

**EXTENSION APPLICATIONS
IN MUTUAL RECOGNITION AND DECENTRALISED PROCEDURES
MEMBER STATES RECOMMENDATIONS**

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This document was produced by the CMD(h) in order to facilitate and harmonise the regulatory issues for submission of applications under Annex II of Regulation (EC) No 1084/2003.

EXTRACTS FROM EUROPEAN LEGISLATION: COMMISSION REGULATION (EC) No 1084/2003

These changes listed below will be regarded as an extension application as referred to in Article 2 of Regulation (EC) No 1084/2003. The extensions of marketing authorisations which fulfil the conditions set out in Annex II to this Regulation shall be examined in accordance with the procedure referred to in Article 17 of directive 2001/83/EC. An extension of the existing marketing authorisation will have to be granted by the national competent authority. The name of the medicinal product will be the same for the extension as it is for the existing marketing authorisation of the medicinal product.

Annex II of Commission Regulation (EC) No 1084/2003

Those fundamental changes to an existing marketing authorisation requiring a new application are listed in Annex II of Commission Regulation (EC) No 1084/2003 (see table below).

Prerequisite: The marketing authorisation holder (MAH) is the same as the MAH of the existing marketing authorisation.

1. CHANGES TO THE ACTIVE SUBSTANCE(S)
(i) Replacement of the active substance(s) by a different salt/ester complex/derivative (with the same therapeutic moiety) where the efficacy/safety characteristics are not significant different
(ii) Replacement by a different isomer, a different mixture of isomers, of a mixture by an isolated isomer (e.g. racemate by a single enantiomer) where the efficacy/safety characteristics are not significant different
(iii) Replacement of a biological substance or product of biotechnology with one of a slightly different molecular structure. Modification of the vector used to produce the antigen/source material, including a new master cell bank from a different source where the efficacy/safety characteristics are not significant different
(iv) A new ligand or coupling mechanism for a radiopharmaceutical
(v) Change to the extraction solvent or the ratio of herbal drug to herbal drug preparation where the efficacy/safety characteristics are not significant different
2. CHANGE TO STRENGTH, PHARMACEUTICAL FORM, ROUTE OF ADMINISTRATION
(i) Change of bioavailability
(ii) Change of pharmacokinetics e.g. change in rate of release
(iii) Change or addition of a new strength/potency
(iv) Change or addition of a new pharmaceutical form
(v) Change or addition of a new route of administration ¹

¹ For parenteral administration, it is necessary to distinguish between intra-arterial, intravenous, intramuscular, subcutaneous and other routes.

More information about extension applications can be found in the Notice to Applicants (Volume 2A/Chapter 1) and in Commission communication 98/C 229 of 22 July 1998 (section E9).

GENERAL PRINCIPLES

- The first authorised medicinal product in the particular line, so-called “originator product” for the purpose of this document, is defined as the first product for which a marketing authorisation was granted to a given marketing authorisation holder (MAH) for a given active substance. The marketing authorisation of an originator product could be based on any legal basis according to Directive 2001/83/EC, i.e. stand-alone applications according to article 8.3(i) and articles 10, 10a, 10b or 10c.
- The changes mentioned in the Annex II of the Commission Regulation (EC) No 1084/2003 are considered as extensions of an existing marketing authorisation and defined by an originator product. The MAH of the extension application is the same as the MAH of the originator product.
- Without prejudice of the provisions of Annex II of Commission Regulation (EC) No 1084/2003, a new application for an extension should be made in accordance with the provisions of article 8.3(i) and articles 10, 10a, 10b or 10c of Directive 2001/83/EC. The extension application has to have the same legal basis as the original product.
- The provisions of the mutual recognition or the decentralised procedure can be applied to extension applications. For medicinal products approved through purely national marketing authorisation procedures, the MAH will have to harmonise the whole dossier and the product information (SPC, PL, labelling) in all concerned Member States before submitting an extension application through a mutual recognition or decentralised procedure.
- When a medicinal product has been granted an initial marketing authorisation, any extension shall be considered as belonging to the same global marketing authorisation, in particular for the purpose of the rules on data and market protection.
- Although Commission Regulation (EC) No 1084/2003 does not apply to products authorised nationally, the position of the Member States is that the same definition should be used for products approved through a national procedure in order to ensure consistency.
- When the applicant chooses the mutual recognition or the decentralised procedure for an extension application, there is no longer the possibility to resubmit a national procedure after withdrawal of this application.
- For purpose of the mutual recognition or decentralised procedure, the Member States recommend that most of changes listed in Annex II are considered as extensions of existing marketing authorisations except changes to the active substance listed below:

