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NOTICE TO APPLICANTS

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Procedures for marketing authorisation
CHAPTER 1
MARKETING AUTHORISATION

November 2005

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

CHAPTER 1 Marketing Authorisation

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1. INTRODUCTION

1.1 Objectives

The primary purpose of the 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 of the Community pharmaceutical legislation are given in this chapter. More detailed explanations concerning the different procedures for marketing authorisation are provided in Chapters 2 - 7.

1.2 Status

This Notice to Applicants has been prepared in accordance with Article 6 of Regulation (EC) No 726/2004[1] and Annex I of Directive 2001/83/EC[2] on the Community code relating to medicinal products for human use, as last amended by Directive 2004/24/EC[3] and by Directive 2004/27/EC[4]. It is intended to facilitate the interpretation and application of the Community pharmaceutical legislation. 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 Community pharmaceutical legislation must be met and that this Notice to Applicants represents the harmonised view of the Member States, the European Medicines Agency (EMEA) and the Commission on how those requirements may be met.

References throughout the Notice to Applicants to provisions of Directive 2001/83/EC must be read as references to the directive as last amended, unless it is otherwise expressly stated.

A brief overview of the hierarchy of Community texts and of the obligations incumbent on marketing authorisation holders is given in Annexes I and II, respectively. It is intended for information only. In case of doubt about the legal status or rank of different texts, or of the legal obligations of marketing authorisation holders, reference should be made to the legal texts themselves.

1 OJ L 136, 30.4.2004, p.1.
2 OJ L 331, 28.11.2001, p. 67.
3 OJL 136, 30.4.2004, p. 85.
4 OJ L 136, 30.4.2004, p. 34.

2. MARKETING AUTHORISATION

A medicinal product may only be placed on the market in the European Economic Area (EEA) when a marketing authorisation has been issued by the competent authority of a Member State (or EEA country) for its own territory (national authorisation) or when an authorisation has been granted in accordance with Regulation (EC) No 726/2004 for the entire Community (a Community authorisation). The marketing authorisation holder must be established within the EEA.

Article 48 of the Treaty establishing the European Community (Chapter 2 Right of establishment) reads:

> '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, be treated in the same way as natural persons who are nationals of Member States.
> "Companies or firms" means companies or firms constituted under civil or commercial law, including co-operative societies, and other legal persons governed by public or private law, save for those which are non-profit-making'.

For the purpose of applying this definition in the context of the pharmaceutical legislation it should be clarified that 'non profit-making' organisations can be marketing authorisation holders.

European Economic Area (EEA)

Norway, Iceland and Liechtenstein form the EEA with the 25 Member States of the European Union. These countries 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 Norway, Iceland and Liechtenstein. 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 Norway, Iceland and Liechtenstein. According to Decision N° 74/1999 of the EEA Joint Committee when decisions on approval of medicinal products are taken by the Community, Norway, Iceland and Liechtenstein will take corresponding decisions on the basis of relevant acts. Consequently, these States are concerned by the single European market for medicinal products. Therefore, where in Article 2 of Regulation (EC) No 726/2004 and Article 8 of Directive 2001/83/EC, reference is made to the applicant being established in the Community, this is extended to include Norway, Iceland and Liechtenstein.

The marketing authorisations granted by Norway, Iceland and Liechtenstein are eligible for the mutual recognition procedure in the same way as the marketing authorisations granted by Member States.

Monaco

An agreement between the Community and the Principality of Monaco entered into force on 1 May 2004, Council Decision 2003/885/EC of 17 November 2003

concerning the conclusion of the Agreement on the application of certain Community acts on the territory of the Principality of Monaco (O.J. 19.12.03 L 332/42). On the basis of this agreement and the special arrangements agreed between France and the Principality of Monaco in an agreement of 6 January 2003, the French authorities assume the role of competent authorities as far as the application of the medicinal products legislation to products manufactured in Monaco is concerned. The French authorities are responsible for the issue of marketing authorisations for Monaco and conduct inspections on manufacturing sites of medicinal products in Monaco. Batches from Monaco have to be considered as batches which have already undergone controls in a Member State and are therefore exempted from further controls and retesting. The batches may be regarded as released in France, though the place of sites is in Monaco.

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 (EC) No 726/2004 ("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 for the same medicinal product[5] in more than one Member State and the marketing authorisation holder has received a marketing authorisation in a Member State, the applicant/marketing authorisation holder shall submit an application in the Member States concerned using the procedure of mutual recognition. The Member States concerned should then recognise the marketing authorisation already granted by the reference Member State and authorise the marketing of the product on their national territory.

If no marketing authorisation has been granted in the Community, the applicant may make use of a decentralised procedure and submit an application in all the Member States where it intends to obtain a marketing authorisation at the same time, and choose one of them as reference Member State. Based on the assessment report prepared by the reference Member State and any comments made by the concerned Member State, marketing authorisation should be granted in accordance with the decision taken by the reference Member State and concerned Member State in this decentralised procedure.

The mutual recognition procedure and the decentralised procedure are detailed in Chapter 2 and the number of dossiers and languages required by Member States are detailed in Chapter 7. See also sections 3.2 and 5.4 of this chapter.

5 For an explanation of what constitutes the "same medicinal product" in this context, see section E.3 of Commission communication on the Community marketing authorisation procedures for medicinal products *(Official Journal C 229, 22/7/1998 p. 4 - 17).*

The marketing authorisation shall contain the summary of product characteristics according to Article 11 of Directive 2001/83/EC and the labelling and the package leaflet according to Articles 54, 55, 59 and 63.

2.2 Community authorisations

The Community will grant marketing authorisations for medicinal products:

- referred to in the Annex to Regulation (EC) No 726/2004, which may only be authorised via the centralised procedure (mandatory scope);
- referred to in Article 3(2) of Regulation (EC) No 726/2004, relating to products containing new active substances, products which constitute a significant therapeutic, scientific or technical innovation or products for which the granting of a Community authorisation would be in the interest of patients or animal health at Community level. The applicant has to request confirmation that the product is eligible for evaluation through the centralised procedure (optional scope) and the EMEA will decide on the matter; and
- a generic medicinal product of a centrally authorised medicinal product if not using the option in Article 3(3) of Regulation (EC) No 726/2004

Guideline on Therapeutic areas within the mandatory scope of the Centralised Procedure for the evaluation for Marketing Authorisation Applications with reference to Article 3 and Point 3 of Annex of Regulation (EC) No 726/2004 (EMEA/282954/2005)[6]

In order to obtain a Community authorisation, an application must be submitted to the EMEA. See also section 3.1 of this chapter.

The scientific evaluation of the application is carried out within the Committee for Medicinal Products for Human Use (CHMP) 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, 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.

The marketing authorisation shall contain the summary of product characteristics according to Article 11 of Directive 2001/83/EC and the labelling and the package leaflet according to Articles 54, 55, 59 and 63.

See also Chapter 4 for details of the centralised procedure and Chapter 7 for number of dossiers and languages required.

6 http://www.emea.eu.int/htms/general/direct/legislation/legislationhuman.htm

2.3 Notion of 'global marketing authorisation'[7]

Article 6(1) second subparagraph of Directive 2001/83/EC provides that when a medicinal product has been granted an initial marketing authorisation, any additional strengths, pharmaceutical forms, administration routes, presentations as well as any variations and extensions shall also be granted an authorisation or be included in the initial marketing authorisation. All these marketing authorisations shall be considered as belonging to the same global marketing authorisation, in particular for the purpose of the application of Article 10(1) of the directive, which relates to the procedure for the authorisation of generic products and lays down rules on data and market exclusivity and on the so-called European Reference Product.

Thus, the global marketing authorisation contains the initial authorisation and all variations and extensions thereof, as well as any additional strengths, pharmaceutical form, administration routes or presentations authorised through separate procedures and under a different name, granted to the marketing authorisation holder of the initial authorisation. Where a product is initially authorised nationally and, subsequently, an additional strength, pharmaceutical form, administration route or presentation is authorised through the centralised procedure, this shall also be part of the same global marketing authorisation.

The implications of the notion of global marketing authorisation for the purpose of the application of rules on data and market exclusivity are referred to in section 6 below.

Multiple applications of the same marketing authorisation holder are covered by the notion of 'global marketing authorisation'.

2.4 Validity of the marketing authorisation

2.4.1 Renewal

Marketing authorisations granted in the Community shall have an initial duration of five years (Articles 14(1) of Regulation (EC) No 726/2004 and 24(1) of Directive 2001/83/EC). After these five years, the marketing authorisation may be renewed on the basis of a re-evaluation of the risk-benefit balance. To this end, the marketing authorisation holder shall provide the EMEA or the national competent authority with a consolidated version of the file in respect of quality, safety and efficacy, including all variations introduced since the marketing authorisation was granted, at least six months before the marketing authorisation ceases to be valid (Articles 14(2) of Regulation (EC) No 726/2004 and 24(2) of Directive 2001/83/EC). Once renewed, the marketing authorisation shall be valid for an unlimited period unless the Commission or the national competent authority decides, on justified grounds relating to pharmacovigilance, to proceed with one additional five-year renewal (Articles 14(3) of Regulation (EC) No 726/2004 and 24(3) of Directive 2001/83/EC).

[7] Global Marketing Authorisation has to be read in the light of Article 6(1) of Directive 2001/83/EC; it does not mean a 'world wide Marketing Authorisation'.

Recommendations regarding the content of the consolidated file for the renewal are provided in the Guideline on the Processing of Renewals in the Centralised Procedure rev 3[8] and MRFG Guideline on the processing of renewals in the mutual recognition and decentralised procedure[9].

2.4.2 Cessation of the marketing authorisation if the medicinal product is not marketed

Principles for the marketing authorisation

According to Article 24(4) to (6) of Directive 2001/83/EC and Article 14(4) to (6) of Regulation (EC) No 726/2004 any authorisation which within three years of its granting is not followed by the actual placing on the market of the authorised product in the authorising Member State or on the Community market shall cease to be valid. When an authorised product previously placed on the market in the authorising Member State or in the Community is no longer actually present on the market for a period of three consecutive years, the authorisation for that product shall cease to be valid. The competent authority may, in exceptional circumstances and on public health grounds grant exemptions. Such exemptions must be duly justified.

