EUROPEAN COMMISSION
ENTERPRISE DIRECTORATE-GENERAL

Single market : management & legislation for consumer goods
Pharmaceuticals : regulatory framework and market authorisations

Brussels,
ENTR/F2/BL D(2002)

Final – Revision 1

NOTICE TO APPLICANTS

VOLUME 2A

Procedures for marketing authorisation

CHAPTER 1

MARKETING AUTHORISATION

November 2002

This Chapter 1 Marketing Authorisation will be included in The Rules governing Medicinal Products in the European Community
The Notice to Applicants Volume 2A Procedures for marketing authorisation

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[1]CHAPTER 1 MARKETING AUTHORISATION

Final Revision 1 November 2002

1. Introduction

1.1 Objectives

The primary purpose of any rules governing medicinal products is to safeguard public health. However, this objective must be achieved by means which do not hinder the development of the pharmaceutical industry or trade in medicinal products within the Community. Thus, the pharmaceutical legislation of the European Community has consistently pursued the twin objectives: the protection of public health and the free movement of medicinal products.

General principles are given in this chapter, with detailed explanations concerning the procedures are given in the other chapters.

1.2 Status

This Notice to applicants has been prepared in accordance with Article 6 of Regulation (EEC) No. 2309/93[1] and the Annex 1 of Directive 2001/83/EC of the European Parliament and of the Council on the Community code relating to medicinal products for human use[2], and is intended, in addition to other documents like the Commission Communication (98/C229/03), to facilitate the interpretation and application of the Community Regulations and Directives. It is not legally binding and in case of doubt, reference should be made to the appropriate Community Directives and Regulations. It is important when reading this text to appreciate that the legal requirements of the Directives and Regulations must be met and that this Notice to applicants represents the harmonised view of the Member States, the EMEA and the Commission on how those requirements may be met.

Information on the hierarchy of the Community texts is given in Appendix I.

2. Marketing Authorisation

A medicinal product may only be placed on the market in the European Union when a marketing authorisation has been issued by the competent authority of a Member State for its own territory (national authorisation) or when an authorisation has been granted in accordance with Regulation (EEC) No. 2309/93 for the entire Community (a Community authorisation). The marketing authorisation holder, which encompasses the terms 'holder of the marketing authorisation' and 'person responsible for placing the medicinal product on the market', must be established within the EEA.

Based on Article 48 of the Treaty establishing the European Community, being 'established' means that "Companies or firms formed in accordance with the law of a Member State and having their registered office, central administration or principal place of business within the Community shall, for the purposes of this Chapter (Chapter 2 of the Treaty), be treated in the same way as natural persons who are nationals of Member States. Companies or firms means

[1] OJ L 214 24.8.1993, p.1.
[2] OJ L 331 28.11.2001, p. 67.

companies or firms constituted under civil or commercial law, including cooperative societies, and other legal persons governed by public or private law, save for those which are non-profit-making". However, for the purpose of applying this definition in the context of the pharmaceutical legislation it should be clarified that 'non profit-making' organisations can of course be marketing authorisation holders.
Norway, Iceland and Liechtenstein are part of the EEA (European Economic Area) with the 15 Member States of the European Union. The EFTA (European Free Trade Association) States Norway, Iceland and Liechtenstein have, through the EEA agreement, adopted the complete Community acquis on medicinal products and are consequently parties to the Community procedures.

Where in this chapter reference is made to Member States of the Community this should be read to include these EFTA States.

The only exemption from this is that legally binding acts from the Community (e.g. Commission decisions) do not directly confer rights and obligations but have first to be transposed into legally binding acts in these EFTA States. According to Decision N° 74/1999 of the EEA Joint Committee when decisions on approval of medicinal products are taken by the Community, these EFTA States will take corresponding decisions on the basis of relevant acts. Consequently, these EFTA States are concerned by the single European market for medicinal products. Therefore, where in Article 2 of Regulation (EEC) No. 2309/93 and Article 8 of Directive 2001/83/EC reference is made to the applicant being established in the Community, this is extended to include these EFTA States.

Information on the legal issues concerning the Marketing Authorisation Holder is given in Appendix II

2.1 National authorisations

The competent authorities of the Member States are responsible for granting marketing authorisations for medicinal products which are placed on their markets, except for medicinal products which are authorised under Regulation (EEC) No. 2309/93 ("Community Authorisations" - see Section 2.2 of this chapter).

In order to obtain a national marketing authorisation, an application must be submitted to the competent authority of the Member State.

In cases where national authorisations are requested in more than one Member State in a mutual recognition procedure, the applicant submits an application in one of the Member States and once the marketing authorisation has been granted, the applicant submits applications in other concerned Member States, requesting them to mutually recognise the marketing authorisation already granted. The mutual recognition procedure is detailed in Chapter 2 and the number of dossiers and languages required by Member States are detailed in Chapter 7.
(See also sections 3.3 and 5.2 of this chapter).

2.2 Community authorisations

The Community is responsible for the granting of marketing authorisations for medicinal products:

- developed by means of one of the biotechnological processes referred to in Regulation (EEC) No. 2309/93, Annex, Part A, which may only be authorised by a Community authorisation following an evaluation according to the centralised procedure;

- medicinal products referred to in Regulation (EEC) No. 2309/93, Annex, Part B, for which the applicant has chosen the centralised procedure leading to a Community authorisation.

In order to obtain a Community authorisation, an application must be submitted to the EMEA (see Chapter 4 for details of the procedure and Chapter 7 for number of dossiers and languages required). See also section 3.1 of this chapter.

The scientific evaluation of the application is carried out within the Committee for Proprietary Medicinal Products (CPMP) of the EMEA, and a scientific opinion is prepared. The opinion is sent to the European Commission which drafts a Decision. Having consulted the Member States through the relevant Standing Committee, normally the Commission adopts the Decision and grants a marketing authorisation (see Chapter 6 of the Notice to applicants for further details on the decision making process).

Such a marketing authorisation is valid throughout the Community and confers the same rights and obligations in each of the Member States as a marketing authorisation granted by that Member State.