Section 1. Change(s) to the active substance(s). For changes covered by items 1. (i), (ii), (iii), (iv) and (v) the application will not be considered as an extension if the active substance is considered as a new active substance (ref. Definition of a new active substance in Notice to applicants, Volume 2A, Chapter 1-Appendix III). In these cases, a new dossier should be provided. Otherwise, these changes could be considered as extensions.

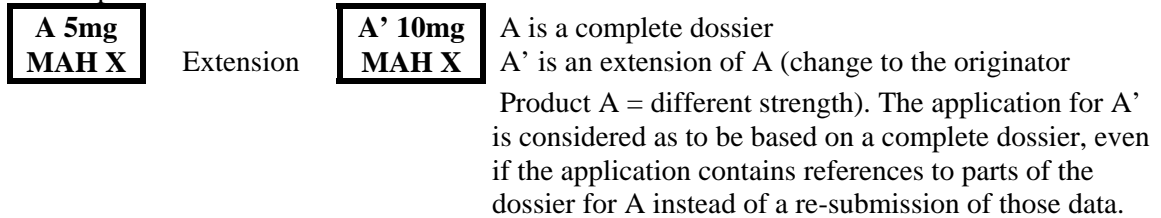
The consequences are the following:

- . For those extensions of marketing authorisations granted through a national procedure, national procedure and mutual recognition/decentralised procedure are acceptable;
 - . For those changes of marketing authorisations which are not considered as extensions, the mutual recognition/decentralised procedure only is acceptable.
- Applicants are advised to consult their Reference Member State for general recommendations.

EXTENSION APPLICATIONS ACCORDING TO THE LEGAL BASIS

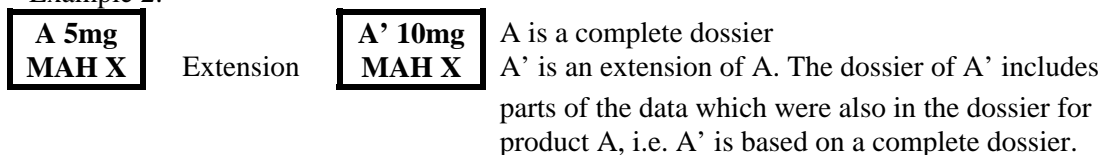
- **A complete application according to Art. 8.3(i) of Dir. 2001/83/EC:**
1) When the extension is a change to a product which was granted a marketing authorisation, referring to a complete dossier (e.g. new strength, pharmaceutical form...).

Example 1:



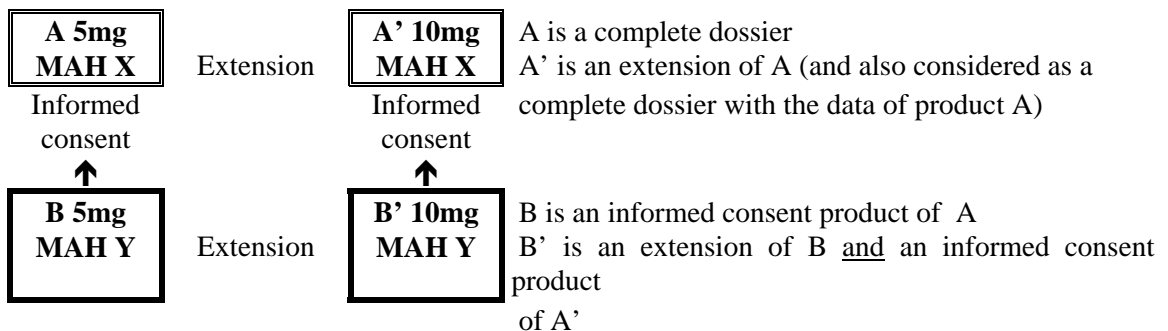
- 2) When an applicant chooses the option to complete the appropriate dossier for an extension of a nationally approved originator product in order to use the mutual recognition procedure (see specific situations, point 2).