The determination of the start of the three year period from the granting of the marketing authorisation should be the date when the medicinal product can be marketed by the marketing authorisation holder, taking into account, e.g. the market exclusivity and other protection rules which have to be respected.

The marketing authorisation will remain valid if at least one presentation of the marketing authorisation is placed on the market and if at least one pack-size of the existing pack-sizes for that presentation is marketed. For the purposes of the application of these rules, a marketing authorisation shall comprise the initial authorisation and all variations and extensions granted to the marketing authorisation holder under the same name.

For the purposes of the application of Article 24(4) to (6) of Directive 2001/83/EC and Article 14(4) to (6) of Regulation (EC) No 726/2004, a medicinal product is "placed on the market" at the date of release into the distribution chain. It is the date when the product comes out of the control of the marketing authorisation holder.

For centrally authorised medicinal products "placed on the Community market" means that the medicinal product is at least marketed in one Member State of the Community. For nationally authorised products "placed on the market in the authorising Member State" means that the medicinal product is on the market of the Member State which has granted the marketing authorisation. This is independent of the authorisation procedure used (decentralised, mutual recognition or purely national procedure).

8 http://www.emea.eu.int/htms/general/direct/legislation/legislationhuman.htm
9 http://heads.medagencies.org/

A medicinal product ceases to be placed on the market when the marketing authorisation holder ceases to release it in the distribution chain.

Information regarding the placing of a medicinal product on the market should be provided in accordance with Article 23a of Directive 2001/83/EC and Article 13(4) of Regulation (EC) No 726/2004. After a marketing authorisation has been granted, the holder of the authorisation shall inform the competent authority of the authorising Member State or the EMEA of the date of actual marketing of the medicinal product in that Member State or in the Community, taking into account the various presentations authorised. The holder shall also notify the national competent authority or the EMEA if the product ceases to be placed on the market, either temporarily or permanently. Such notification shall, otherwise than in exceptional circumstances, be made no less than 2 months before the interruption in the placing on the market of the product. Upon request by the national competent authority or the EMEA, particularly in the context of pharmacovigilance, the marketing authorisation holder shall provide the national competent authority or the EMEA with all data relating to the volume of sales of the medicinal product, and any data in his possession relating to the volume of prescriptions.

Transitional arrangements

Article 24(4) to (6) of Directive 2001/83/EC as amended by Directive 2004/27/EC shall apply to marketing authorisations already granted. However, the three year period which may lead to the marketing authorisation ceasing to be valid will be counted only from the date of application of the new provisions in each Member State.

The same applies for products authorised through the centralised procedure. Article 14(4) to (6) of Regulation (EC) No 726/2004 shall apply to marketing authorisations already granted. However, the three year period which may lead to the marketing authorisation ceasing to be valid will be counted only from the date of application of the new provisions, i.e. 20 November 2005.

2.5 Invented 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 shall contain the name of the medicinal product, which may be either a single invented name, or a common or scientific name (when available, the International Non-Proprietary Name of the active substance(s)) accompanied by a trade mark or the name of the marketing authorisation holder.

In the case of Community authorisations granted following applications through the centralised procedure, it is important that applicants identify at an early stage an invented name which would be valid throughout the Community when using the centralised procedure (see Chapter 4 section 3.1). However, in exceptional cases, the Commission may authorise the use of a different invented name in a Member State where the proposed invented name has been cancelled, opposed or objected to under trade-mark law (Article 6(1) of Regulation (EC) No 726/2004).

In cases where companies wish to market the same medicinal product under more than one invented name, then separate applications for separate authorisations must be submitted. The European Commission must be informed of this intention in advance and it shall authorise it when there are objective verifiable reasons relating to public health regarding the availability of medicinal products to health care professionals and/or patients, or for co-marketing reasons (Article 82(1) of Regulation (EC) No 726/2004; see also Chapter 4 section 3.1).

See also 'Guideline on the acceptability of invented name for human medicinal products processed through centralised procedure' available at www.emea.eu.int.

For applications through the mutual recognition and decentralised procedures, 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.

Where a generic of a medicinal product authorised through the centralised procedure is authorised by the competent authorities of the Member States, the generic medicinal product has to be authorised under the same name in all the Member States where the application has been made. For these purposes, all the linguistic versions of the international non-proprietary name shall be considered to be the same name (Article 3(3) of Regulation (EC) No 726/2004).

2.6 Transparency

In accordance with Article 21 of Directive 2001/83/EC, the national competent authorities are obliged to make publicly accessible the marketing authorisation together with the summary of the product characteristics, as well as the assessment report for each marketing authorisation granted, together with the reasons for their opinion, after deletion of any information of a commercially confidential nature. The justification shall be provided separately for each indication applied for.

As regards products authorised through the centralised procedure, notification of the marketing authorisation shall be published in the Official Journal of the European Union and the EMEA shall publish the assessment report of the CHMP together with the reasons for its opinion, after deletion of any information of a commercially confidential nature (Article 13 of Regulation (EC) No 726/2004).

3. MARKETING AUTHORISATION PROCEDURES

3.1 Centralised procedure

For medicinal products which fall within the mandatory scope of the centralised procedure in accordance with the Annex to Regulation (EC) No 726/2004, the application is submitted to the EMEA. An application shall likewise be submitted to the EMEA for medicinal products which fall within the optional scope of the centralised procedure in accordance with Article 3(2) and 3(3) of Regulation (EC) No 726/2004 where the applicant wishes to obtain a Community marketing authorisation.

Following the scientific evaluation and upon receipt of the opinion, the European Commission drafts a Decision on a Community marketing authorisation and, after consulting the Standing Committee for Medicinal Products for Human Use, grants a marketing authorisation.

3.1.1 Conditional marketing authorisation

[COMPLETED WHEN COMMISSION REGULATION ADOPTED]

3.1.2 Orphan medicinal products

Regulation (EC) No 141/2000 of 16 December 1999 on orphan medicinal products[10] entered into force on 22 January 2000 and applies from 27 April 2000, the date of adoption of its implementing regulation, Commission Regulation (EC) No 847/2000[11].

The aim of the legislation on orphan medicinal products is to stimulate research and development of medicinal products for rare diseases by providing incentives to sponsors in order to ensure access to treatment for patients suffering from rare diseases. Incentives include a 10-year period of market exclusivity once an orphan medicinal product is 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. In 2000, a new Committee within the EMEA, the Committee for Orphan Medicinal Products, and a designation procedure were established to clearly identify orphan medicinal products eligible for such incentives.

A medicinal product shall be designated as orphan where it can be established that:

(a) it is intended for the diagnosis, prevention or treatment of a life-threatening or chronically debilitating condition affecting not more than five in 10 thousand persons in the Community at the time when the application is made, or

    it is intended for the diagnosis, prevention or treatment of a life-threatening, seriously debilitating or serious and chronic condition in the Community and that without incentives it is unlikely that the marketing of the medicinal product in the Community would generate sufficient return to justify the necessary investment;

and

(b) there exists no satisfactory method of diagnosis, prevention or treatment of the condition in question that has been authorised in the Community or, if such method exists, that the medicinal product will be of significant benefit to those affected by that condition.

10 OJ L 18, 22.1.2000. p. 1.

11 OJ L 103, 28.4.2000, p. 5.

Once a product has been designated as orphan, the requirements for establishing the quality, safety and efficacy of a medicinal product prior to placing it on the market apply equally to orphan medicinal products as for medicinal products not designated as such. Regulation (EC) No 141/2000 provides direct access to the centralised procedure for marketing authorisations for medicinal products designated as orphans. With the adoption of Regulation (EC) No 726/2004, from 20 November 2005 all marketing authorisations for products designated as orphans will have to be granted in accordance with the centralised procedure.

Prior to the granting of a marketing authorisation, the Committee for Orphan Medicinal Products may review the designation as an orphan medicinal product to establish if the criteria for the designation are still met. In accordance with Article 5(12) of Regulation (EC) No 141/2000, a designated orphan medicinal product will be removed from the Community Register of Orphan Medicinal Products if it is established before the marketing authorisation is granted that the designation criteria are no longer met.

Once authorised, the period of market exclusivity commences from the date of the granting of the Community marketing authorisation[12]. 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 safer, more effective or otherwise clinically superior to the originator.

The definitions of a ‘similar medicinal product’ and ‘clinically superior’, in this context, are laid down in Article 3 of Commission Regulation (EC) No 847/2000.

Where an application for a marketing authorisation is applied for and an orphan designated medicinal product already has been authorised for the condition which covers the proposed therapeutic indication being applied for, and a period of market exclusivity is in force, the applicant must address in Module 1.7 of the application the possible ‘similarity’ with the authorised orphan medicinal product, and if applicable, justify that one of the derogations laid down in Article 8(3) of Regulation (EC) No 141/2000 applies.

3.2 Decentralised procedure and mutual recognition procedure

Evaluation of the operation of marketing authorisation procedures has revealed the need to revise the mutual recognition procedure in order to improve the opportunities for cooperation between Member States. Therefore, Directive 2004/27/EC has introduced the decentralised procedure and the coordination group, which is responsible to settle any disagreements arising from the decentralised and mutual recognition procedures.

12 Before application of Regulation (EC) No 726/2004, the period of market exclusivity would commence to run from the date of marketing authorisation pursuant to Regulation (EEC) No 2309/93 or from the date of marketing authorisation in all Member States in accordance with the procedures for mutual recognition.

Both the decentralised and the mutual recognition procedures are based on the recognition by national competent authorities of a first assessment performed by the authorities of one Member State. To allow operation of the system, applicants for marketing authorisation are obliged to include in their applications copies of any authorisation previously obtained in other Member States as well as a list of those Member States in which an application for authorisation is under examination (article 8(3)(l) of Directive 2001/83/EC). In addition, the dossier on which the marketing authorisation is based must be regularly updated (see section 5.1.1 below).