2.3 (Trade) Name of a Medicinal Product

A marketing authorisation is granted to a single marketing authorisation holder who is responsible for placing the medicinal product on the market. The marketing authorisation includes, when available, the INN (International Non-Proprietary Name) of the active substance(s) and when branded, a single invented name (trade name).

In the case of Community authorisations granted following applications through the centralised procedure, it is important, that applicants identify at an early stage a trade name which would be valid throughout the Community when using the centralised procedure (see Chapter 4 section 3.1). In cases where companies wish to market the same medicinal product with a second trade name, then a separate application for a separate second authorisation must be submitted. The European Commission must be informed of this intention in advance (see Chapter 4 section 3.1). However, in exceptional and particular cases, the Commission could authorise the use of a different trade name in a Member State where the proposed trade name has been cancelled, opposed or objected to under trade-mark law.

For applications through the mutual recognition procedure, it is recommended whenever feasible that the same name for a given medicinal product should be used in all Member States. If a different name is to be used, it should be quoted in a covering letter from the applicant to the relevant competent authorities. As for the centralised procedure, in cases where companies wish to market the same medicinal product with a second trade name, a new application for a separate second authorisation must be submitted.

3. Marketing Authorisation procedures

3.1 Centralised procedure

For medicinal products which satisfy the criteria of the Annexes to Regulation (EEC) No. 2309/93, the application is submitted to the EMEA. Following the scientific evaluation and upon receipt of the opinion, the European Commission drafts a Decision on a Community marketing authorisation and grants a marketing authorisation.

As stated in the Commission Communication (98/C229/03), in order to maintain coherence and to preserve the unity of the Community Single Market, where the same marketing authorisation holder wishes to place on the market another medicinal product with the active substance which is already the subject of a Community authorisation, the Commission considers that the centralised procedure should be used when the therapeutic indication is within the third level of the ATC code. In cases where the applicant does not apply for a Community authorisation as described above, the therapeutic indication(s) authorised by the Community should not be part of the national authorisation. In such a context, the Commission will consider the benefit of referring the case to the EMEA through a referral procedure in accordance with Articles 30 or 31 of Directive 2001/83/EC in order to preserve the above-mentioned coherence.

3.2 Mutual recognition procedure

This procedure is based on the mutual recognition by concerned Member States of a national marketing authorisation granted by the reference Member State. The concerned Member State refers to the reference Member State that issued the national marketing authorisation on which the mutual recognition procedure is based.

At the end of the mutual recognition procedure, a national marketing authorisation will be issued in the concerned Member States. The harmonisation is maintained through mutual recognition procedure for variations, line extensions (see section 5 of this chapter) and renewals.
Mutual recognition procedures may arise in the following instances:

i) in accordance with Article 28 of Directive 2001/83/EC: where "In order to obtain the recognition according to the procedures laid down in this Chapter in one or more of the Member States of an authorisation issued by a Member State, the holder of the authorisation shall submit an application to the competent authorities of the Member State or Member States concerned";

ii) in accordance with Article 18 of Directive 2001/83/EC: "Where a Member State is informed in accordance with Article 8 (3) (*l*) that another Member State has authorised a medicinal product which is the subject of an application for authorisation in the Member State concerned, that Member State shall forthwith request the authorities of the Member State which has granted the authorisation to forward to it the assessment report referred to in the second paragraph of Article 21 (4)";

iii) applications made in accordance with Directive 87/22/EEC[3], (i.e. 'ex-concertation' medicinal products whether List A or B) for which the Committee had issued an opinion before 1 January 1995 had benefited from a Community procedure and therefore such products also benefit from automatic access to the mutual recognition procedure;

iv) for medicinal products for which there has been a Community referral in accordance with Article 30 (divergent decisions) or Article 31 (Community interest) of Directive 2001/83/EC, the harmonisation achieved is maintained through the mutual recognition procedure.

3 OJ L 015, 17.1.1987, p. 38.

3.3 Independent National procedures

Independent national procedures will continue, but are strictly limited from 1 January 1998 to the initial phase of mutual recognition (granting of the marketing authorisation by the reference Member State) and to medicinal products which are not to be authorised in more than one Member State.

However, national independent procedures can continue to be followed for medicinal products with a well established use demonstrated in accordance with Article 10 (1) (a) (ii) of Directive 2001/83/EC, this well established use being based on 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. This case is detailed in the section 4.1, paragraph 4.1.2 "Bibliographic references/applications" of this chapter.

Independent national procedures can also be used for line extensions of authorised medicinal products as far as no a priori harmonisation has been achieved (see section 5.2 of this chapter).

3.4 Community referrals

Where there may be a risk to public health from a medicinal product which is the subject of the mutual recognition procedure, the matter is resolved by a binding Community decision following a scientific evaluation of the issues involved within the CPMP. The same approach is applied in cases of divergent decisions between Member States or in cases of Community interest:

i) in accordance with Article 29 of Directive 2001/83/EC, where one or more Member States cannot mutually recognise an authorisation already granted due to a risk to public health, the matter is referred to the CPMP for application of the procedure laid down in Article 32 of Directive 2001/83/EC. The referral can only be made by the Member States concerned by the application. The expression 'risk to public health' refers to the quality, safety and efficacy of the medicinal product;

ii) in accordance with Article 30 of Directive 2001/83/EC: "If several applications submitted in accordance with Article 8, 10 *(l)* and Article 11 have been made for marketing authorisation for a particular medicinal product, and Member States have adopted divergent decisions concerning the authorisation of the medicinal product or its suspension or withdrawal from the market, a Member State, or the Commission or the person responsible for placing the medicinal product on the market may refer the matter to the Committee for application of the procedure laid down in Article 32";

iii) in accordance with Article 31 of Directive 2001/83/EC: "The Member States or the Commission or the applicant or holder of the marketing authorisation may, in specific cases where the interests of the Community are involved, refer the matter to the Committee for the application of the procedure laid down in Article 32". The applicant or the marketing authorisation holder referred to are those of the concerned medicinal product(s);

iv) in accordance with Article 36 of Directive 2001/83/EC: "Where a Member State considers that the variation of the terms of a marketing authorisation which has been granted in accordance with the provisions of this chapter or its suspension or withdrawal is necessary for the protection of public health, the Member State concerned shall forthwith refer the matter to the Committee for the application of the

procedures laid down in Articles 32, 33 and 34". Article 37 of Directive 2001/83/EC concerns the 'ex-concertation' medicinal products.

v) Variations to marketing authorisations which have been considered within the scope of the ex-concertation procedure or the mutual recognition procedure, or to products that have been subject of any referral described above, follow the procedure set out in Regulation (EC) No 541/95[4], as amended.