Example 2:



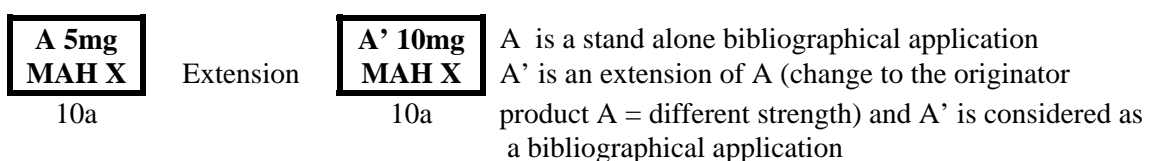
- **An application according to Art. 10c of Dir. 2001/83/EC (informed consent application)**
Usually when the extension is a change to a product which was granted a marketing authorisation according to Art. 10c.

Example 3:



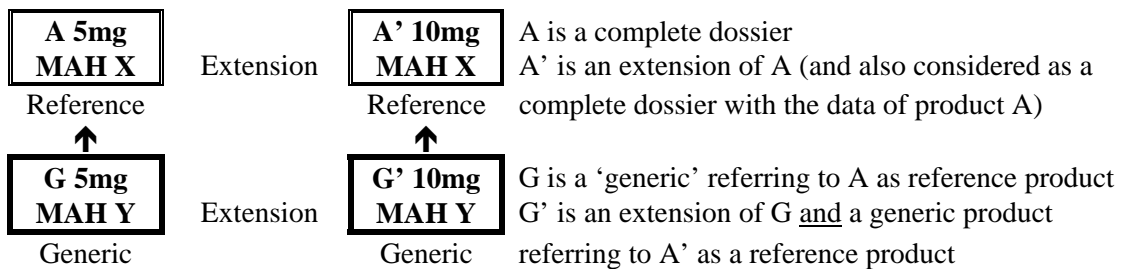
- **An application according to Art. 10a of Dir. 2001/83/EC (bibliographical application)**
When the extension is a change to a product which was granted a marketing authorisation according to Art.10a.

Example 4:



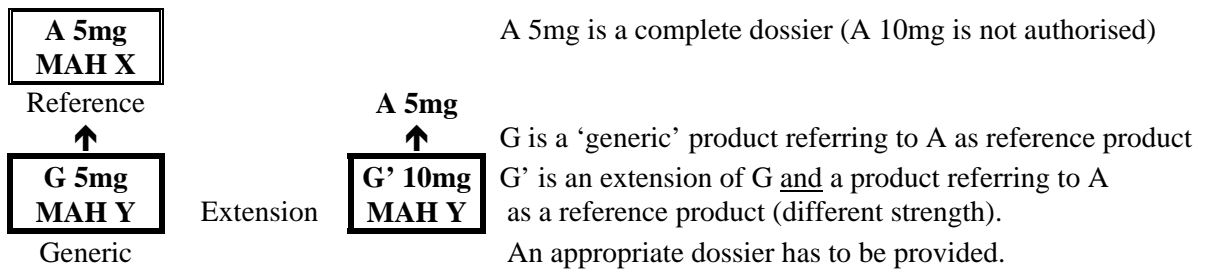
- **An application in accordance to Art. 10.1 of Dir. 2001/83/EC (generic application)**
When the extension is a change to a generic product as defined in article 10(2)(b)