3.2.1 Decentralised procedure

For medicinal products not falling within the mandatory scope of the centralised procedure, the applicant may request one or more concerned Member State(s) to approve a draft assessment report, summary of product characteristics (SPC), labelling and package leaflet as proposed by the chosen reference Member State. An application is submitted to the competent authorities of the reference Member State and the concerned Member State(s), together with the information and particulars referred to in Articles 8, 10, 10a, 10b, 10c, and 11 of Directive 2001/83/EC. The applicant must give an assurance that the dossier, including the proposed SPC, labelling and package leaflet, is identical as submitted in all Member States concerned (reference Member State and concerned Member State). Differences in proposed prescription status and names of the medicinal product are acceptable, in line with national rules in force.

At the end of the decentralised procedure with a positive agreement, a national marketing authorisation will be issued in the reference Member State and the concerned Member State. The harmonisation is maintained through the procedures of Regulation (EC) No 1084/2003 for the examination of variations and the use of the decentralised and mutual recognition procedures for extensions.

Decentralised procedures may arise in the following instances:

i) in accordance with Articles 28(1) and 28(3) of Directive 2001/83/EC, which respectively provide that: "With a view to the granting of a marketing authorisation for a medicinal product in more than one Member State, an applicant shall submit an application based on an identical dossier in these Member States" and “In cases where the medicinal product has not received a marketing authorisation at the time of application, the applicant shall request the reference Member State to prepare a draft assessment report, a draft summary of the product characteristics and a draft of the labelling and package leaflet.”;

ii) in accordance with Article 17 of Directive 2001/83/EC, where a Member State notes that another marketing authorisation application for the same medicinal product being examined in another Member State, the Member State concerned shall decline to assess the application and shall advise the applicant that the decentralised procedure applies.

(iii) generic medicinal products of centrally authorised products, referred to in Article 3(3) of Regulation (EC) No 726/2004, may also be authorised in national, decentralised or mutual recognition procedures.

3.2.2 Mutual recognition procedure

This procedure is based on the mutual recognition by concerned Member State(s) 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 State(s). The harmonisation is maintained through the procedures of Regulation (EC) No 1084/2003 for the examination of variations and the use of the decentralised and mutual recognition procedures for extensions and renewals.

Mutual recognition procedures arise in the following instances:

i) in accordance with Article 28(1) and 28(2) of Directive 2001/83/EC, which respectively provide that: "With a view to the granting of a marketing authorisation for a medicinal product in more than one Member State, an applicant shall submit an application based on an identical dossier in these Member States" and “Where the medicinal product has already received a marketing authorisation at the time of application, the concerned Member States shall recognise the marketing authorisation granted by the reference Member State. To this end, the marketing authorisation holder shall request the reference Member State either to prepare an assessment report on the medicinal products or, if necessary update any existing assessment report”;

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, it shall reject the application unless it was submitted in compliance with Articles 27 to 39.";

iii) applications made in accordance with Directive 87/22/EEC[13], (i.e. ‘ex-concertation’ medicinal products) for which the Committee had issued an opinion before 1 January 1995. These products benefited from a Community procedure and therefore such products also gain automatic access to the mutual recognition procedure. Even if these medicinal products do not have a fully harmonised SPC, it is considered that an opinion including a SPC was given by the CPMP with a view to have harmonised product information.

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

13 OJ L 015, 17.1.1987, p. 38.

v) for medicinal products for which there has been a Community referral in accordance with Article 31 (Community interest) of Directive 2001/83/EC, and a complete harmonisation of the SPC (sections 4 and 5) has been achieved, the harmonisation achieved is maintained through the mutual recognition procedure.

vi) generic medicinal products of centrally authorised products, referred to in Article 3(3) of Regulation (EC) No 726/2004, may also be authorised in national, decentralised or mutual recognition procedures.

3.3 Procedure for homeopathic medicinal products

According to Article 13 of Directive 2001/83/EC, Member States have to ensure that homeopathic medicinal products placed on the market within the Community are registered according to Articles 14 and 15 or authorised according to Article 16 of that directive.

3.4 Procedure for traditional herbal medicinal products (traditional-use registration)

In order to overcome difficulties encountered by Member States in applying in the same way the pharmaceutical legislation to herbal medicinal products, specific provisions have been introduced in the Community code relating to medicinal products for human use for traditional herbal medicinal products. According to Articles 16a to 16i of Directive 2001/83/EC, introduced by Directive 2004/24/EC, a specific registration procedure is foreseen for herbal medicinal products fulfilling the criteria of a traditional herbal medicinal product.

This registration procedure is intended for herbal medicinal products with a long tradition, which do not fulfil the requirements for a marketing authorisation, in particular those requirements whereby an applicant can demonstrate by detailed references to published scientific literature that the constituent or the constituents of the medicinal products has or have a well-established medicinal use with recognised efficacy and an acceptable level of safety.

The simplified procedure allows the registration of herbal medicinal products without requiring particulars and documents on tests and trials on safety and efficacy, provided that there is sufficient evidence of the medicinal use of the product throughout a period of at least 30 years, including at least 15 years in the Community.

According to Article 16c(1)(c) of Directive 2001/83/EC bibliographical or expert evidence to the effect that the medicinal product in question, or a corresponding product has been in medicinal use throughout a period of at least 30 years preceding the date of the application, including at least 15 years within the Community. Medicinal use which has taken place on the territory of a new Member State is to be taken into account for the purpose of application of Article 16c(1)(c) even if it has partly or fully occurred before the accession of that State to the European Union.

Applications for registration of traditional herbal medicinal products have to fulfil the same requirements as applications for a marketing authorisation with regard to the manufacturing of these products and their quality.

The long tradition makes it possible to reduce the need for clinical data, in so far as the efficacy of the medicinal product is plausible on the basis of its long-standing use and experience as testified by bibliographic or expert evidence.

Claimed indications must be exclusively appropriate to traditional herbal medicinal products, which by virtue of their composition and purpose, are intended and designed for use without the supervision of a medical practitioner for diagnostic purposes or for prescription or monitoring of treatment.

Applicants must substantiate the safety of the medicinal product by the means of a bibliographic review of safety data together with an expert report, complemented by any necessary data, which the Member State's competent authority may request.

Results of pharmaceutical (physico-chemical, biological or microbiological) tests must be submitted to demonstrate the quality of the traditional herbal medicinal product.

The presence in herbal medicinal products of vitamins and minerals, the safety of which is well documented, does not prevent these products to be eligible for registration, provided that the action of the vitamins/minerals is ancillary to that of the herbal active ingredients regarding the specified claimed indications.

Having regard to the particularities of herbal medicinal products, a Committee for Herbal Medicinal Products (HMPC) has been established at the EMEA. The HMPC is responsible for various tasks concerning the simplified registration and authorisation of medicinal products as provided for in Directive 2004/24/EC and in Regulation (EC) No 726/2004, including involvement in referral procedures concerning such products.

With a view to further facilitating the registration of certain traditional herbal medicinal products in the EU, a list of herbal substances, preparations and combinations thereof for use in traditional herbal medicinal products is established on the basis of the scientific opinion of the HMPC. Applicants can refer to the list, however they would still need to demonstrate the quality of the medicinal products they seek to register.

Another major task of the HMPC is to establish Community herbal monographs for the application of both the traditional use and well-established use provisions and to serve as a basis for simplified registration or bibliographical marketing authorisation applications.

In order to promote harmonisation, Member States should recognise registrations of traditional herbal medicinal products granted by another Member State based on Community herbal monographs or consisting of substances, preparations or combinations thereof contained in the above-mentioned list. For other products, Member States should take due account of such registrations.

3.5 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.

In addition, as provided for in Article 30(2) of Directive 2001/83/EC, harmonisation of authorisations for medicinal products authorised in the Community is to be promoted via a coordinated approach for referring medicinal products, for which divergent decisions have been adopted, to the EMEA and the Committee for Medicinal Products for Human Use (see section 4).

Independent national procedures can also be used for extensions of authorised medicinal products as far as no a priori harmonisation has been achieved for the initial marketing authorisation (see section 5.4 of this chapter).

3.6 Procedures according to Article 126a of Directive 2001/83/EC

In order to increase availability of medicinal products, in particular on smaller markets, Article 126a of Directive 2001/83/EC provides that, in the absence of a marketing authorisation or of a pending application for authorisation for a medicinal product, which has already been authorised in another Member State, a Member State may for justified public health reasons authorise the placing on the market of that medicinal product. In such cases, the competent authority of the Member State has to inform the marketing authorisation holder in the Member States in which the medicinal product concerned is authorised, of the proposal to authorise the placing on the market under this Article.

When a Member State avails itself of this possibility, it shall adopt the necessary measures in order to ensure that the requirements for the labelling and package leaflet, classification of the medicinal product, advertising, pharmacovigilance and supervision and sanctions are complied with. For the specific mechanisms chosen by the Member States to implement this provision, we refer to the relevant national legislation implementing Directive 2004/27/EC.

The publicly available register of the medicinal products authorised to be placed on the market under Article 126a is available at the Commission web-site: http://pharmacos.eudra.org/.

