this harmonisation, two ways can be followed:

- Harmonisation of the national MA in the new MS via variations, initiation of the Repeat Use Procedure involving new concerned MSs and after its finalisation maintenance of the same MA number (code), or
- Withdrawal of the national MA and use of the Repeat Use Procedure with a new MA application.

These options should be considered by both ACs Competent Authorities and MA holders on case by case basis.

3. Ex-concertation products

The so-called ex-concertation products are those medicinal products, which have been authorised according to the specific procedure set up by Directive 87/22/EEC⁶ and involving the former CPMP or CVMP. As these products had been assessed on a European level by the former CxMP, it was not considered necessary to force them through a re-assessment by the new CxMP when the modern authorisation procedures were established in 1993. As a consequence, Directive 93/39/EEC⁷ (and 93/40/EEC for veterinary medicinal products) provided in its Article 15b that the provisions on variations of national marketing authorisations should apply by analogy to “medicinal products authorised by Member States following an opinion of the Committee given in accordance with Article 4 of Directive 87/22/EEC before 1 January 1995”.⁸ (This former Article 15b has now become Article 37 of Directive 2001/83 and Article 41 of 2001/82/EC.) Those marketing authorisations remain valid and do not require to be re-evaluated under the centralised procedure of Regulation 2309/93. However, the company could choose to withdraw the national marketing authorisations and to reapply for a Community marketing authorisation under Regulation 2309/93. In any case, the Commission Communication of 1998 highlights that the SmPC for the ex-concertation products shall be identical and shall remain identical in all concerned Member States (section E.7).

An ex-concertation product that obtained a national marketing authorisation in the ACs can be maintained as a national authorisation after accession, if in the EU15 it still is authorised nationally. Although in the EU the national MAs of ex-concertation products are according to Art. 37 varied by the same mechanisms as

⁵ VMRF/162/02 "Procedure on the granting of marketing authorisations by CAVDRI drug regulatory authorities for veterinary medicinal products authorised/to be authorised in EU member states following the mutual recognition procedure"

⁶ Council Directive 87/22/EEC of 22 December 1987 on the approximation of national measures relating to the placing on the market of high-technology medicinal products, particularly those derived from biotechnology, OJ L 15 of 17.1.1987, p. 38.

⁷ Council Directive 93/39/EEC of 14 June 1993 amending Directive 65/65/EEC, 75/318/EEC and 75/319/EEC in respect of medicinal products, OJ L 214 of 24.8.1993, p. 22.

⁸ As this provision provides for the continued management of marketing authorisations granted by Member States following the opinion of the former CPMP in accordance with Directive 87/22/EEC, this latter was of no use any more and was repealed by Council Directive 93/41 of 14 June 1993 repealing Directive 87/22/EEC on the approximation of national measures relating to the placing on the market of high-technology medicinal products, particularly those derived from biotechnology, OJ L 214 of 24.8.1993, p. 40.

required for products authorised by MRP, there is no legal obligation to use these mechanisms for variations of products in ACs. A harmonisation with the SmPC of the national authorisations in the EU15 is however highly recommended. If by contrast the company has chosen to abandon the national marketing authorisations in the EU 15 and to obtain a Community authorisation instead, the national authorisation in the AC becomes inapplicable too.

Ex-concertation products can thus remain as national MAs on the ACs markets, without inclusion in MRP, on the condition that the MAH of the “same” product did not opt for the centralised authorisation in the EU. Therefore, information on the regulatory status and the history of ex-concertation products in the EU is important to differentiate between products, those whose MA may remain national and those which are in conflict with Regulation (EEC) No. 2309/93.

The transposition of the EC legislation requires also application of the provision for the 10 years exclusivity period for products "having been authorised according to the procedure laid down in Article 2(5) of Council Directive 87/22/EEC" (Art. 10(1)(a)(iii) of 2001/83/EC and Art. 13(1)(a)(iii) of 2001/82/EC). A list of such products and the dates of their first EU authorisation is therefore under preparation.

C. Implementation of outcomes of referral procedures

As already discussed within PERF II, decisions issued further to referral procedures are binding in their entirety upon those to whom they are addressed. The effects of a decision therefore depend on its addressee. At present, referral decisions are only addressed to those Member States named as addressees in the decision. Such decisions do not apply to Member States not mentioned or later acceding to the Community.

However, the harmonisation reached by such referral decisions should not be lost, even if they are addressed to certain Member States only, and should, in principle, be extended to the whole enlarged Community. If not, it might be necessary to trigger another referral procedure, this time including the Member State/s to which the original decision was not addressed. A pre-accession harmonisation is therefore highly advisable, and should be encouraged already within the updating of medicinal products on the ACs markets. In practice, the Commission would expect the ACs to follow the decision in all cases.

The involvement of Acceding Countries in pending referral procedures at the day of accession is not possible in each and every case. However, as the inclusion of ACs into a pending procedure could decrease future disharmony, it would be recommendable to include the ACs, their products and their MAHs on a voluntarily basis via Type II variation in case of SPC modification (Type IB variation in case of SPC adjustment of generic product as a consequence of referral procedure for originator, if relevant). It should be noted that harmonisation through referral procedures is a Pan European task where innovative and generic industry from both existing MSs and ACs should be involved.

Once the harmonisation has been obtained, it should be maintained in the ACs / new MSs. The information on the practical application and its outcomes laid down in the MRFG document [“Recommendation for Mutual Recognition Procedure after finalisation of an arbitration procedure with the positive opinion by the CPMP and a positive decision by the EU-Commission”](#) should be followed.