- in accordance with Article 5(3) of Regulation (EC) No 541/95 as amended (Type I variations): "Within 10 days of the end of the procedure mentioned in paragraph 2 of this Article, and in cases of divergent positions among the national competent authorities of the concerned Member States leading to a refusal, the marketing authorisation holder may refer the matter to the Agency for application of Article 35 (2) of Directive 2001/83/EC

- in accordance with Article 7(5) of Regulation (EC) No 541/95 as amended (type II variations): "If within the period foreseen in paragraph 3, mutual recognition by one or more national competent authorities of the draft decision of the national competent authority of the reference Member State is not possible, reference shall be made to the provisions of Article 35 (2) of Directive 2001/83/EC

Articles 32, 33 and 34 apply in like manner and need to be read in the variation procedure scenario.

See also chapter 3 of the Notice to applicants Volume 2A.

4. Application types

The legal requirements and the procedures for making an application for a marketing authorisation are set out in Directive 2001/83/EC, and in Regulation (EEC) No. 2309/93.

A brief description of these requirements and procedures is set out in this chapter. It is important, however, that the requirements and procedures are not confused with the content of the application dossier, guidance on which is given in "The Rules Governing Medicinal Products in the European Union, Volume 2B Notice to Applicants: Presentation and content of the dossier".

- 4.1 Complete/full and independent ('stand-alone'/'self-standing') applications
  - 4.1.1 Mixed data applications
  - 4.1.2 Bibliographic references/applications
- 4.2 Abridged applications
  - 4.2.1 Informed consent from a MAH for an essentially similar medicinal product
  - 4.2.2 Product essentially similar to a product authorised for 6 or 10 years
    - Particular case: different use, route, doses
- 4.3 Application for a 'fixed combination' product

[4] OJ L 015, 11.3.1995, p.7.

4.1 Complete/full and independent ('stand-alone'/'self-standing') applications

An application for marketing authorisation must be accompanied by the particulars and documents set out in Article 8 of Directive 2001/83/EC and therefore the results of:

- physico-chemical, biological or microbiological tests,
- pharmacological and toxicological tests,
- clinical trials

are included in the dossier.

4.1.1 Mixed data

Mixed data applications are applications where published scientific literature is presented together with original results of tests and trials. The legal basis of such applications according to Directive 2001/83/EC, as indicated in the application form in Part 1/Module 1 will depend on the following considerations:

- Where references to published literature are made in order to replace any test or trial, such applications are made according to Article 10 (1) (a) (ii) and the conditions listed below, in particular the existence of a 'well established use' must be demonstrated;

- In Article 8 – complete/full and independent applications – relevant literature references have to be submitted anyhow and can be supportive data without having to demonstrate a 'well established use'.
The competent authority will subsequently conduct the evaluation in the context of the legal basis of such an application.

4.1.2 Bibliographic references/applications

According to Article 10 (1) (a) (ii) of Directive 2001/83/EC it is possible to replace results of pharmacological and toxicological tests or clinical trials by detailed references to published scientific literature (information available in the public domain) if it can be demonstrated that the constituent(s) of a medicinal product have a well established medicinal use, with recognised efficacy and an acceptable level of safety. Article 10 (2) of Directive 2001/83/EC provides that where pursuant to the above provisions references to published data are submitted (bibliographical applications), the provisions of Annex I of Directive 2001/83/EC shall apply in like manner. They are considered as full and independent applications.

Annex I of Directive 2001/83/EC gives some explanation on the meaning of 'well established medicinal use'. It contains sections concerning the demonstration of safety and efficacy of well established use.

This new piece of legislation applies to any medicinal product, chemical or biological substance, particularly where there is no original/reference medicinal product to which essential similarity can be claimed. This is the case for instance for 'old' medicinal products. (For the definition of original and reference medicinal product see section 4.2 item 6 of this chapter).

a. Well established use:

Annex I of Directive 2001/83/EC provides that for the purpose of demonstrating that the constituent(s) of a medicinal product have a well established use, with an acceptable level of safety and with recognised efficacy, the following criteria should be taken into account:

- the time over which a substance has been used with regular application in patients,
- quantitative aspects of the use of the substance, taking into account the extent to which the substance has been used in practice, the extent of use on a geographical basis and the extent to which the use of the substance has been monitored by pharmacovigilance or other methods,
- the degree of scientific interest in the use of the substance (reflected in the published scientific literature) and the coherence of scientific assessments.

Therefore different periods of time may be necessary for establishing well established use of different substances. In any case, however, the period of time required for establishing a well established medicinal use of a constituent of a medicinal product must not be less than one decade from the first systematic and documented use of that substance as a medicinal product in the EU.

Evidence must be supplied to demonstrate that a constituent has been extensively used for the 10 year period. Accordingly, whilst data demonstrating less extensive use (e.g. use in clinical trials, compassionate use, named patient supply) may be submitted, this cannot replace the need to demonstrate extensive use for that 10 year period.
Where relevant, the prevalence of the condition/disease should be taken into account when demonstrating such extensive use.

Use as 'medicinal product' is not only synonymous with 'use as authorised medicinal product'.

Well established use refers to the use for a specific therapeutic use. If well-known substances are used for entirely new therapeutic indications for which the requirements of the Annex I to Directive 2001/83/EC cannot be fulfilled, it is not possible to solely refer to a well established use and additional data on the new therapeutic indication together with appropriate safety data should be provided (i.e. example of 'mixed data' – see section 4.1.1).

b. Documentation to be submitted:

- The applicant is encouraged to provide a detailed description of the strategy used for the search of published literature and the justification for inclusion of references in the application. As provided in Directive 2001/83/EC Annex I, "all documentation, both favourable and unfavourable, should be communicated".