4. COMMUNITY REFERRALS

In certain circumstances in the framework of marketing authorisations granted by the competent authorities of the Member States, a Community procedure, involving a scientific opinion by the CHMP leading to the adoption of a Commission decision addressed to the Member States, can be triggered. These are the commonly called Community “referrals”, which may be triggered in the following situations:

i) in accordance with Article 29 of Directive 2001/83/EC, where one or more Member States cannot recognise an authorisation already granted in a mutual recognition procedure or a final assessment and product information prepared in a decentralised procedure due to a potential serious risk to public health, the points of disagreement shall be referred to the coordination group. Where the Member States concerned by the procedure fail to reach an agreement within the coordination group, the matter is referred to the CHMP for application of the procedure laid down in Articles 32 to 34 of Directive 2001/83/EC. This referral is automatic in the sense that, once a Member State has raised a concern on the grounds of potential serious risk to public health within the meaning of Article 29(1), withdrawal of the marketing authorisation application in that Member State does not prevent the concern from being analysed within the coordination group and, in absence of an agreement therein, the EMEA. The expression 'potential serious risk to public health' is defined in guidance published by the Commission. [INSERT LINK TO GUIDELINES ONCE PUBLISHED]

ii) in accordance with Article 30(1) of Directive 2001/83/EC: "If two or more applications submitted in accordance with Article 8, 10, 10a, 10b 10c and 11 have been made for marketing authorisation for a particular medicinal product, and if Member States have adopted divergent decisions concerning the authorisation of the medicinal product or its suspension or revocation, a Member State, the Commission or applicant or the marketing authorisation holder may refer the matter to the Committee for Medicinal Products for Human Use, […], for the application of the procedure laid down in Articles 32, 33 and 34";

iii) in accordance with Article 30(2) of Directive 2001/83/EC: "In order to promote harmonisation of authorisations for medicinal products authorised in the Community, Member States shall, each year, forward to the coordination group a list of medicinal products for which a harmonised summary of product characteristics should be drawn up. The coordination group shall lay down a list taking into account the proposals from all Member States and shall forward this list to the Commission. The Commission or a Member State, in agreement with the Agency and taking into account the views of interested parties, may refer these products to the Committee […]".

iv) in accordance with Article 31 of Directive 2001/83/EC: (1) "The Member States or the Commission or the applicant or the marketing authorisation holder shall, 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 Articles 32, 33 and 34 before any decision is reached on a request for a marketing authorisation or on the suspension or revocation of an authorisation, or any other variation to the terms of a marketing authorisation which appears necessary, in particular to take account of the information collected in accordance with Title IX [Pharmacovigilance]. […]"; (2) "Where the referral to the CHMP concerns a range of medicinal products or a therapeutic class, the Agency may limit the procedure to certain specific parts of the authorisation." In that event, Article 35 shall apply to those

medicinal products only if they were covered by the authorisation procedures referred to in this chapter [decentralised and mutual recognition procedures]."

v) in accordance with Article 36(1) of Directive 2001/83/EC: "Where a Member State considers that the variation of a marketing authorisation which has been granted in accordance with the provisions of this Chapter [decentralised and mutual recognition procedures] or its suspension or withdrawal is necessary for the protection of public health, the Member State concerned shall forthwith refer the matter to the Agency for the application of the procedures laid down in Articles 32, 33 and 34".

According to Article 37 of Directive 2001/83/EC, Article 36 applies by analogy to 'ex-concertation' medicinal products, which therefore have to follow the mutual recognition procedure.

vi) Variations to marketing authorisations which have been granted through the ex-concertation procedure or the decentralised or mutual recognition procedures and to marketing authorisations which have been the subject of any referral as described above[14], follow the procedures set out in Regulation (EC) No 1084/2003:

- in accordance with Article 5(11) of Regulation (EC) No 1084/2003 (Type I B variations): "Within 10 days of the end of the procedure mentioned in paragraph 2 of this Article, the marketing authorisation holder or the competent authorities of the concerned Member States may refer the matter to the Agency for application of Article 35(2) of Directive 2001/83/EC."

- in accordance with Article 6(12) of Regulation (EC) No 1084/2003 (type II variations): "If within the period laid down in paragraph 9 of this Article, mutual recognition by one or more of the competent authorities of the draft decision of the competent authority of the reference Member State is not possible, the procedure referred to in Article 35(2) of Directive 2001/83/EC shall apply."

- in accordance with Article 6(13) of Regulation (EC) No 1084/2003 (type II variations): "If within 10 days of the end of the procedure mentioned in paragraph 8 of this Article, where one or more competent authorities of the Member states concerned are of the opinion that the variation cannot be accepted, the marketing authorisation holder may refer the matter to the Agency for application of Article 35(2) of Directive 2001/83/EC". See also chapter 3 of the Notice to applicants Volume 2A.

vii) in accordance with Article 16h(c) of Directive 2001/83/EC: "As regards referrals to the Agency under Chapter 4 of Title III, in relation to herbal medicinal products as referred to in Article 6a, to perform the tasks set out in Article 32 and Article 16h(d) of Directive 2001/83/EC: "Where other medicinal products containing herbal substances are referred to the Agency

14 With the exception of a partial harmonisation within the meaning of paragraph 49 of the judgement of the European Court of Justice in case C-39/03 P "Artegodan" (national marketing authorisations granted on a purely national basis outside mutual recognition subject to a harmonisation limited to the clinical particulars of the summary of product characteristics).

under Chapter 4 of Title III, to give an opinion on the herbal substance where appropriate."

5. 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 (EC) No 726/2004.

A brief description of these requirements and procedures is set out in this chapter for applications:

- according to Article 8(3) of Directive 2001/83/EC;
- according to Article 10 of Directive 2001/83/EC, relating to generic medicinal products and similar biological medicinal products;
- according to Article 10a of Directive 2001/83/EC, relating to applications relying on well established medicinal use supported by bibliographic literature;
- according to Article 10b of Directive 2001/83/EC, relating to applications for new fixed combination products;
- according to Article 10c of Directive 2001/83/EC, relating to informed consent from a marketing authorisation holder for an authorised medicinal product.

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

5.1 Basic requirements

5.1.1 Continuous update of marketing authorisation

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 ensure that scientific progress and new regulatory requirements are respected, in accordance with Article 23 of Directive 2001/83/EC, Annex I to Directive 2001/83/EC and Article 16 of Regulation (EC) No 726/2004. In particular, any information which may influence the evaluation of the benefits and the risks of the medicinal product shall be promptly supplied.

In addition, the marketing authorisation holder should inform the competent authorities relating to any pharmacovigilance concerns according to Article 104 of Directive 2001/83/EC.

After the withdrawal of a reference product, there is no longer an obligation on the originator company to update the dossier underlying the marketing authorisation of the reference medicinal product. It may be the case that the reference medicinal product is withdrawn after the application for a generic medicinal product is authorised or submitted. However, also for generic 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 reference dossier combined with periodic safety update reports of the marketing authorisation holder of the generic dossier still provide satisfactory information on the safety and efficacy of the product.

5.1.2 Standardised nomenclatures and quality standards

The European Directorate for the Quality of Medicines (EDQM) of the Council of Europe provides standardised nomenclatures and quality of standards for medicinal substances and products, which are published in the European Pharmacopoeia.

5.1.3 Standard Terms

The standard terms for pharmaceutical forms, routes of administration and containers are contained in the "List of Standard Terms for pharmaceutical dosage forms, routes of administration and containers" published by the European Directorate for the Quality of Medicines (EDQM) of the Council of Europe.

5.1.4 Evaluation of the potential environmental risk

In Article 8(3)(ca) of Directive 2001/83/EC the evaluation of the potential environmental risks posed by the medicinal product is required. All applicants/marketing authorisation holders should take into account the CHMP Note for Guidance 'On Environmental Risk Assessment of Medicinal Products for Human Use'.

5.2 Applications according to Article 8(3) of Directive 2001/83/EC

An application for marketing authorisation must be accompanied by the particulars and documents set out in Article 8(3) of Directive 2001/83/EC and therefore the following documentation shall be included in the dossier:

- pharmaceutical (physico-chemical, biological or microbiological) tests,
- preclinical (toxicological and pharmacological) tests,
- clinical trials.

For such applications, the relevant published literature also has to be submitted and these scientific publications can be used as supportive data.

Where Module 4 and/or 5 consists of a combination of reports of limited non-clinical and/or clinical studies carried out by the applicant and of bibliographical references this kind of application has also to be submitted according to Article 8(3) of Directive 2001/83/EC. See also Annex I to Directive 2001/83/EC, section on mixed marketing authorisation application.

5.3 Applications according to Article 10 of Directive 2001/83/EC

According to Article 10(1) of Directive 2001/83/EC, the applicant shall not be required to provide the results of pre-clinical and clinical trials if he can demonstrate the medicinal product is:

> A generic medicinal product or a similar biological medicinal product of a reference medicinal product which has been authorised under Article 6 of Directive 2001/83/EC for not less than 8 years. This type of application refers to information that is contained in the dossier of the authorisation of the reference product. This information is generally not completely available in the public domain. Authorisations for generic or similar biological medicinal products are therefore linked to the 'original' authorisation. This does not however mean that withdrawal of the authorisation for the reference product leads to the withdrawal of the authorisation for the generic product (case C-223/01, AstraZeneca, judgment of the European Court of Justice of 16 October 2003).
>
> The generic or similar biological medicinal product, once authorised, can however only be placed on the market 10 or 11 years after the authorisation of the reference medicinal product, depending on the exclusivity period applicable for the reference medicinal product.

It should be noted, however, that these periods of protection shall only apply to applications for reference products submitted once the provisions of Directive 2004/27/EC and Regulation (EC) No 726/2004 start to apply; see section 6 of this chapter on data and marketing exclusivity.

Information regarding the requirements and conditions on similar biological medicinal products is to be found on: http://www.emea.eu.int/pdfs/human/biosimilar/043704en.pdf

For applications for generic or similar biological medicinal products in the mutual recognition and decentralised procedures, the reference Member State should justify the choice of the legal basis according to Article 10. The concerned Member States should in the validation phase rely on the information given in the application form in Module 1 and the information provided by the reference Member State.. 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.

5.3.1 Reference medicinal product

A definition of reference medicinal product is given in Article 10(2)(a) of Directive 2001/83/EC, from which it follows that the reference product shall mean a medicinal

product authorised under Article 6, in accordance with the provisions of Article 8. Article 6 lays down the principle that no medicinal product may be placed on the market of a Member State unless a marketing authorization has been issued. In turn, Article 8 provides that in order to obtain a marketing authorization an application shall be made to the competent authority by an applicant established in the Community and containing the particulars and documents listed in that provision.