Example 5:



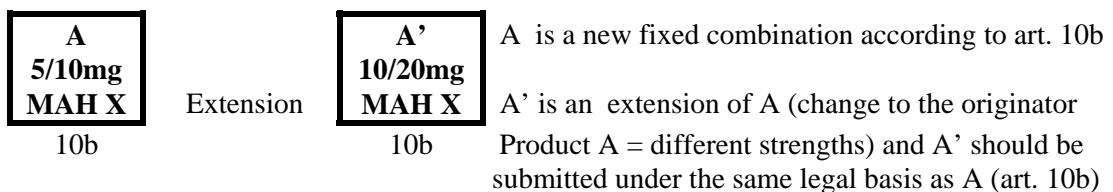
- **An application in accordance to Art. 10.3 of Dir. 2001/83/EC (hybrid application)**
When the extension is a change to a product referring to a reference medicinal product (e.g. new strength, pharmaceutical form...)

Example 6:



- **An application according to Art. 10b of Dir. 2001/83/EC (new fixed combination)**
When the extension is a change to a product which was granted a marketing authorisation according to Art.10b.

Example 7:



SPECIFIC SITUATIONS

In practice, three different situations could be envisaged depending on the procedure that was used for granting a marketing authorisation to the originator product.

1. Situations where the originator product was granted marketing authorisations through a Community procedure

Commission Regulation (EC) No 1084/2003 is applicable to changes to existing marketing authorisations of medicinal products which have been granted a marketing authorisation to a marketing holder through a Community procedure, i.e.:

- Medicinal products authorised within the scope of Directive 87/22/EEC, so called “ex-concertation products”.
- Medicinal products authorised through a mutual recognition or a decentralised procedure as foreseen in Articles 27 to 39 of Directive 2001/83/EC.
- Medicinal products which have been subject to a referral through Articles 30 of Directive 2001/83/EC.

When fundamental changes require a new application, pursuant to Annex II of this Regulation, the mutual recognition or decentralised procedure must be used, as foreseen in Article 27 to 39 of Directive 2001/83/EC. In other terms, after one Member State has granted a marketing authorisation for an extension of a marketing authorisation granted through a community procedure, any submission of a national application for the same extension should be considered as invalid.

Note: the Member State chosen to act as reference Member State for the Community procedure should remain the same unless there is a good rationale for the applicant to change.

2. Situations where the originator product was granted marketing authorisations through national procedures

Commission Regulation (EC) No 1084/2003 is not applicable to independent national marketing authorisations which have not benefited from any Community procedure.

However, extensions of national marketing authorisations cannot be excluded from the scope of mutual recognition (see also Commission communication 98/ C229 of 22 July 1998). Therefore, for situations where the originator product was granted marketing authorisations through independent national procedures only, national and mutual recognition/decentralised procedures are acceptable on a voluntary basis of the applicant.

To allow more flexibility, the Member States reached an agreement that parallel national and mutual recognition/decentralised procedures are acceptable for the same product and that parallel mutual recognition/decentralised procedures are also acceptable (note: this position is different from the one published in the November MRFG 1998 press release).

Two options are possible for the applicant, national procedures (option 1) or a mutual recognition/decentralised procedure (option 2).

Option 1: national procedures

The originator product was granted marketing authorisations through independent national procedures only. The applicant wishes to apply for an extension application through national procedures. In that particular case, national regulations will apply.