- The documentation submitted by the applicant should cover all aspects of the assessment and must include a review of the relevant literature, taking into account pre- and post-marketing studies and published scientific literature concerning experience in the form of epidemiological studies and in particular of comparative epidemiological studies. All documentation, both favourable and unfavourable, should be communicated. If documentation is lacking, a justification should be given.

- The reference must refer to 'published scientific literature'. The term 'published' literature implies that the text must be freely available in the public domain and published by a reputable source, preferably peer-reviewed.

- Scientific monographs may offer an overview on published scientific literature which - together with the full texts referred to - may be used in addition to other documents for a bibliographical application. These monographs can help to avoid duplication of work and bring about gradual harmonisation in the evaluation of medicinal products.

- It must be stressed that assessment reports such as the EPAR for Community marketing authorisations which are made publicly available by competent authorities for reasons of transparency cannot be considered to supply sufficient information to meet the requirements of Annex I of Directive 2001/83/EC.

- Copies of the full text of the literature, including necessary translations must be submitted.

c. Expert reports:

- The Expert Reports (Part I C or module 2 of the CTD) must clearly state the grounds for using published references under the conditions set out in Annex I of Directive 2001/83/EC. This would include the completion of all of the tabular formats provided in "The rules Governing Medicinal Products in the European Union, Volume 2B Notice to Applicants: Presentation and content of dossier" where relevant, unless there is a justification that the study is not relevant for the medicinal product.

- When some parts of the dossier are not complete, particular attention must be paid to explain why.

- Whenever information on specific points is missing, justification must be given in the expert report as to why demonstration of an acceptable level of safety/recognized efficacy can be supported although some studies are lacking. The reasons for their absence must be given. The Expert report must explain the relevance of any data submitted which concern a product different from the product intended for marketing and a judgement must be made to what extent the product studied can be considered as similar to the product which will be granted a marketing authorisation in spite of the existing differences.

- Post-marketing experience with other products containing the same constituents is of particular importance and applicants should put a special emphasis on this issue.

d. Bibliographical application and mutual recognition/national procedure

As for other applications, the mutual recognition procedure is compulsory in the case of bibliographical applications intended for authorisation in more than one Member State and for which the use of the centralised procedure is neither mandatory nor chosen by the applicant. Commission Communication 98/C229/03 clarified, however, that in the case of a medicinal product with a well established use demonstrated in accordance with Article 10 (1) (a) (ii) of Directive 2001/83/EC, this well established use being based on data referring to an existing group of products with different SPCs in the Member States, national independent procedures could continue to be followed as far as no Community harmonisation of the use of the constituent(s) of the said product exists, the purposes of Article 18 of Directive 2001/83/EC being not to provide harmonisation of an entire therapeutic class or a complete group of products.

Article 28 of Directive 2001/83/EC remains, of course, applicable and MAH/applicants are therefore always free to ask for mutual recognition, if they want to.

4.2 Abridged applications

According to Article 10 (1) (a) (i) and (iii) first paragraph of Directive 2001/83/EC the applicant shall not be required to provide the results of pharmacological and toxicological tests or the results of clinical trials if he can demonstrate:

"i) either that the medicinal product is essentially similar to a product authorised in the country concerned by the application and that the person responsible for the marketing of the original proprietary medicinal product has consented to the pharmacological, toxicological or clinical references contained in the dossier on the original medicinal product being used for the purpose of examining the application in question" (so-called 'INFORMED CONSENT' application)
"iii) or that the medicinal product is essentially similar to a product which has been authorised within the Community, in accordance with Community provisions in force, for not less than six/ten years and is marketed in the Member State for which the application is made" (so-called 'GENERIC' application).

These types of application refer to information that is contained in the dossier of another 'original' authorisation. This information is generally not completely available in the public domain. "Generic" and 'informed consent' authorisations are therefore linked to the 'original' authorisation. Legislation has based the possibility to submit 'informed consent' and 'generic' applications on the assumption that the following fundamental conditions are met:

1. Reference must be made to the dossier of an original product for which a marketing authorisation has been granted on the basis of a complete dossier. Therefore, generic/informed consent applications referring to mixed data dossiers, to bibliographical dossiers or to 'fixed combination' dossiers are acceptable (because all relevant information is in the dossier of the original product).

The dossier of an abridged dossier does not contain all relevant information. Therefore, an abridged application referring to an abridged dossier is not possible.

The dossier of a new strength, new pharmaceutical form, new indication (called deliberately 'line extensions' see section 5.2) of an existing medicinal product from the same marketing authorisation holder based on a complete dossier is also considered as a complete dossier. An essentially similar product (informed consent or generic) can refer to the dossier of the line extension of the original medicinal product. Therefore, a line extension for a generic medicinal product can be applied for by reference to the line extension of the original medicinal product.

2. Reference must be made to the dossier of an original product which is at the disposal of the competent authority concerned and for which a Marketing Authorisation has been granted. This implies that abridged applications may only be lodged with authorities which actually hold the dossier of the original product. This principle has explicitly been recognised in Commission Communication (98/C229/03) which states that "for an abridged application concerning a medicinal product essentially similar to one already covered by a Community authorisation, the centralised route must be used in all cases. Therefore generic applications referring to Community marketing authorisation dossier for medicinal products which are essentially similar to Community authorised products falling under the scope of

Part B of the Annex to Regulation (EEC) No 2309/93, must follow the centralised procedure." The same principle applies, of course, also in the national context.

3. Reference must be made to an existing authorisation: a generic/informed consent application can only be applied for after an original marketing authorisation has been granted. It is not possible to submit an abridged application referring to an original product simultaneously with an application for an authorisation for the original product.