Besides, Article 6(1) contains the notion of global marketing authorisation as the initial marketing authorisation and any additional strengths, pharmaceutical forms, administration routes or presentations, as well as any variations and extensions. Each product within the global marketing authorisation may be chosen as the reference product.

Reference must be made to the dossier of a reference product for which a marketing authorisation has been granted in the Community on the basis of a complete dossier in accordance with Articles 8(3), 10a, 10b or 10c of Directive 2001/83.. The application form in Module 1 of the dossier for the generic product should clearly identifing the reference product. Generic applications referring to dossiers based on well-established use or to combination dossiers or informed consent dossiers are acceptable because all relevant information is in the dossier of the original medicinal product. On the contrary, the dossier for a generic application does not contain all relevant information concerning the medicinal product. Therefore, a generic application referring to a generic dossier is not possible.

Reference must be made to a product which is or has been authorised, i.e. a marketing authorisation has been granted for the reference product but it may have ceased to exist. Therefore an application for a generic medicinal product cannot be filed simultaneously with an application for a reference product.

The Act of Accession 2003[15] contains transitional arrangements for Cyprus, Lithuania, Malta, Poland and Slovenia; it allows marketing authorisations listed in Part Four of the Act of Accession and issued under national law prior to the date of accession to remain valid until they are renewed in compliance with the acquis, latest until the dates set in the Act of Accession. Because they have not been authorised in accordance with the acquis, these products, until their marketing authorisations are renewed in compliance with the acquis, cannot be used as reference products.

“European reference medicinal product”

According to Article 10(1) of Directive 2001/83/EC a generic application can also be submitted in a Member State where the reference medicinal product has never been authorised. In this case, the applicant has to identify in the application form the name of the Member State in which the reference medicinal product is or has been authorised. It is also a prerequisite that the period of data exclusivity has expired in the Member State of the reference medicinal product (see section 6).

15 The Treaty of Accession 2003 of the Czech Republic, Estonia, Cyprus, Latvia, Lithuania, Hungary, Malta, Poland, Slovenia and Slovakia, signed in Athens on 16 April, 2003. http://europa.eu.int/comm/enlargement/negotiations/treaty_of_accession_2003/

At the request of the competent authority of the Member State in which the application is submitted, the competent authority of the other Member State shall transmit, within a period of one month, a confirmation that the reference medicinal product is or has been authorised together with the full composition of the reference product and if necessary other relevant documentation.

The documentation requested must be relevant for the assessment of the generic medicinal product submitted. [REFERENCECE TO EMEA-CMD COMMON GUIDANCE ONCE AVAILABLE]

5.3.2 Generic medicinal product

Directive 2001/83/EC defines a generic medicinal product in Article 10(2)(b) as a medicinal product which has:

- the same qualitative and quantitative composition in active substances as the reference product,
- the same pharmaceutical form as the reference medicinal product,
- and whose bioequivalence with the reference medicinal product has been demonstrated by appropriate bioavailability studies.

The different salts, esters, ethers, isomers, mixtures of isomers, complexes or derivatives of an active substance shall be considered to be the same active substance, unless they differ significantly in properties with regard to safety and/or efficacy. In such cases, additional information providing proof of the safety and/or efficacy of the various salts, esters, ethers, isomers or mixtures thereof or derivatives of an authorised active substance must be supplied by the applicant. The various immediate-release oral pharmaceutical forms shall be considered to be one and the same pharmaceutical form. Bioavailability studies need not be required of the applicant if he can demonstrate that the generic medicinal product meets the relevant criteria as defined in the detailed guideline 'The Investigation of Bioavailability and Bioequivalence' [16] (see also annex IV of this chapter).

If additional information concerning changes to the nature of the active substance cannot establish the absence of a significant difference with regard to safety or efficacy then it may be necessary to submit the results of pre-clinical tests and clinical trials in accordance with the requirements of Article 10(3) (see section 5.3.5) or for the active substance to be designated as a new active substance as defined in Annex III at the end of this Chapter.

The competent authorities will determine the validity of such applications on a case by case basis and will rely upon the summary evidence provided in Modules 1 and 2 of the application dossier and, if available, on the assessment report of another competent authority.

16 http://www.emea.eu.int/pdfs/human/ewp/140198en.pdf

'Same qualitative and quantitative composition'

This requirement that the generic and reference products have the same qualitative and quantitative composition extends only to the active substance(s) and not to the other ingredients of the product. However, differences in excipient composition or differences in impurities must not lead to significant differences as regards safety and efficacy. The competent authorities will evaluate these differences in the light of all scientific knowledge at their disposal. See also ruling of the European Court of Justice in case C-74/03, Smithkline Beecham, judgment of 20 January 2005.

The decision whether a different form of the active substance is to be regarded as a new active substance should be taken by the competent authorities on a case-by-case basis.

'Same pharmaceutical form'

This criterion relating to the same pharmaceutical form contained in the definition of generic medicinal product is evaluated with reference to the standard terms for pharmaceutical dosage forms established by the European Pharmacopoeia. A generic product and a reference product may be considered to have the same pharmaceutical form if they have the same form of administration as defined by the Pharmacopoeia. Furthermore, Article 10(2)(b) of the amended Directive provides that the various immediate release oral forms, which would include tablets, capsules, oral solutions and suspensions, shall be considered the same pharmaceutical form for the purposes of Article 10.

According to the European Court of Justice, in determining the pharmaceutical form of a medicinal product, account must be taken of the form in which it is presented and the form in which it is administered, including the physical form. In that context, medicinal products which are presented in the form of a solution to be mixed in a drink for administration to the patient, are to be treated as having the same pharmaceutical form, provided that the differences in the form of administration are not significant in scientific terms. (See Case C-106/01, Novartis, judgment of 29 April 2004).

'Bioequivalence'

The definition and demonstration of bioequivalence should be made in accordance with the published guidance, 'The Investigation of Bioavailability and Bioequivalence'. Exemptions from the need to demonstrate bioequivalence (i.e. where bioequivalence may be presumed) are included in guidelines but should be addressed in the dossier and in the Overall Summaries and Overviews.

Where bioequivalence cannot be demonstrated through bioavailability studies, for example for locally applied and locally acting drugs, Article 10(3) requires that the results of appropriate pre-clinical tests or clinical trials shall be provided and this Article provides the correct legal basis for the application.

The need for appropriate bioavailability studies should be addressed in the dossier and in the overall summaries and overviews. The Guideline on Bioavailability and Bioequivalence is available at http://www.emea.eu.int/pdfs/human/ewp/140198en.pdf

5.3.3 Application according to Article 10(3) of Directive 2001/83/EC

Article 10(3) requires that, in certain circumstances in the framework of an application under Article 10, the results of the appropriate pre-clinical tests or clinical trials shall be provided. These applications will thus rely in part on the results of pre-clinical tests and clinical trials for a reference product and in part on new data.

In such cases the results of tests and trials supplied must be consistent with the data content standards required in the Annex to the Directive 2001/83/EC as amended by Directive 2003/63/EC. Summary data or bibliographic data would not usually suffice.

Article 10(3) considers three circumstances where such additional data will be necessary:

- where the strict definition of a 'generic medicinal product' is not met;
- where bioavailability studies cannot be used to demonstrate bioequivalence (for example where the new product is supra-bioavailable);
- where there are changes in the active substance(s), therapeutic indications, strength, pharmaceutical form or route of administration of the generic product compared to the reference product.

Some guidance on the appropriate additional studies required is indicated in the table given in Annex IV at the end of this Chapter.

5.3.4 Similar biological medicinal product

In Article 10(4) of Directive 2001/83/EC, it is stated that where a biological medicinal product which is similar to a reference biological product, does not meet the conditions in the definition of generic medicinal products, owing to, in particular, differences relating to raw materials or differences in manufacturing processes of the similar biological medicinal product and the reference biological medicinal product, the results of appropriate pre-clinical tests or clinical trials relating to these conditions must be provided. The type and quantity of supplementary data to be provided must comply with the relevant criteria stated in Annex I of Directive 2001/83/EC and the related detailed guidelines. The results of other tests and trials from the reference medicinal product's dossier shall not be provided. Guidance is available at the website of the EMEA http://www.emea.eu.int.

5.4 Applications according to Article 10a of Directive 2001/83/EC

According to Article 10a of Directive 2001/83/EC it is possible to replace results of the pre-clinical and clinical trials by detailed references to published scientific literature (information available in the public domain) if it can be demonstrated that the active substances of a medicinal product have been in well established medicinal use within the Community for at least ten years, with recognised efficacy and an acceptable level of safety. In this regard, the provisions of Annex I of Directive 2001/83/EC shall apply.

Well-established medicinal use

Annex I of Directive 2001/83/EC lays down specific rules for the demonstration of a well established medicinal use, with recognised efficacy and an acceptable level of safety.

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, 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 Community.

Evidence must be supplied to demonstrate that a constituent has been extensively used for the 10-year period, although "medicinal use" does not exclusively mean "use as an authorised medicinal product", so that proof of medicinal use may be submitted even in the absence of a marketing authorisation. 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.

Well-established use refers to the use for a specific therapeutic use. If well-known substances are used for entirely new therapeutic indications, it is not possible to solely refer to a well established use and additional data on the new therapeutic indication together with appropriate pre-clinical and human safety data should be provided. In such a case, Article 8(3) of Directive 2001/83/EC should be used as legal basis for the marketing authorisation application.

Extensive medicinal use (well-established use) which has taken place on the territory of a new Member State is to be taken into account for the purpose of application of Article 10a even if it has partly or fully occurred before the accession of that State.

Documentation

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.

The documentation and the Overall summaries and Overall overview/summaries 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. If parts of the dossier are incomplete, particular attention must be paid to explain in the Overall overview/summaries why.

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.

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

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.

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

5.5 Application according to Article 10b of Directive 2001/83/EEC

In accordance with Article 10b of Directive 2001/83/EC: "In the case of medicinal products containing active substances used in the composition of authorised medicinal products but not hitherto used in combination for therapeutic purposes, the results of new pre-clinical tests or new clinical trials relating to that combination shall be provided in accordance with Article 8(3)(i), but it shall not be necessary to provide scientific references relating to each individual active substance".

