EUROPEAN COMMISSION
ENTERPRISE AND INDUSTRY DIRECTORATE-GENERAL

Consumer goods
Pharmaceuticals

Revision 2

NOTICE TO APPLICANTS

Medicinal Products for Human Use

VOLUME 2B
Presentation and content of the dossier-Part 1
Summary of the dossier Part 1A
or
Module 1: Administrative information
Application form
USER GUIDE FOR THE APPLICATION FORM

March 2005

This application form will be included in:

The Rules governing Medicinal Products in the European Community
The Notice to Applicants - Volume 2B - Presentation and content of the dossier-1998 edition
or
The Notice to Applicants - Volume 2B - Common Technical Document-Module 1- Administrative information-2001 edition

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PURPOSE AND GENERAL RULES

This User guide has been prepared in order to facilitate the work of applicants when completing the application form as part of an application for a marketing authorisation of a medicinal product for human use.

How to fill in the application form?
The application form has been prepared to be filled in by the applicant in case of an application made either by national route or by Mutual Recognition or Centralised procedures.

This application form can be used either for applications made with the CTD format or the old EU format.

In the case of a mutual recognition procedure an application form should be filled in for all competent authorities where the application is made.
The same applicant should apply in all concerned member states.
Since some information may differ between member states (e.g. name of the product, marketing authorisation holder, legal status, contact persons etc…), the appropriate sections should be replicated where necessary.
For relevant sections, the applicant is requested to specify to which Member State the information relates.

Where EEA is indicated in the application form, the applicant should understand EEA countries including EU countries.

Usually, a completed separate application form is required for each strength and pharmaceutical form. For centralised procedures a combined application form is acceptable.

Square boxes indicate that multiple choices are possible while round boxes indicate that one choice excludes the other possibilities.
Where necessary, the fields can be duplicated.

Which language should be used?

- English should be used for a centralised procedure.
- English should be used for a mutual recognition procedure, except in some Member States where the national language should be used (please refer to Volume 2A, Chapter 7 of the current version of the NTA).
- National language should be used preferably in the case of a national application, except if subsequent mutual recognition procedure is already considered and if the national competent authority where this application is made accepts English (please refer to Volume 2A, Chapter 7 of the current version of the NTA).

ADMINISTRATIVE DATA

DECLARATION and SIGNATURE

In this declaration, data are identical to the information provided in Sections 2.1, 2.2 and 2.4.

Product (Invented) name
A list of the different proposed invented names and marketing authorisation holders in the concerned member states should be appended to the application form (annex 6.19).

Active Substance(s)
Strength (s)
The two fields "Active substance" and "strength" should be considered as linked.
If more than one active substance, the two fields should be filled for each active substance e.g.:

Acetylsalicylic acid	Ascorbic acid
200mg	10mg

Pharmaceutical form
The pharmaceutical form should be described as in the current version of standard terms from the Ph. Eur.

Applicant
For MRP applications, the applicant should be the same than the MAH in the RMS.

1. TYPE OF APPLICATION

1.1 This application concerns

For the Mutual Recognition Procedure,
The procedure number is the Mutual Recognition Procedure number allocated by the RMS.
"First Use" means the first Mutual Recognition Procedure.
All the concerned Member states should be indicated.
"Repeat use" means a new use ("wave") of the same mutual recognition procedure made to include new concerned member state(s).
When applying for a repeat use, the applicant should complete "first use" by stating the member states which have recognised the marketing authorisation during the first use and complete, when necessary, section 5.2 indicating the country(ies) where the application has (have) been withdrawn during the "first use".

For each subsequent use the applicant should indicate the rank (2nd, third, fourth…) and state the member states which have recognised the marketing authorisation during the first use and subsequent finalised use of the procedure.

In the case of a national application, the application number is allocated by some member states prior to the official application and therefore should be indicated.
No specific format can be given for this application number.

1.2 Orphan Medicinal Product Information

This section is to be completed by all applicants, whether they are the holder of an orphan designation or not.