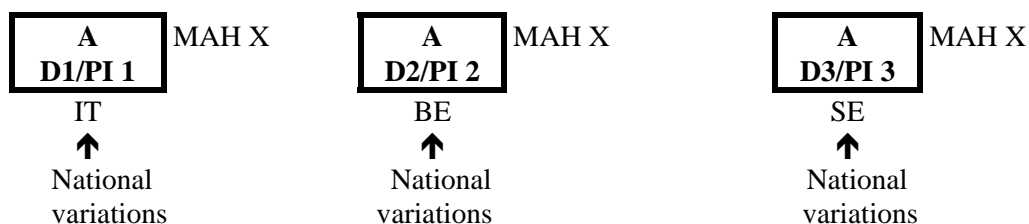
Option 2: mutual recognition or decentralised procedure

The originator product was granted marketing authorisations through independent national procedures only. The applicant was granted/applied for a marketing authorisation for an extension in the reference Member State and wishes to use a mutual recognition/decentralised procedure of the first authorisation in another concerned Member States. In accordance with the Commission communication 98/C229: “prior to any mutual recognition/decentralised procedure for extensions, the applicant will have to harmonise the already approved national SPC, PL and labelling (product information) in order to support his applications in all the concerned Member States with the same dossier”.

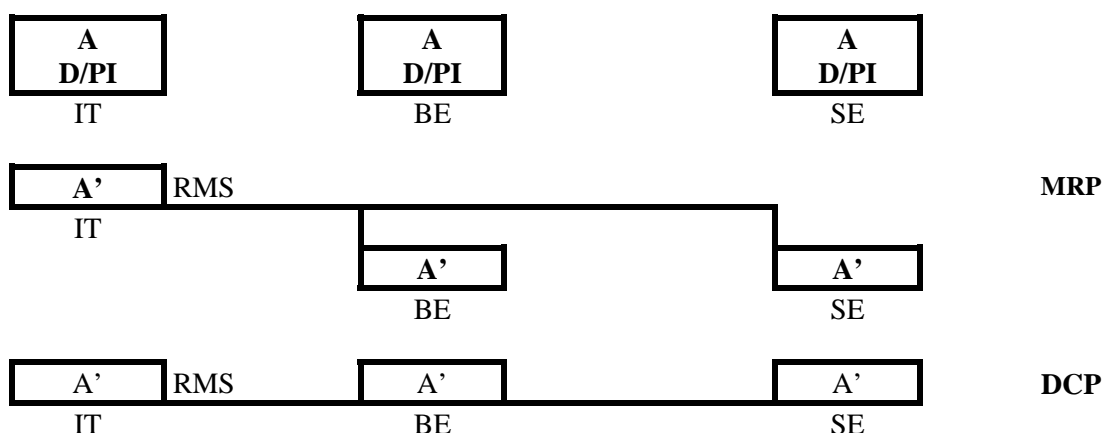
Two different scenarios are acceptable to harmonise the product information of the nationally approved originator product:

- **either by national variation procedures:** the applicant should indicate that the purpose of the variation is harmonisation of the SPC, PL and labelling prior to a mutual recognition/decentralised procedure for an extension and should provide relevant information on the licensed status in other Member States. The applicant should also testify that the same relevant information was (i) included in the previous dossier submitted, (ii) updated subsequently, in all CMSs involved in the procedure. The applicant is responsible for any necessary co-ordination with the national authorities during the national variation phase. When the relevant parts of the dossiers of the originator product (including product information) are the same in all concerned Member States, then the mutual recognition/decentralised procedure of the first authorisation granted in the RMS can start for the extension.

Example 1: Originator product A, Marketing Holder (MAH) X, 3 independent national MA in 3 different Member States with 3 different dossiers D and 3 different product information (PI). National variations are submitted in the Member States in order to harmonise the dossiers and the SPCs.



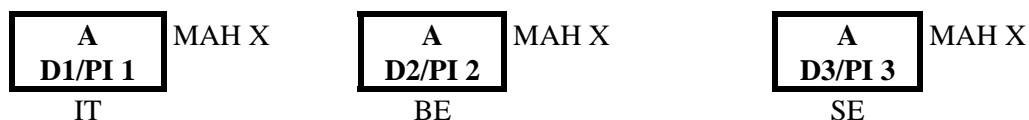
Where the relevant parts of the dossiers D of product A including product information are the same, then the mutual recognition or the decentralised procedure of the first authorisation granted in the RMS can start for the extension of product A (A’).