The combination of active substances within a single pharmaceutical form of administration according to this provision is a so-called 'fixed combination'.

Strictly speaking, any combination is a new and unique medicinal product requiring a separate marketing authorisation and SPC. Therefore a new 'combination' medicinal product will have an independent period of data exclusivity and market protection from its first authorisation within the Community. Consequently generic/informed consent applications referring to "combination" dossiers are acceptable

An authorisation for a 'combination' medicinal product is not considered to fall within the scope of the global marketing authorisations for the individual active substances as described in Article 6(1) of Directive 2001/83/EC.

Applications for fixed-combination medicinal products can be accepted and validated under Article 10b on condition that the individual substances have been authorised in the EEA via a Community or national procedure.

It follows from the wording of Article 10b as well as from Part II.5 of Annex I to the directive that a full dossier comprising all the information of modules 1 to 5 has to be provided in relation to the fixed-combination. As with any application for a new medicinal product such a full dossier can be either a dossier based solely on own tests and trials performed by the applicant or on a mixed dossier. Any absence of specific fixed-combination data should be duly justified by the applicant with reference to scientific and regulatory considerations.

Article 10b does not contain a requirement for the inclusion of data on the individual active substances. It is nevertheless possible to include information on the individual substances in the application for a fixed-combination. This will typically occur where the applicant tries to justify the absence of certain specific data on the combination by reference to the information available on the individual substances. Such information could consist of literature or actual data which would either be provided by the applicant himself or would be referred to by means of a letter of access from the marketing authorisation holders of the product(s) containing the individual substance(s). In absence of such a letter of access, reference can only be made to data held in the dossier of another medicinal product upon expiry of the relevant data exclusivity period. This will require the applicant to name the "reference" individual product(s) and provide detailed information on its authorisation status.

It will be up to the scientific assessment to review the data and the justifications submitted, identifying any missing information which would prevent the approval of the fixed-combination.

5.6 Applications according to Article 10c of Directive 2001/83 /EC

A derogation from the requirements to submit all of the information required in Article 8(3)(i) is provided by Article 10c of Directive 2001/83/EC for so-called ‘informed consent’ marketing authorisation applications. Despite the fact that the provision contains some criteria that are common to the definition of a generic medicinal product in Article 10, Article 10c does not concern generic medicinal products.

According to Article 10c: “Following the granting of a marketing authorisation, the authorisation holder may allow use to be made of the pharmaceutical, preclinical and clinical documentation contained in the file on the medicinal product, with a view to examining subsequent applications relating to other medicinal products possessing the same qualitative and quantitative composition in terms of active substances and the same pharmaceutical form.”

It is a prerequisite for the use of article 10c that consent has been obtained for all three modules containing the pharmaceutical, preclinical and clinical data. It is not possible to use Article 10c a legal basis for an application consisting of the applicant’s own module 3 and for which consent has been given for modules 4 and 5. In such cases the legal basis for the application is Article 8(3).

The applicant must show proof that the marketing authorisation holder of the reference product has consented that the dossier of that product is used for the purpose of examining the application in question. 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.

The 'informed consent' product applicant must have permanent access to the documentation or be in possession of this information in order to fully carry out his responsibilities. For the information contained in the Active Substance Master File a new letter of access in connection with the informed consent application should be included, without prejudice to the restrictions on access to the Manufacturer Restricted Part of the Active Substance Master File.

For competent authorities, demonstration of the 'informed consent' is a formal condition which must be fulfilled, when the informed consent application is submitted. An authenticated letter from the party granting consent is required and must specify the name of the benefiting party and the products concerned. The withdrawal of the informed consent at a later stage has no direct consequences on the existence/validity of the marketing authorisation.

6. DATA EXCLUSIVITY AND MARKET EXCLUSIVITY

6.1 Data exclusivity and market exclusivity period for reference medicinal products

6.1.1 Data and market exclusivity for applications submitted after the implementation of the amended legislation

Directive 2004/27/EC, amending Directive 2001/83/EC, and Regulation (EC) No 726/2004 have introduced new rules concerning the periods, from the initial marketing authorisation of the reference product, during which generic product applicants cannot rely on the dossier of the reference product for the purposes of submitting an application, obtaining marketing authorisation or placing the product on the market.

For products authorised by the national competent authorities, according to the first subparagraph of Article 10(1) of Directive 2001/83/EC as amended by Directive 2004/27/EC, the applicant shall not be required to provide the results of pre-clinical tests and of clinical trials if he can demonstrate that the medicinal product is a generic of a reference medicinal product which is or has been authorised under Article 6 for not less than eight years in a Member State or in the Community.

According to the second subparagraph of Article 10(1), generic products authorised in this way shall not be placed on the market until ten years have elapsed from the initial authorisation of the reference product. (This ten year period may be extended to eleven if the conditions of the fourth subparagraph of Article 10(1) are fulfilled, see section 6.2 below).

The period of eight years from initial authorisation of the reference product provides a period of so-called “data exclusivity”, after which valid applications for generic products can be submitted and lead to the granting of a marketing authorisation. The period of ten years from initial authorisation of the reference product provides a period of so-called “market exclusivity” after which generic products authorised in this way can be placed on the market.

The same periods of protection apply in the case of centrally authorised products pursuant to Article 14(11) of Regulation (EC) No 726/2004.

6.1.2 Data and market exclusivity for applications submitted before the implementation of the amended legislation

According to Article 89 of Regulation (EC) No 726/2004, the new periods of protection do not apply to those reference medicinal products for which the initial application for authorisation was submitted before 20 November 2005.

Equally, Directive 2004/27/EC makes it clear in Article 2 that the new periods of protection do not apply to those reference medicinal products for which an application for authorisation has been submitted before the date of transposition referred to in Article 3 of the same legal text (i.e. 30 October 2005).

Products for which the initial submission was made prior to the dates referred above continue to benefit from the previous periods of protection which are:

- 10 years for national authorisations granted by the following Member States: Belgium, Germany, France, Italy, the Netherlands, Sweden, United Kingdom, Luxemburg;

- 6 years for national authorisations granted by the following Member States: Austria, Denmark, Finland, Ireland, Portugal, Spain, Greece, Poland, Czech Republic, Hungary, Lithuania, Latvia, Slovenia, Slovakia, Malta, Estonia, Cyprus and also Norway, Liechtenstein and Iceland;

- 10 years for all medicinal products authorised through the centralised procedure;

- 10 years for all medicinal products authorised following an opinion of the CPMP in accordance with Article 4 of Directive 87/22/EEC (ex-concertation procedure).

For the purposes of the application of the mentioned provisions, the date of submission of an application, and not the date of validation by the competent authority, determines the periods of protection applicable.

Evidence of the date of authorisation of the reference product should be provided where possible in the application for the generic marketing authorisation.

In mutual recognition or decentralised procedures if the protection period in a concerned Member State is longer than in the reference Member State, mutual

recognition in the concerned Member State is not possible before the expiry of the longer period.

6.1.3 Relevant periods of protection in the case of the "European Reference medicinal product"

As stated above (section 5), Article 10(1) of Directive 2001/83/EC allows a generic application to be submitted only if the reference product has been authorised for a given period of time. In addition, a generic application is possible under that provision even "if the reference medicinal product was not authorised in the Member State in which application for the generic product is submitted". In that case, a reference product authorised in another Member State must be identified. It should be noted that the use of this provision will only be possible if the reference product is out of data protection in the Member State where it is authorised.

6.1.4. Protection periods and global marketing authorisation

For the notion of global marketing authorisation, see section 2.3. The global marketing authorisation contains the initial authorisation and all variations and extensions thereof, as well as any additional strengths, pharmaceutical form, administration routes or presentations authorised through separate procedures and under a different name, granted to the marketing authorisation holder of the initial authorisation.

In accordance with Article 6(1) of Directive 2001/83/EC, all these presentations of a given product shall be considered as part of the same marketing authorisation for the purposes of applying the rules on data and marketing protection.

This means that for a reference medicinal product, the start of the data and market exclusivity periods is the date when the first marketing authorisation was granted in the Community. New additional strengths, pharmaceutical form, administration routes, presentations as well as any variation and extensions do not restart or prolong this period. All additional strengths, pharmaceutical form, administration routes, presentations as well as any variation and extensions have the same end point of the data and market exclusivity periods, namely 8 and 10 years after the first marketing authorisation was granted, respectively. This will apply even if the new presentation has been authorised to the same marketing authorisation holder through a separate procedure and under a different name[17].

This ten-year period can only be prolonged in the case of certain new indications, as described in the following subsection.

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17 Even before the adoption of Directive 2004/27/EC and the introduction of the notion of "global marketing authorisation", the European Court of Justice had interpreted the data protection provisions of Directive 2001/83/EC as not affording a new period of protection to the development of an original product even where the development was authorised through a separate procedure and under a different name. See Case C-106/01, Novartis, judgment of 29 April 2004, where a new presentation had been authorised to the same marketing authorisation holder through a separate procedure (informed consent procedure, in combination with the provision of bridging data under Article 10(1)(a) last subparagraph of Directive 2001/83/EC before its amendment by Directive 2004/27/EC) and under a different name.

6.2 Extension of the ten year period in Article 10(1) in the case of new therapeutic indications

In accordance with the fourth subparagraph of Article 10(1) of Directive 2001/83/EC, the ten year period of marketing protection may be extended by one year in the event of authorisation of new therapeutic indications representing a significant clinical benefit in comparison with existing therapies. The additional year of marketing protection applies to the global marketing authorisation for the reference medicinal product. Generic products, with or without the new therapeutic indication, may not be placed on the market until expiry of the eleventh year.

To benefit from the additional year, the new indication must be approved during the first eight years since the initial marketing authorisation. The overall period of protection cannot exceed eleven years. Therefore, this provision can be used only once per 'global marketing authorisation' within the meaning of Article 6(1) of Directive 2001/83/EC.