1.2.1 Has Orphan designation been applied for for this medicinal product?

Regulation (EC) No 141/2000 of 16 December 1999 and Commission Regulation (EC) No 847/2000 of 27 April 2000, introducing an EU public health policy on orphan medicinal products, came into effect in April 2000. This legislation aims to stimulate research and development of medicinal products for rare diseases by providing incentives to the pharmaceutical industry. Incentives include a 10-year period of market exclusivity once authorised, protocol assistance, eligibility for Community and Member State initiatives which support research and development of orphan medicinal products, unreserved access to the centralised procedure and the possibility to request fee reductions from the EMEA. Medicinal products eligible for these incentives are clearly identified through a procedure for orphan designation.

The applicant should note whether an application for orphan designation, for the medicinal product concerned, has ever been submitted to the EMEA for the condition that is the subject of the application for marketing authorisation, and if 'yes', the EMEA procedure number (EMEA/OD/XXX/year) should be provided together with details of the status as follows:
- if a designation application is pending, tick this option ;
- if orphan designation has been granted, note details of the date of designation (i.e.

date Commission Decision on designation was granted), whether or not the designation was based on the 'significant benefit' criterion in accordance with Article 3(1)(b), Regulation (EC) No 141/2000, and the Number in the Community Register of Orphan Medicinal Products (EU/X/XX/XXX). A copy of the Commission Decision on orphan designation should be attached as an Annex;

- if orphan designation has been refused, provide the date of the Commission Decision refusing the designation and its reference;
- if an application for designation has at any time been submitted and subsequently withdrawn, note the date of withdrawal by the sponsor.

1.2.2 Information relating to orphan market exclusivity

In accordance with Article 8 of Regulation (EC) No 141/2000, when an orphan medicinal product is authorised throughout the EU, a 10-year period of market exclusivity commences from the date of the granting of the marketing authorisation and protects an originator's medicinal product for the authorised 'orphan' therapeutic indication. Similar medicinal products will not be granted a marketing authorisation for the same therapeutic indication unless the originator gives consent, is unable to supply sufficient quantity of the medicinal product, or the second applicant demonstrates that although 'similar', the medicinal product is 'clinically superior' to the originator.

The definition of 'similar' and 'clinically superior' in this context is defined in Article 3 of Commission Regulation (EC) No 847/2000 of 27 April 2000.

All applicants are requested to indicate whether or not any other medicinal product has been granted orphan designation in the EU for the condition relating to the indication proposed in the application for marketing authorisation.

To complete this section of the application form the applicant should check the "Community Register of orphan medicinal products for human use" that is available on the Website of the European Commission (http://pharmacos.eudra.org/F2/register/index.htm).
The 'find'function available under the edit menu in the toolbar may be of assistance in searching for a particular condition.
Section 1.2.2 can be replicated where necessary.

If the condition has been the subject of an orphan designation:

- the corresponding EU orphan designation number(s) (EU/X/XX/XXX) should be provided
- the applicant should indicate whether or not any designated orphan medicinal product(s) has been granted a marketing authorisation in the EU.

If any of the designated orphan medicinal products have been granted a marketing authorisation:

- the applicant should specify, repeating the fields as necessary:
    - Name, strength, pharmaceutical form of the authorised product:
    - Name of the marketing authorisation holder:
    - Marketing authorisation number(s):
    - Date of authorisation:

- the applicant should indicate whether or not the medicinal product which is the subject of the application for marketing authorisation is 'similar' to any of the authorised Orphan medicinal products.
- a critical report should be submitted in module 1.7.1 of the application for marketing authorisation addressing the possible similarity with the authorised orphan medicinal product(s) and concluding on similarity or "non" similarity.