4. Competent authorities must check that a product, to which reference is made, is still authorised at the time of application. If the original/reference (see paragraph 6 for definitions) authorisation is withdrawn after a generic/informed consent application has been lodged but before the authorisation has been granted, competent authorities may nevertheless grant the generic marketing authorisation if there are no public health concerns which lead to the withdrawal/suspension of the original product. If a marketing authorisation holder of an original medicinal product asks for the withdrawal of an authorisation in favour of an authorisation for a medicinal product of which the composition in active substances, the strength and the pharmaceutical form are the same but which differs regarding excipients while maintaining the same efficacy and safety, both formulations can be a reference for an application for an essentially similar medicinal product.

5. The main principle underlying Community pharmaceutical legislation is the protection of public health. Marketing authorisations for medicinal products are dynamic and not static and the dossier underlying a marketing authorisation must be regularly updated in order to assure that scientific progress and new regulatory requirements are respected, in accordance with Article 23 of Directive 2001/83/EC, with the introduction of the Annex I of Directive 2001/83/EC and with Article 15 of Regulation (EEC) No 2309/93. After the withdrawal of an original product, there is no longer an obligation on the originator company to update the dossier underlying the marketing authorisation of the original medicinal product. It may be the case that the original medicinal product is withdrawn after the abridged application is authorised. However, also for abridged dossiers the obligation exists to keep the Quality part up to date and to supplement the dossier with pharmacovigilance data (periodic safety update reports) over time. This will enable the competent authorities to check that the references to the originator dossier combined with periodic safety update reports of the marketing authorisation holder of the abridged dossier still provide satisfactory information on the safety and efficacy of the product.

6. Essential similarity: the product applied for under the abridged procedure must be essentially similar to the original/reference medicinal product. In this context the following definitions are applicable.

An original medicinal product is a medicinal product that has been authorised within the Community for not less than 6 or 10 years. The marketing authorisation of this medicinal product is based on a complete dossier.

A reference medicinal product is a version of the original medicinal product which is marketed in the Member State for which the application is made and which is used to claim essential similarity. In this Member State the reference medicinal product can be authorised for less than 6/10 years. This reference medicinal product might be of another strength or pharmaceutical form or be approved for other indications or have other excipients than the original medicinal product.

A medicinal product used as comparison for bioequivalence study, where a bioequivalence study is applicable, is a version of the original medicinal product that is authorised within the Community. This medicinal product is normally the same as the reference medicinal product.

The application form in Part 1/Module 1 of the dossier should be completed using these definitions where applicable.

Directive 2001/83/EC does not define the concept of an essentially similar medicinal product. According to the minutes of the meeting of the Council of Ministers in December 1986 at which Directive 87/21/EEC[5] was adopted, and following an interpretation delivered by the European Court of Justice in its Judgement in Case C-368/96 which reconfirmed and refined the definition given in that minutes, a medicinal product is essentially similar to an original/reference medicinal product where it satisfies the criteria of having

- the same qualitative and quantitative composition in terms of active principles/substances,

- the same pharmaceutical form and,

- of being bioequivalent

unless it is apparent in the light of scientific knowledge that it differs significantly from the original product as regards safety or efficacy.

In the context of this specific provision, both the term 'same qualitative and quantitative composition of active principles' and the term 'same pharmaceutical form' must be understood broadly:

- the term 'same qualitative and quantitative composition of active principles' covers all products containing the same active substance and having the same properties with regard to safety and efficacy.

A definition on what has to be understood by new active substance is given in the Appendix III of this chapter.

Active substance(s) in the form of different salts, esters, derivatives, etc. but with the same active therapeutic moiety should (normally) not be considered as a new active substance, unless they differ significantly from each other in properties regarding safety or efficacy.
Evidence on same properties regarding safety and efficacy of a different salt, ester, other derivative of an active substance should be provided by the applicant when he claims that the medicinal product for which the application is submitted is essentially similar to an authorised medicinal product containing another salt, ester or other derivative of the same active substance. (See Appendix IV of this chapter).
The decision whether a different form of the active substance is to be classified as a new active substance should be taken by the competent authorities of the Member States/EMEA on a case-by-case basis.

For applications in the mutual recognition procedure, the concerned Member States should in the validation phase rely on the application form in Part 1/ Module 1 of the application and the reference Member State should justify the choice of the legal basis according to Article 10 (1) (a) (iii) first paragraph or second paragraph. Any scientific objection based on an evaluation of the Quality, Safety, and Efficacy parts of the dossier should be raised during the subsequent mutual recognition procedure.

Concerning the composition of the product with respect to other ingredients (excipients), they can be different but may not lead to a medicinal product which differs significantly from the original medicinal product as regard efficacy and safety;

5 OJ L 015, 17.1.1987, p.36.

- the reference for the pharmaceutical form is the European Pharmacopoeia document "STANDARD TERMS – Pharmaceutical dosage forms – Routes of administration – Containers – January 2000". All oral solid pharmaceutical forms for immediate release (e.g. tablets and capsules) must be regarded as the 'same pharmaceutical form' for the purpose of the concept of essential similarity.

- for products derived from biotechnology, the concept of 'essential similarity' is difficult to apply because the criteria of demonstrating the chemical, pharmaceutical and biological equivalence of larger molecules e.g. proteins, are not defined.. A Guideline will address the comparability of biological and biotechnological medicinal products.

Bioequivalence: the need for appropriate bioavailability studies should be addressed in the dossier and Expert Report, (see Guideline on Bioavailability and Bioequivalence in "The Rules Governing Medicinal Products in the European Union" Volume 3).

4.2.1 'Informed consent' applications

The person responsible for the marketing of the original medicinal product must have consented to the pharmacological, toxicological or clinical references contained in the dossier on the original medicinal product being used for the purpose of examining the 'informed consent' application in question.

In these circumstances the applicant must have permanent access to the references or be in possession of this information (without prejudice to the closed part of the Drug Master Dossier), in order to fully carry out his responsibilities.

It is up to the contracting parties to consider, as a term of their contractual agreement, whether the 'informed consent' can be withdrawn by the consenting parties and what the consequences of the withdrawal of the informed consent would be.

For competent authorities, demonstration of the 'informed consent' is a formal condition which must be fulfilled, when the informed consent application is submitted. A withdrawal of the informed consent at a later stage has no direct consequences on the existence/validity of the Marketing Authorisation.