Every application for a new indication must be assessed by the competent authority to determine whether the new therapeutic indication brings a significant clinical benefit in comparison with existing therapies. In the case of products authorised in accordance with Regulation (EC) No 726/2004, Commission decisions authorising new therapeutic indications will contain a clear statement of whether the new indication represents a significant clinical benefit in comparison with existing therapies. In the case of medicinal products authorised through the decentralised or mutual recognition procedures, the assessment report by the reference Member State will contain a clear statement of whether the new indication represents a significant clinical benefit in comparison with existing therapies.

This year of protection (+1) adding to the periods referred to in the previous section (8+2) shall apply only to those reference medicinal products for which the initial application for authorisation is submitted after the new rules of Directive 2004/27/EC, amending Directive 2001/83/EC, and of Regulation (EC) No 726/2004 start to apply.

[INSERT CROSS REFERENCE TO GUIDELINE ON THE NOTIONS OF "NEW INDICATION" AND "SIGNIFICANT CLINICAL BENEFIT BY COMPARISON TO EXISTING THERAPIES" ONCE PUBLISHED]

6.3. One year period of protection for new indications of well-established substances

Article 10(5) of Directive 2001/83/EC reads: "In addition to the provisions laid down in paragraph 1, where an application is made for a new indication for a well-established substance, a non-cumulative period of one year of data exclusivity shall be granted, provided that significant pre-clinical or clinical studies were carried out in relation to the new indication."

The data exclusivity period is non-cumulative to other periods of protection: it refers exclusively to the data concerning the new indications.

Every application for a new indication must be assessed by the competent authority to determine whether the new indication for a well established substance is based on significant pre-clinical or clinical studies. In the case of products authorised in accordance with Regulation (EC) No 726/2004, Commission decisions authorising new therapeutic indications for well established substances will contain a clear statement of whether the new indication is based on significant preclinical or clinical studies. In the case of medicinal products authorised through the decentralised or mutual recognition procedures, the assessment report by the reference Member State will contain a clear statement of whether the new indication is based on significant preclinical or clinical studies.

A new indication submitted after the new rules of Directive 2004/27/EC, amending Directive 2001/83/EC, and of Regulation (EC) No 726/2004 start to apply may benefit from the year of protection referred to in this section.

A well established substance is an active substance included in the relevant medicinal product which can be shown to have a well-established use in accordance with the requirements of indent (a) in section 1 ("Well established medicinal use") of Part II of the Annex to Directive 20001/83/EC as amended by Directive 2003/63/EC. This does not however mean that the medicinal product concerned must have been authorised under the legal basis of the well established use procedure.

[INSERT CROSS REFERENCE TO GUIDELINE ON THE NOTIONS OF "NEW INDICATION" AND "SIGNIFICANT TESTS AND TRIALS" ONCE PUBLISHED]

6.4. One year period of protection for data supporting a change of classification

Article 74a of Directive 2001/83/EC reads: "Where a change of classification of a medicinal product has been authorised on the basis of significant pre-clinical tests or clinical trials, the competent authority shall not refer to the results of those tests or trials when examining an application by another applicant for or holder of marketing authorisation for a change of classification of the same substance for one year after the initial change was authorised."

The 1-year period of protection covers significant pre-clinical or clinical trials carried out for the purpose of substantiating an application for a change of classification. The interpretation by competent authorities of the notion of significant pre-clinical tests or clinical trials under Article 74a will be without prejudice to the interpretation of that phrase under Article 10(5).

When adopting a decision authorising a change of classification of a medicinal product, the competent authority must assess whether the change is based on significant preclinical tests or clinical trials. In the case of products authorised in accordance with Regulation (EC) No 726/2004, Commission decisions authorising a change of classification will contain a clear statement of whether the change is based on significant preclinical tests or clinical trials. In the case of medicinal products authorised by the Member States, the decision of each competent authority authorising the change will contain a clear statement of whether the change is based on significant preclinical tests or clinical trials.

A change of classification authorised after the new rules of Directive 2004/27/EC, amending Directive 2001/83/EC, and of Regulation (EC) No 726/2004 start to apply may benefit from the year of protection referred to in this section.

[INSERT REFERENCE TO GUIDELINE ONCE AVAILABLE]

7. VARIATIONS AND EXTENSIONS

Throughout the life of a medicinal product, the marketing authorisation holder is responsible for the product which is placed on the market 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 or more substantial changes, and procedures for the approval of such amendments have been set out in Regulations (EC) No 1084/2003 (which replaced Regulation (EC) No 541/95) and No 1085/2003 (which replaced Regulation (EC) No 542/95), subsequently referred to as the variation regulations and in national legislation. Regulation (EC) No 1085/2003 applies to Community marketing authorisations and Regulation (EC) No 1084/2003 applies to national authorisations arising from mutual recognition, decentralised or ex-concertation procedures and to national authorisations whose summary of product characteristics (sections 4 and 5) have been completely harmonised through a Community referral procedure.

In the 2003 variation regulations, new categories of variations, namely notifications type IA and type IB, have been introduced. Furthermore, clarification has been provided to draw a clear line between the terms variations to and extension of a marketing authorisation and the conditions of submission or parallel/consequential notifications/variations. Finally, the existing provisions governing urgent safety restrictions and the follow up of such measures have been modified to provide more information on the scope of variations and extensions to marketing authorisations and to the procedures to be followed.

For medicinal products that have been authorised nationally but not via mutual recognition, decentralised or ex-concertation procedures, and which have not been the subject of a Community referral leading to a full harmonisation of the SPC (sections 4 and 5), procedures for changes/variations are set out in national legislation. Such procedures are not necessarily the same as those set out in Community legislation.

7.1 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/acceptance of any previous variation, except where an extension application must be presented pursuant to Annex II of the Regulations (EC) No 1084/2003 or (EC) No 1085/2003.

Minor variation

Type IA and Type IB: variations listed in Annex I of the Variation Regulations, which concern an amendment to the contents of the documentation of the dossier, and fulfil the conditions set out in that same Annex. These variations are introduced through a notification procedure.

Major variation

Type II: any change to the marketing authorisation, which is not a Type IA or Type IB notification and which is not regarded as an extension to the marketing authorisation is considered as a Type II variation. These variations are introduced through an approval procedure.

Variations to introduce a different therapeutic use or posology shall be supported by clinical data and pre-clinical data if justified.

7.2 Extensions: applications in accordance with Annex II of Regulations (EC) No 1084/2003 and No 1085/2003

Changes to a marketing authorisation listed in Annex II of Regulations (EC) No 1084/2003 and No 1085/2003 are regarded as "extensions" of the marketing authorisation. Further guidance on whether a change leads to an extension or variation can be found in the EC guideline 'Categorisation of extensions versus variations applications' available at http://pharmacos.eudra.org/F2/eudralex/vol-2/home.htm.

Extensions fall outside the definition of a variation to a marketing authorisation and applications for extensions are examined by the national competent authority or the Community in accordance with the procedure for granting a new marketing authorisation.

Even if they are authorised in accordance with the procedure for granting a new marketing authorisation, according to Article 6(1) of Directive 2001/83/EC, 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. This means that for an original medicinal product, the start of the data exclusivity period is the date when the first marketing authorisation was granted in the Community. Extensions do not restart or prolong this period; they will have the same end point of the data exclusivity period. 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.

It should be noted, however, that the Community pharmaceutical legislation does not prevent a marketing authorisation holder from submitting any of the changes listed in Annex II to the variation regulations as a separate full application for marketing authorisation, with a different name and different summary of product characteristics. This type of application is an independent application and not an extension. Nevertheless it will be regarded as belonging to the same global marketing authorisation for the purposes of data and market exclusivity.

The provisions of the mutual recognition or the decentralised procedure can be applied to extensions to national marketing authorisations (which were initially harmonised,) 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.

If the applicant chooses to submit a completely new independent dossier without any cross-references to the dossier supporting the existing national authorisations, such prerequisite harmonisation is not needed.

In the case where a marketing authorisation initially was granted for the same medicinal product through purely national authorisation procedures in different Member States and the applicant does not harmonise these marketing authorisations or submit a new independent dossier, only a national procedure remains applicable.

7.3 Changes to the labelling and package leaflet

Where a variation (type I or II) requires consequential change to the summary of product characteristics, labelling or package leaflet, this will be considered as part of the variation and the corresponding updated documents should be provided in the variation application.

However, changes to the labelling or the package leaflet not connected with the summary of product characteristics are examined in accordance with Article 61(3) of Directive 2001/83/EC and are outside the scope of the Variation Regulations. The proposed changes are submitted to the authority competent for marketing authorisation. If the competent authority has not opposed a proposed change within 90 days following the introduction of the request, the applicant may put the change into effect.

In the frame of a mutual recognition or decentralised procedures, the marketing authorisation holder should inform the reference Member State of the changes required at national level in order to maintain harmonisation of labelling and package leaflet. [REFERENCE TO CMD GUIDELINE WHEN AVAILABLE]

7.4 Urgent safety restrictions

The Variation Regulations also include provisions for the marketing authorisation holder or the competent authority to take provisional urgent safety restrictions in the event of a risk to public health.

Urgent safety restriction means an interim change to the product information concerning particularly one or more of the following items in the summary of product characteristics, the indications, posology, contraindications and warnings due to new information having a bearing on the safe use of the medicinal product.

Where the marketing authorisation holder takes such provisional urgent safety restriction, he shall forthwith inform the appropriate national competent authority or the EMEA (in the case of authorisations granted by the member States or the Community, respectively). If the national competent authority/EMEA has not raised any objections within 24 hours of the receipt of that information, the urgent safety restriction is deemed accepted. The urgent safety restrictions shall be implemented within a time frame, as agreed with the national competent authority/EMEA. The corresponding application in accordance with the procedure for a Type II variation reflecting the urgent safety restriction shall be submitted immediately to the national competent authority/EMEA and in any case no later than 15 days after the initiation of the urgent safety restriction.