If the medicinal product, which is the subject of the application for marketing authorisation is deemed to be "similar" to an orphan medicinal product covered by orphan market exclusivity provisions:

- the applicant should submit in module 1.7.2 of the application for marketing authorisation justification that one of the derogations laid down in Article 8.3, paragraphs (a) to (c) of the Regulation (EC) No 141/2000 applies, that is:
  (a) the holder of the marketing authorisation for the original orphan medicinal product has given his consent to the second applicant, or
  (b) the holder of the marketing authorisation for the original orphan medicinal product is unable to supply sufficient quantities of the medicinal product, or
  (c) the second applicant can establish in the application that the second medicinal product, although similar to the orphan medicinal product already authorised, is safer, more effective or otherwise clinically superior.

1.3. Is this an application for a change to your existing marketing authorisation as referred to in Annex II of Regulations (EC) no 1084/2003 or1085/2003, or any national legislation , where applicable ?

Certain changes to a marketing authorisation are considered to fundamentally alter the terms of a marketing authorisation and therefore cannot be considered as a variation. For these changes, set out in Annex II of regulations (EC) 1084/2003 and 1085/2003, a new application must be made.
If the applicant of the present application ticks "Yes," he must be the same as the marketing authorisation holder of the existing marketing authorisation. (see also purpose and general rules).
Applications for changes or additions falling under the scope of Annex II can only be submitted for the existing marketing authorisation by the marketing authorisation holder.
An application for a line-extension should be made under the same legal basis as the originator MA, either a complete application or an abridged one, as appropriate.

- **For existing marketing authorisation in the Community / Member State where the application is made:**

Only one entry is possible for the name of the MAH as well as for the complete name of the existing medicinal product.
The section dealing with the name of the existing product should be understood as the approved complete name of the medicinal product i.e.: invented name , strength when applicable and pharmaceutical form.

All marketing authorisation numbers of each presentation should be given (when applicable).

- **Is the present application a line extension ?**

Section 1.3.1. The change to your existing marketing authorisation is considered to be a line extension

All changes falling under the scope of Annexe II of the regulations (EC) 1084/2003 and 1085/2003 are considered as "line-extensions" except those relating to the active substance where the active substance is viewed as a "new active substance" as defined in Appendix III of Chapter I –Volume 2A of the Notice to Applicants and for which the applicant should fill section 1.3.2

Section 1.3.2. The change to your existing marketing authorisation is not considered to be a line extension

1.4 This application is submitted in accordance with the following article in Directive 2001/83/EC as amended

This Section should be completed for each application and only one box should be ticked. When requested, the information concerning the name of products is the approved complete name of the medicinal product i.e.: invented name, strength when applicable and pharmaceutical form.

1.4.1. A complete and independent application / Stand-alone application

Since the applicant is the marketing authorisation holder of the existing marketing authorisation and the legal basis of the extension is the same than the one used previously (Art. 8.3.(i) or 10.1 (a) (ii)of Dir 2001/83/EC as amended) for the existing marketing authorisation, for extensions, cross references to pre-clinical and clinical data could be made.

1.4.2. An abridged application

Article 10.1.(a)(i) - so called "informed consent application"

The medicinal product for which the current application is made is considered as essentially similar to the authorised product to which the consent has been given by the existing marketing authorisation holder to use their data (pharmacological, toxicological and/or clinical) in support of this application.

Article 10.1.(a)(iii)

The applicant should tick the box related to this legal base **and** the appropriate box "first paragraph" or "last paragraph" depending on the situation in the member state where the application is made.

Please refer to the "Member States Recommendation for applications submitted according to Article 10.1 a) iii) when the strength or the pharmaceutical form of the Reference product differs between RMS/CMS(s)". This document is available on the web site http://heads.medangencies.org.

first paragraph - so called "generic application"

The medicinal product for which the current application is made is essentially similar to the so called reference product.

This medicinal product must have been authorised within the Community, in accordance with Community provisions in force, for not less than 6/10years.

For each national competent authority where the application is made, information on the reference product in this member state should be given.

This medicinal product must be marketed in the Member State for which the application is made.

The name of the medicinal product used for the bioequivalence study is the approved complete name of the medicinal product. Only one MAH should be named and one complete name for the existing medicinal product.