4.2.2 'Generic' applications

The medicinal product to which the essential similarity is claimed must:
1. have been authorised within the Community, in accordance with Community provisions in force,
2. have been authorised within the Community for not less than 6/10 years
3. be marketed in the Member State for which the application is made.

The term within the Community, in accordance with Community provisions in force must be read to cover authorisations issued/maintained in countries where the Community pharmaceutical Acquis has become applicable and binding.

The data protection period of six years shall be extended to 10 years in the case of high-technology medicinal products within the meaning of Part A in the Annex to Directive 87/22/EEC or of a medicinal product within the meaning of Part B in the Annex to that Directive for which the procedure laid down in Article 2 thereof has been followed. Furthermore, a Member State may also extend this period to 10 years by a single Decision

covering all the products marketed on its territory where it considers this necessary in the interest of public health.

In accordance with the above provision and decisions taken by Member States, the current period of exclusivity is as follows:

- 10 years for all medicinal products submitted through the centralised procedure of Regulation (EEC) No. 2309/93;
- 10 years for all medicinal products which have been authorised following an opinion of the CPMP in accordance with Article 4 of Directive 87/22/EEC (ex-concertation procedure);
- 10 years (by single decision) for other medicinal products in Belgium, Germany, France, Italy, the Netherlands, Sweden, United Kingdom and Luxembourg;
- 6 years in Austria, Denmark**,** Finland, Ireland, Portugal, Spain, Greece and also Norway and Iceland;

Evidence of the date of authorisation for more than 6/10 years should be provided in the application for marketing authorisation.

Implications for the mutual recognition procedure: if the data protection period is equal in all the CMS(s), no problem will arise. If, however, the protection period in the CMS is longer than in the RMS, mutual recognition in the CMS is not possible before the expiry of the longer period.

'Marketed' must be understood as 'authorised' as the medicinal product has been authorised under a 'marketing authorisation'. If a marketing authorisation still exists and the competent authority is informed that the medicinal product is not on the market, the competent authority should consider the reasons carefully. Confirmation that the medicinal product is authorised in the Member States involved in the procedure should be provided in the application for marketing authorisation (Application form in Part 1/ Module 1).

The European Court of Justice, in its Judgement in Case C-368/96, has confirmed that, if the three above conditions are fulfilled, a generic authorisation may be issued for all therapeutic indications and all dosage forms, doses and dosage schedules already authorised for the originator product, even if some of those indications, dosage forms, doses, had been authorised for a period shorter than 6/10 years. The terminology in Directive 65/65/EEC which has been mentioned in this judgement is no longer used in practice. The equivalent terminology is pharmaceutical form for dosage form, strength for dose and posology for dosage schedule.

The medicinal product to which essential similarity is claimed must be either the original medicinal product or a line extension thereof. Referring to the above mentioned Court Case, the requirement for authorisation for at least 6/10 years in the Community does not apply to line extensions used as reference products beyond the 6/10 years data exclusivity period of the original medicinal product.

Particular case: different use, route, doses (applications under Article 10 (1) (a) (iii) last paragraph)

The possibility of using references to an originator dossier (without the originators consent) in order to support a generic application is, however, not limited to the above case: Article 10

(1) (a) (iii), last paragraph clearly provides: "However, where the medicinal product is intended for a different therapeutic use from that of the originator product marketed or is to be administered by different routes or in different doses, the results of appropriate pharmacological and toxicological tests and/or of appropriate clinical trials must be provided." This means that generic authorisations may be extended to cover more or other indications, strengths and pharmaceutical forms than the originator product, if sufficient 'bridging' data are submitted by the applicant.

For all abridged applications, applicants must always demonstrate the safety and efficacy of the medicinal product and justify the content of the application in the Expert Reports. Some guidance on the appropriate additional studies required is indicated in the table given in the Appendix IV.
A complete Quality Part of the dossier must always be submitted.

4.3 Application for a 'fixed combination' medicinal product

In accordance with Article 10 (1) (b) of Directive 2001/83/EC: "In the case of new medicinal products containing known constituents not hitherto used in combination for therapeutic purposes, the results of pharmacological and toxicological tests and of clinical trials relating to that combination must be provided, but it shall not be necessary to provide references relating to each individual constituent". Strictly speaking, any fixed combination is a new and unique medicinal product requiring a separate marketing authorisation and SPC. It can be considered as complete/full, independent application. Therefore, generic/informed consent applications referring to 'fixed combination' dossiers are acceptable.

5. Variations and extensions

Throughout the life of a medicinal product, the MAH is responsible for the product which circulates in the marketplace and is also required to take into account technical and scientific progress, and to make any amendments that may be required to enable the medicinal product to be manufactured and checked by means of generally accepted scientific methods.

Such amendments may involve administrative and/or more substantial changes, and procedures for the approval of such amendments have been set out in the Regulations (EEC) No 541/95 as amended, and (EEC) No 542/95[6] as amended and in national legislation.
The Regulation (EEC) No. 542/95 as amended applies to Community marketing authorisations and the Regulation (EEC) No. 541/95 as amended applies to national authorisations arising from a mutual recognition procedure or ex-concertation procedures or to Community referrals.

5.1 Variations to marketing authorisations

A variation to the terms of a marketing authorisation is an amendment to the contents of the documents referred to in *Articles 8, 9, 10, 11* and Annex I of Directive 2001/83/EC, such as they exist at the moment of the decision on the marketing authorisation or after approval of any previous variation, except where a new application for a marketing authorisation must be presented pursuant to Annex II of the Regulations (EEC) No. 541/95 and (EEC) No 542/95 as amended.

- Minor variation

6 OJ L 055, 11.3.1995, p.15.

Minor variations or variations Type I are listed in Annex I to the Regulations (EEC) No. 541/95 and (EEC) No 542/95.

- Major variation
Major variations or variations Type II mean variations which can neither be deemed to be Type I variations within the meaning of preceding definition, nor changes for which a new application must be presented pursuant to Annex II of the Regulations (EEC) No. 541/95 and (EEC) No 542/95 as amended.

For medicinal products that have been authorised nationally however not via a mutual recognition procedure, procedures for changes/variations are set out in national legislation. Such procedures are not necessarily the same as those set out in Community Legislation.