Where the national competent authority/Commission imposes provisional urgent safety restriction, the marketing authorisation holder shall be obliged to implement the urgent safety restrictions within a time frame, as agreed with the national competent authority/EMEA. The corresponding application in accordance with the procedure for a Type II variation, reflecting the urgent safety restriction, shall be submitted immediately to the national competent authority/EMEA and in any case not later than 15 days after the initiation of the urgent safety restriction.

In all cases the appropriate documentation in support of the change shall be included in the application.

8. PLASMA MASTER FILE PROCEDURE AND VACCINE ANTIGEN MASTER FILE PROCEDURE

The use of the Plasma Master File (PMF) and Vaccine Antigen Master File (VAMF) certification systems is optional.

The PMF is a stand-alone documentation, which is separate from the dossier for marketing authorisation. It provides all relevant detailed information on the characteristics of the entire human plasma used as a starting material and/or a raw material for the manufacture of sub/intermediate fractions, constituents of the excipient and active substance(s), which are part of medicinal products or medical devices incorporating stable derivatives of human blood or human plasma.[18].

The VAMF is a stand-alone part of the marketing authorisation application dossier for a vaccine. One given VAMF contains all relevant information of biological, pharmaceutical and chemical nature for one given vaccine antigen, which is common to several vaccines from the same applicant or marketing authorisation holder.

The PMF/VAMF certification procedure is aimed at simplifying the tasks of both applicants and competent authorities by:

- Reducing the number of dossier submissions and data evaluations carried out for the same plasma or vaccine antigen.

[18] Referred to in Directive 2000/70/EC of the European Parliament and of the Council of 16 November 2000 amending Council Directive 93/42/EC as regards medical devices incorporating stable derivatives of human blood or human plasma (OJ L 313, 13.12.2000, p. 22).

- Harmonising the data for a given plasma/antigen present in several medicinal products.

- Ensuring consistency throughout the European Community.

The certification procedure consists of a centralised assessment of the PMF/VAMF application dossier submitted by the applicant or marketing authorisation holder, which results in a certificate of compliance to Community legislation, issued by the EMEA. This certificate is valid throughout the European Community.

As a second step, the competent authority that will grant or has granted the marketing authorisation for the concerned medicinal product(s) (plasma-derived medicinal products for PMFs, vaccines for VAMFs) takes into account the certification, re-certification or variation of the PMF/VAMF on the concerned medicinal product(s).

Further guidance on the procedural and scientific aspects related to the PMF/VAMF certification procedure is available at the EMEA website[19].

[19] http://www.emea.eu.int. See in particular documents EMEA/CPMP/4548/03 (VAMF) and EMEA/CPMP/4663/03 (PMF)

ANNEX I

HIERACHY OF THE COMMUNITY TEXTS

TREATIES

These are the «constitutional» rules establishing the objectives and competencies of the European Community (EC) and the European Union (EU) and the rules for the operation of the Community institutions.

European integration is based on four **founding treaties**:

- The Treaty establishing the European Coal and Steel Community (ECSC), which was signed on 18 April 1951 in Paris, entered into force on 23 July 1952 and expired on 23 July 2002;

- The Treaty establishing the European Economic Community (EEC) and the Treaty establishing the European Atomic Energy Community (Euratom), which were both signed in Rome on 25 March 1957, and entered into force on 1 January 1958. These Treaties are often referred to as the "Treaties of Rome". When the term "Treaty of Rome" is used, only the EEC Treaty is meant;

- The Treaty on European Union, which was signed in Maastricht on 7 February 1992, entered into force on 1 November 1993. It introduced new forms of co-operation between the Member State governments, on foreign and security policy and on "justice and home affairs". By adding this inter-governmental co-operation to the existing "Community" system, the Maastricht Treaty created a new structure with three "pillars" which is political as well economic. This is the “European Union” (EU).

The **founding treaties have been amended** on several occasions, in particular when new Member States acceded in 1973 (Denmark, Ireland, United Kingdom), 1981 (Greece), 1986 (Spain, Portugal), 1995 (Austria, Finland, Sweden) and 2004 (ten new Member States). There have also been more far-reaching reforms bringing major institutional changes and introducing new areas of responsibility for the European institutions:

- The Merger Treaty, signed in Brussels on 8 April 1965 and in force since 1 July 1967, provided for a Single Commission and a Single Council of the then three European Communities;

- The Single European Act (SEA), signed in Luxembourg and the Hague, and which entered into force on 1 July 1987, provided for the adaptations required for the achievement of the Internal Market;

- The Maastricht Treaty, apart from introducing the new European Un ion Treaty, amended the EC Treaty and changed the name of the European Economic Community to simply "the European Community" (EC).

- The Treaty of Amsterdam, signed on 2 October 1997, entered into force on 1 May 1999: it amended and renumbered the EU and EC Treaties. Consolidated versions of the EU and EC Treaties are attached to it. The Treaty of Amsterdam changed the articles of the Treaty on European Union, identified by letters A to S, into numerical form;

- The Treaty of Nice, signed on 26 February 2001, entered into force on 1 February 2003.

SECONDARY LAW

Community acts adopted by the Community institutions. A first distinction can be drawn according to their legal effects.

1. Legally binding acts

According to Article 249 of the EC Treaty, the following legally binding acts can be adopted by the European Parliament acting jointly with the Council, the Council, or the Commission:

a) Regulation

A regulation is an act of general application, binding in its entirety and directly applicable in all Member States. It does not require any transposition by the national authorities.

b) Directive

A directive is a legal act binding upon the Member States to which it is addressed, as far as the results to be achieved are concerned; leaving the national authorities the choice of form and methods.

A directive always leads to complementary national measures. In order to take effect a directive must be transposed into the legal order of the Member States.

c) Decision

A decision is a legal act binding in its entirety upon those to who it is addressed (Member State or natural or legal person).

Article 254 of the EC Treaty specifies the moment when the above legally binding acts enter into force or take effect.

The Community Pharmaceutical Law is based on EC Treaty provisions. The legal acts concerning medicinal products for human use are usually based on Article 95 of the Treaty (approximation of laws). Some existing pieces of legislation in the field were adopted pursuant to Articles 94 (approximation of laws)or 308 (Action necessary to attain one of the objectives of the Community where the necessary power has not been provided for by the Treaty). Some legal acts concerning medicinal products for human use (e.g. Regulation (EC) No 726/2004) are also based on Article 152(4) of the

Treaty on account of the provisions relating to veterinary medicinal products contained therein.

2. 'Soft law'

a) Resolution

A resolution is a declaratory act not 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.

A resolution is rather a political than a legal act, it does not create a legal obligation.

b) Communication

A Communication is an act not provided for by the EC Treaty, 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 of legally binding acts with Commission communications.

c) Guidelines

Guidelines are 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 when those acts so provide, 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 committees are not legally binding; they present the best or more appropriate way to fulfil an obligation laid down in the Community rules.

d) Notice to applicants

The Notice to Applicants is guidance adopted pursuant to Article 6 of Regulation (EC) No 726/2004 and Annex I of Directive 2001/83/EC. The Commission publishes this guidance in "The rules governing medicinal products in the European Union", Volume 2 "Notice to applicants human medicinal products". Volume 2 is divided in

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

ANNEX II

LEGAL ISSUES CONCERNING THE MARKETING AUTHORISATION HOLDER

The Marketing Authorisation Holder 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 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 marketing authorisation holder may be a natural or legal person.

The marketing authorisation holder must be established in the European Community including the EEA.

Applications for a marketing authorisation shall be accompanied by the name or corporate name and permanent address of the marketing authorisation holder.

The name and permanent address of the marketing authorisation holder must appear in the summary of product characteristics (SPC), on the labelling and the package leaflet of the medicinal product.

The marketing authorisation holder 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 marketing authorisation dossier must be the subject of an application and be authorised by the same authority as the original authorisation;

- shall notify Competent Authorities of the date of actual marketing and of the date when the product ceases to be placed on the market;

- 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;

- shall supply any new information which may entail a variation or influence the evaluation of the risks and benefits of the product or to inform of any prohibition or restriction, and shall answer any request from the Competent Authorities for the provision of additional information necessary for the evaluation of the benefits and risks or demonstrating that the risk-benefit balance remains favourable;

- when the marketing authorisation holder 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 undergo an inspection of the manufacturing site at the request of the Competent Authorities;

- shall supply, at the request of competent authorities, data on sales and prescriptions of their medicinal products;

- shall submit an application for renewal of the marketing authorisation at least six months before the expiry date and shall include in the application a consolidated version of the file in respect of quality, safety and efficacy, including all variations since the marketing authorisation was granted;

- 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 comply with the relevant provisions relating to the communication of information relating to pharmacovigilance concerns to the general public;

- shall have a scientific service in charge of scientific information on the concerned medicinal product;

- shall be responsible for advertising of the medicinal product in compliance 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 CHMP any cases where the competent authorities have adopted divergent decisions or where the interests of the Community are involved. In these cases the marketing authorisation holder 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 marketing authorisation holder 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;

- shall ensure that patients taking part in a compassionate use programme have access to a medicinal product in the period between marketing authorisation and placing on the market.

ANNEX 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 radionuclide, or a ligand not previously authorised as a medicinal product in the European Union, or the coupling mechanism to link the molecule and the radionuclide has not been authorised previously in the European Union.

ANNEX IV

GUIDANCE ON THE APPROPRIATE ADDITIONAL STUDIES REQUIRED FOR APPLICATIONS UNDER ARTICLE 10 OF DIRECTIVE 2001/83/EC OR EXTENSION 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 profile (otherwise, to be considered as a new active substance)
b)	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
c)	different strength same route/ pharmaceutical form and posology	Bioavailability (cf. guideline)
d)	suprabioavailable products i) same dosage intervals but reduced doses intended to achieve same plasma/blood concentrations as a function of time	Bioavailability studies may suffice (see paragraph 5 of Bioequivalence guideline).
e)	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.