The origin of the batch used in the bioequivalence study should be clearly defined by stating the member state where this batch originates since the composition in excipients of the reference product could defer from one member state to another.

When an application is made under **article 10.1 (a)(iii) last paragraph of Directive 2001/83/EC as amended**, one or more difference(s) should be indicated compared to the original product.

2. MARKETING AUTHORISATION APPLICATION PARTICULARS

2.1. Name(s) and ATC code

2.1.1. Proposed invented name of the medicinal product in the Community/ Member State/Iceland/Lichtenstein/ Norway

The information is identical to the one in section "Declaration and Signature.

2.1.2. Name of the active substance(s)

The active substance should be declared by its recommended INN, accompanied by its salt or hydrate form if relevant (for further details, consult the Guideline on the SPC).
If there is more than one active substance, this field should be duplicated.

2.1.3. Pharmacotherapeutic group (Please use current ATC code)

The more complete combination corresponding to the claimed therapeutic use of the product should be given. Consequently, this section should be duplicated where needed.
The two fields "ATC Code" and "Group" are linked and should be both completed.

2.2. Strength, pharmaceutical form, route of administration, container and pack sizes

2.2.1. Strength and pharmaceutical form

The pharmaceutical form should be described as in the current version of standard terms from the Ph. Eur. Only the full term should be mentioned (not the short term).
The information should be in accordance with the one in Section 2.1.2.

2.2.2. Route of administration (use current list of standard terms - European Pharmacopoeia)

This field can be duplicated where needed. Example: IV and IM

2.2.3. Container, closure and administration device(s), including description of material from which it is constructed (use current list of standard terms - European Pharmacopoeia).

For each presentation, the proposed container, closure and administration device should be indicated.
Consequently the whole section should be duplicated when needed.

The information from 2.2.3.2.to 2.2.3.5 will be linked to one pack size and type of pack (e.g for parenteral suspensions or solution the shelf-life could be different depending the size of the poutch). Consequently sections 2.2.3.2 to 2.2.3.5 may need to be replicated for different pack sizes of the same type of pack.

2.3. Legal status

2.3.1. Proposed dispensing/classification

2.3.2. For products subject to medical prescriptions

The legal status may differ from one presentation to another.
Consequently, this section may need to be replicated where needed. (not applicable for centralised procedures).

2.4. Marketing authorisation holder / Contact persons / Company

The fields related to telephone, telefax, e.mail can be duplicated in order to indicate more than one number.

2.4.1. Proposed marketing authorisation holder/person legally responsible for placing the product on the market in the Community / each MS

2.5. Manufacturers

The fields related to telephone, telefax, e.mail can be duplicated in order to indicate more than one number.
Fields should be duplicated for each manufacturer.

2.5.1. Authorised manufacturer(s) (or importer) responsible for batch release in the EEA (in accordance with Article 40 and Article 51 of Directive 2001/83/EC as amended and MRAs in operation where such Batch Release is foreseen)(as shown in the package leaflet and where applicable in the labelling or Annex II of the Commission Decision)

The authorised manufacturer(s) responsible for batch release in the EEA should be mentioned in this section. If outside the EEA, only the information concerning the importer should be specified.

2.5.1.2. Batch control/Testing arrangements

Unless a MRA or other Community arrangement is in operation with the third country concerned, applicants are reminded that each production batch has to undergo all the controls required by Art 51 of Directive 2001/83/EC as amended, in the EEA.

2.5.2. Manufacturer(s) of the medicinal product and site(s) of manufacture: (Note: including manufacturing sites of any diluent/solvent presented in a separate container but forming part of the medicinal product)

Sites mentioned in sections 2.5.1 and 2.5.1.2 should only be repeated here when they have a specific function in the manufacturing of the medicinal product.
In the case of a manufacturing site outside the EEA, applicants should note that the manufacturing (import) authorization holder mentioned in section 2.5.1 of the application form is responsible for ensuring that standards of GMP equivalent to those in force in the Community are followed by the manufacturer and that the Competent Authority responsible for issuing the import authorization may approach the importer for further information.