5.2 Extensions: applications in accordance with Annex II of the Regulations (EEC) No 541/95 as amended, and (EEC) No 542/95 as amended

Certain changes to a marketing authorisation are considered to fundamentally alter the terms of the marketing authorisation and therefore cannot be considered as a variation. For these changes, set out in Annex II of the above-mentioned Regulations, a new application must be made. This procedure has been chosen because the time period of 210 days was considered necessary in order to evaluate these changes. As the case may be, a new marketing authorisation or a modification of the existing marketing authorisation will have to be granted by the Community or by the Competent Authority.

Applications for changes or additions falling under the scope of Annex II of the above-mentioned Regulations can only be submitted for the existing marketing authorisation by the marketing authorisation holder. Such an application must be in conformity with Article 8 and 10(1) of Directive 2001/83/EC. For such an application the table in the Appendix IV of this chapter provides some guidance.

All changes falling under the scope of the Annex II of the above-mentioned Regulations are defined as ‘line extensions’ except those relating to the active substance where the active substance is viewed as a ‘new active substance’ (See Appendix III).

The legal basis for an application of a “line-extension” corresponds to the legal basis of the initial application for the medicinal product (e.g. the legal basis for a line-extension of a “full/independent application” is again a “full/independent application”). The application form in Part 1/Module 1 of the dossier for the line-extension must be completed accordingly.

The provisions of the mutual recognition procedure can be applied to line extensions of non harmonised national marketing authorisations, where an a priori harmonisation can be achieved:

- through a set of co-ordinated national procedures or
- through the Community procedure foreseen in Article 30 of Directive 2001/83/EC or
- through a complete independent dossier without any cross references to the dossier supporting the existing national authorisations.

Otherwise a national procedure remains applicable.

5.3 Urgent safety restrictions

The above-mentioned Regulations do not impede the marketing authorisation holder or the competent authority from taking provisional urgent safety restrictions in the event of a risk to public health. Where the marketing authorisation holder takes such provisional urgent safety restriction, he shall forthwith inform the appropriate competent authority/Agency. If the competent authority/Agency has not raised any objections within 24 hours, the urgent safety restriction may be introduced and the corresponding application for the variation shall be submitted without delay to the competent authority/Agency.

Where the competent authority/Commission imposes provisional urgent safety restriction, the marketing authorisation holder shall be obliged to submit an application for a variation without delay to the competent authority/Agency.

An urgent safety restriction is defined as an interim change to product information concerning the indication(s), posology, contra-indication(s), warning(s) due to new information having a bearing on the safe use of the product.

APPENDIX I

HIERACHY OF THE COMMUNITY TEXTS

TREATIES

These are the «constitutional» rules of the European Union.

The European Communities are based on three **founding treaties**:
- Treaty of Paris (signed off on 18th of April 1951, in force since 23rd July 1952) establishing the European Coal and Steel Community or ECSC Treaty
- Treaty of Rome (signed off on 25th March 1957, in force since 1st January 1958) establishing the European Atomic Energy Community or EURATOM Treaty and the European Economic Community or EEC Treaty
- Treaty of Brussels (signed off on 8th April 1965, in force since 1st July 1967) so-called the fusion Treaty

They have been modified with **revision treaties**.

- The European Single Act (signed off on 17th February 1986 and 26th February 1986, in force since 1st July 1987) with a view to preparing and establishing the European "Single Market".
- Treaty of Maastricht (signed off on 27th February 1992) which confer to the Communities new fields of inter-governmental decision making authority: common foreign and security policy, and judicial co-operation and domestic affairs. This Treaty established the European Community.
- Treaty of Amsterdam (signed off on 2nd October 1997) with a view to prepare the enlargement.

PHARMACEUTICAL LAW

The Community Pharmaceutical Law is based on EC Treaty provisions.
The various legal acts adopted in this matter are based on:
- Article 37 (ex 43) Common Agricultural Policy
- Article 94 (ex 100) and Article 95 (ex 100A) Harmonisation of the Law of the Member States
- Article 308 (ex 235) Action in the matters where specific power to act has not been provided for by the Treaty
- Article 252 (ex 189C) Codecision Procedure

Original Law
Founding Treaties and Revision Treaties establish the rules for the Community institutions Objectives of the European Community (EC)

EC Competence: all areas where the institutions are empowered to enact Community Legislation.

Derivative Law
Law adopted by the Community institutions with the aim to make use of the treaties
Distinction of the texts is done according to their legal strength.

1. Legally binding

According to Article 249 (ex 189) of the EC Treaty:

a) Regulation
Regulation is a general legal act, that is entirely and directly binding with immediate entry into force on the Member States. It does not require any transposition by the national authorities.

b) Directive
Directive is a legal act binding on the Member States as far as the results to be obtained are concerned; the national authorities are allowed to choose form and methods to reach them. A directive always leads to a complementary national legal act. In order to take effect a directive must be transposed into the legislation of the Member States.

c) Decision
Decision is a legal act binding upon those to who it is addressed (Member State or natural or legal person).

2. 'Soft law'

a) Resolution
Resolution is a declaratory act non provided for by the EC Treaty that is published by the Council and the European Parliament in order to inform of their positions on a specific subject, and, where necessary, that invites the Commission to propose the appropriate measures.
Resolution is rather a political than a legal act; it does not create any obligation.

b) Communication
Communication is an act non-provided for by the Treaty of the EC, which is without binding legal effect.
It indicates to governments and economic actors how the Commission is planning to apply or wishes to see applied a given Community rule.
The Court of Justice of the European Communities often supports its interpretation with Commission communications.

c) Notification
According to Article 254 (ex 191) of the EC Treaty, Notifications concern provisions other than those adopted by the Council and the European Parliament within the scope of the co-decision procedure, which shall be notified to the persons to whom they are addressed and take effect upon this notification.

d) Guidelines
Texts covering technical topics, their legal status may differ:
- Guidelines resulting from a formal request laid down in a Community Directive or Regulation are binding and must be complied with when the corresponding Directive or Regulation is implemented. The Commission publishes them e.g. the "Note for guidance on

minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products"

- Guidelines spontaneously drawn up by the scientific committee are not legally binding; they present the best or more appropriate way to fulfil an obligation laid down in the Community rules.

e) Notice to Applicants

The Notice to applicants is a guidance provided for in the Annex I of Directive 2001/83/EC. The Commission publishes this guidance in "The rules governing medicinal products in the European Community", Volume 2: "Notice to applicants for marketing authorisations for medicinal products for human use".