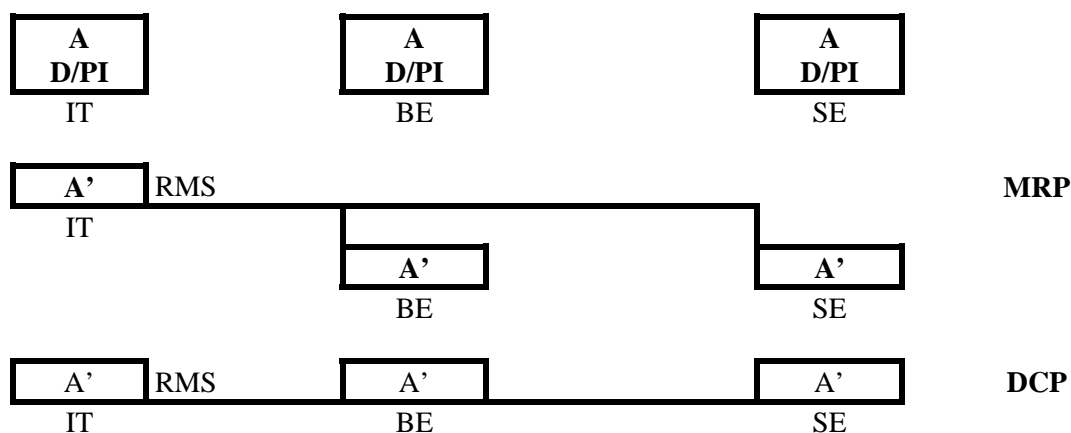
Note: in that scenario, the originator product A remains national and subsequent variations of product A are assessed through national variation procedures. Extension A’ was granted authorisations through a mutual recognition procedure and any subsequent variations of A’ are assessed through mutual recognition variation procedures. However, it is strongly recommended that harmonisation is maintained between marketing authorisations of originator product and extension.

- **or by referral to Article 30 of Directive 2001/83/EC:** a referral procedure is the only way to switch a product approved nationally to a mutual recognition procedure.

Example 2: Originator product A, Marketing Holder (MAH) X, 3 independent national MA in 3 different Member States with 3 different dossiers D and 3 different product information. A referral to Article 30 of Directive 2001/83/EC is made on a voluntary basis by the applicant in order to harmonise the originator product through a referral procedure.



Article 30 of Directive 2001/83/EC is triggered by the applicant. At the end of the referral procedure, dossiers D of product A are the same including the same product information, then the mutual recognition or decentralised procedure of the first authorisation granted in the RMS can start for the extension of product A (A').



Note: in that scenario, for the originator product A as well as the extension A', any subsequent variations of A' are assessed through mutual recognition variation procedures.

② **Another scenario: submission of a complete application**

When the Marketing Holder of the originator product is in possession of all the information required (complete dossier), an alternative could be to complete the dossier of the extension application with data previously submitted in order to apply for a complete application in accordance with Article 8.3 (i) of Directive 2001/83/EC, then the procedure described in Articles 27 to 39 of Directive 2001/83/EC could be used for the extension product without prior harmonisation of the dossiers/Product information of the originator product. Subsequent harmonisation of the line is recommended.

When the originator product was granted a marketing authorisation based on a generic application, this option is not applicable since the Marketing Holder of the originator product is not in possession of all the information required.

3. Situations where the originator product was granted marketing authorisations through a mixture of national and mutual recognition/decentralised procedures

For extensions of originator products authorised through a mixture of national and mutual recognition/decentralised procedures depending on the Member States:

- The mutual recognition or the decentralised procedure has to be followed for extensions of originator products authorised through the mutual recognition or the decentralised procedure;
- National, mutual recognition or decentralised procedures are acceptable for extensions of products authorised nationally, meaning that parallel procedures (national and mutual recognition/decentralised procedure) are acceptable in that particular case.