2.5.3. Manufacturer of the active substance
It is essential that the site(s) actually manufacturing the active substance are mentioned for each source of active substance.
Brokers or supplier details alone are not acceptable

2.5.4. Contract companies used for bioavailability or bioequivalence trials or used for the validation of blood product manufacturing processes.
For the Name and country of origin of the original/reference product, please state the same information already given in section 1.4.2. – Article 10.1. (a) (iii).
A brief description of the duty performed according to the contract should be given.

2.6. <u>Qualitative and quantitative composition</u>

2.6.1. Qualitative and Quantitative composition in terms of the active substance(s) and the excipient(s)
"Quantity/Unit" should not be understood too strictly since, for example, in the case of radiopharmaceutical products , interval of concentration should be indicated or for some excipients used "q.s.p." for a pH , an interval of values will have to be indicated.
Under "reference/monograph standard" should be indicated the current Ph.Eur reference or the reference to an in-house monograph when no Ph Eur monograph exists.

2.6.2. List of materials of animal and/or human origin contained or used in the manufacturing process of the medicinal product?
If a substance is listed, it should be clear that if no Certificate of suitability from TSE is available, appropriate date should be included in the dossier.

2.6.3. Is an EMEA certificate for a Plasma Master File (PMF) issued or submitted in accordance with Directive 2001/83/EC Annex I, Part III, being used for this MAA?
This section should be duplicated when cross references are made to more than one PMF.

2.6.4. Does the medicinal product contain or consist of Genetically Modified Organisms (GMOs) within the meaning of Directive 2001/18/EC?

3. SCIENTIFIC ADVICE

3.1. Was there formal scientific advice given by the CPMP for this medicinal product ?

This section may be replicated where needed.

3.2. Was there scientific recommendation(s) given by Member State(s) for this medicinal product?

This section may be replicated where needed.

4. PAEDIATRIC DEVELOPMENT PROGRAMME

4.1. Is there a paediatric development programme for this medicinal product ?

5. OTHER MARKETING AUTHORISATION APPLICATIONS

5.1. For National applications only, please complete the following in accordance with Art. 8(j)-(L) of Directive 2001/83/EC as amended

5.1.1. Is there another Member State(s) where an application for the same product is pending?

5.1.2. Is there another Member State(s) where an authorisation is granted for the same product?

Where differences are identified by the applicant concerning authorisations granted in other member states through a national procedure, the applicant should explain clearly if different therapeutic indications have been granted in those member states and on which grounds.

5.1.3. Is there another Member State(s) where an authorisation was refused/ suspended/ revoked by competent authorities for the same product?

5.2. Marketing authorisation applications for the same product in the EEA

(i.e.from applicants belonging to the same mother company or group of companies OR which are "licensees" (Same qualitative and quantitative composition in active substance(s) and having the same pharmaceutical form). *Note: refer to Commission Communication 98/C229/03*

For each case (authorised, pending, refused, withdrawn, suspended or revoked) all the information should be linked for one country and the whole section could be duplicated. This whole section 5.2 should be updated by the applicant as soon as a change occurs during the procedure.

5.3. For multiple applications of the same medicinal product

All the information should be linked for one duplicate and the whole section should be replicated for each duplicate application.

Moreover, in case of parallel multiple applications, the applicant is requested to use the same legal basis as for the original authorisation application.

5.4. <u>Marketing authorisation applications for the same product outside the EEA</u>
(i.e. from applicants belonging to the same mother company or group of companies OR which are "licensees" (Same qualitative and quantitative composition in active substance(s) and having the same pharmaceutical form.) *Note: refer to Commission Communication 98/C229/03*

For each case (authorised, pending, refused, withdrawn, suspended or revoked) all the information should be linked for one country and the whole section could be duplicated.

6. ANNEXED DOCUMENTS (where appropriate)

All annexes provided should be identified by the correct identification number.