Volume 2 is divided in

- Volume 2A "Procedures for marketing authorisation"
- Volume 2B "Presentation and content of the dossier"
- Volume 2C "Regulatory guidelines"

APPENDIX II

LEGAL ISSUES CONCERNING THE MARKETING AUTHORISATION HOLDER

The Marketing Authorisation Holder (MAH) is the person who holds the authorisation to place a medicinal product on the market and is responsible for marketing the medicinal product.
The granting of a marketing authorisation (MA) by a competent authority does not discharge the holder from civil and criminal liability as provided for by the law of the Member States.

The MAH may be a natural or legal person.
The MAH must be established in the European Community including the EEA.
Applications for a MA shall be accompanied by the name or corporate name and permanent address of the MAH.
The name and permanent address of the MAH must appear in the Summary of Product Characteristics (SPC), on the labelling and the package leaflet of the medicinal product.

The MAH must fulfil several obligations and assume various responsibilities:

- shall comply with the content and terms of the authorisation. As a consequence of this obligation any changes to the original MA dossier must be the subject of an application and be authorised by the same authority as the original authorisation;
- shall pay the fees to the Competent Authorities involved in the application of marketing authorisation of the medicinal product;
- shall take into account any technical and scientific progress in order to update manufacturing and control operations. These changes shall be subject to the approval of the competent authority;
- when the MAH is not the manufacturer, shall sign a written agreement with the manufacturer in order to guarantee that the manufacturing operations comply with the rules into force and with the manufacturing conditions provided for in the dossier;
- shall furnish proof that the controls have been carried out on the finished product in accordance to the methods described in the documents that accompanied the application;
- shall inform authorities of any information brought to his attention that could lead to a modification in the MA dossier or in the SPC;
- shall submit an application for renewal of the Marketing Authorisation at least three months before the expiry date and shall include in the application the data on pharmacovigilance and other information relevant to the monitoring of the medicinal product;
- shall inform concerned Member States of any action to suspend or withdraw a medicinal product from the market together with the reasons for such action;
- shall have permanently and continuously at his disposal a qualified person in charge of pharmacovigilance for the establishment and maintenance of a pharmacovigilance system and for the preparation of the reports on all suspected serious adverse reactions submitted to the competent authorities;
- shall ensure that all relevant information about suspected adverse reactions and all suspected serious adverse effects are brought to the attention of the Competent Authorities;
- shall maintain detailed records of all suspected adverse reactions occurring within or outside the Community;
- shall have a scientific service in charge of scientific information on the concerned medicinal product;
- shall be responsible for advertising of the medicinal product, and for ensuring compliance of advertising with the applicable provisions;
- shall inform authorities of any prohibition or restriction on use imposed by the authorities of another Member State where the medicinal product has been marketed;

- shall retain and archive all documentation on the medicinal product and, in particular, any documents related to clinical trials;

- may refer to the CPMP any cases where the competent authorities have adopted divergent decisions or where the interests of the Community are involved. In these cases the MAH shall have the opportunity to make his point of view known orally or in writing;

- in the cases of immunological medicinal products and medicinal products derived from human blood or human plasma, the MAH shall submit samples from each batch of the bulk and/or finished product for examination by a State laboratory or a laboratory designated for that purpose.

APPENDIX III

DEFINITION OF A NEW ACTIVE SUBSTANCE

A new chemical, biological or radiopharmaceutical active substance includes:

- a chemical, biological or radiopharmaceutical substance not previously authorised as a medicinal product in the European Union;

- an isomer, mixture of isomers, a complex or derivative or salt of a chemical substance previously authorised as a medicinal product in the European Union but differing in properties with regard to safety and efficacy from that chemical substance previously authorised;

- a biological substance previously authorised as a medicinal product in the European Union, but differing in molecular structure, nature of the source material or manufacturing process;

- a radiopharmaceutical substance which is a radionucleide, or a ligand not previously authorised as a medicinal product in the European Union, or the coupling mechanism to link the molecule and the radionucleide has not been authorised previously in the European Union.

APPENDIX IV

GUIDANCE ON THE APPROPRIATE ADDITIONAL STUDIES REQUIRED FOR ABRIDGED APPLICATIONS OR ANNEX II APPLICATIONS

		Additional data usually required
a)	different salt/ester complex/derivative (with the same therapeutic moiety)	Evidence that there is no change in the pharmacokinetics of the moiety, pharmacodynamics and/or in toxicity which could change the safety/efficacy prodossier (otherwise, to be considered as a new active substance)
b)	different therapeutic use	Clinical data (safety/efficacy), pre-clinical if justified
c)	different route/pharmaceutical form (For parenteral administration, it is necessary to distinguish between intraarterial, intravenous, intramuscular, subcutaneous and other routes) i) new route of administration ii) new pharmaceutical form (same route) (conventional to modified)	Clinical data (safety/efficacy), pharmacokinetics, pre-clinical (e.g. local toxicology), if justified
d)	different posology i) reduction only in the number. of units/dose ii) change in frequency, and/or amount/dose (higher or lower) and/or daily doses	Bioavailability (cf. guideline) Clinical data (safety/efficacy), pharmacokinetics
e)	different strength same route/ pharmaceutical form and posology	Bioavailability (cf. guideline)
f)	suprabioavailable products i) same dosage intervals but reduced doses intended to achieve same plasma/blood concentrations as a function of time ii) other posology	Bioavailability studies may suffice (see paragraph 5 of Bioequivalence guideline). See d) ii)
g)	active substances associated in a different proportion/different posology or if one or more is intended for modified release.	Clinical studies comparing existing/new proportion or dosage regimen, including bioavailability studies.