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Health systems and products
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# NOTICE TO APPLICANTS

# VOLUME 2A
# Procedures for marketing authorisation
# CHAPTER 1
# MARKETING AUTHORISATION

## July 2015

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

# CHAPTER 1 MARKETING AUTHORISATION

# 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 Union. Thus, the pharmaceutical legislation of the European Union has consistently pursued the twin objectives: the protection of public health and the free movement of medicinal products.

General principles of the Union pharmaceutical legislation are given in this chapter. More detailed explanations concerning the different procedures for marketing authorisation are provided in Chapters 2 - 6.

## 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. It is intended to facilitate the interpretation and application of the Union pharmaceutical legislation. It is not legally binding and, in case of doubt, reference should be made to the appropriate Union Directives and Regulations. It is important when reading this text to appreciate that the legal requirements of the Union pharmaceutical legislation must be met and that this Notice to Applicants represents the harmonised view of the Member States, the European Medicines Agency (EMA) and the Commission services on how those requirements may be met.

Guidelines and other interpretative documents to which references are included within this document represent the views of their authors.

References throughout the Notice to Applicants to provisions of Directive 2001/83/EC and Regulation (EC) 726/2004 must be read as references to the directive and the regulation as last amended[3], unless it is otherwise expressly stated.

1 OJ L 136, 30.4.2004, p.1.

2 OJ L 331, 28.11.2001, p. 67.

3 Directive 2012/26/EU of the European Parliament and of the Council of 25 October 2012 amending Directive 2001/83/EC as regards pharmacovigilance, OJ L 299 of 27.10.2012, p. 1 and Regulation (EU) No1027/2012 of the European Parliament and of the Council of 25 October 2012 amending Regulation (EC) No726/2004 as regards pharmacovigilance, OJ L 316 of 14/11/2012, p. 8.

# 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 for its own territory (national authorisation) or when an authorisation has been granted in accordance with Regulation (EC) No 726/2004 for the entire Union (an Union authorisation). The marketing authorisation holder must be established within the EEA.

Article 54 of the Treaty of the functioning of the European Union (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 Union must, 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.

A marketing authorisation lays down the terms under which the marketing of a medicinal product is authorised in the EU. A marketing authorisation is composed of:

(i) a decision granting the marketing authorisation issued by the relevant authority; and

(ii) a technical dossier with the data submitted by the applicant in accordance with Articles 8(3) to 11 of Directive 2001/83/EC and Annex I thereto, Articles 6(2) and 31(2) of Regulation (EC) No 726/2004, or Article 7 of Regulation (EC) No 1394/2007.

**European Economic Area (EEA)**

Norway, Iceland and Liechtenstein form the EEA with the 28 Member States of the European Union. These countries have, through the EEA agreement, adopted the complete Union acquis on medicinal products and are consequently parties to the Union procedures. Where in this chapter reference is made to Member States of the Union this should be read to include Norway, Iceland and Liechtenstein. Legally binding acts from the Union (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 Union, Norway, Iceland and Liechtenstein will take corresponding decisions on the basis of relevant acts. Consequently, these States are concerned with 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 Union, 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.

**Liechtenstein**

Since 1st December 2010 the treaty[4] between Liechtenstein and Austria about automatic recognition of the Marketing Authorisations granted via Mutual Recognition Procedure (MRP) or Decentralised Procedure (DCP) is operational. This allows Liechtenstein to use Marketing Authorisations granted by Austria provided the applicants have identified Liechtenstein as CMS in the application form submitted with MRP or DCP applications. At the end of the procedures, Austria will grant authorisations that will be recognised by Liechtenstein. This marketing authorisation can be considered as a marketing authorisation granted in accordance with the pharmaceutical acquis for the purpose of EU legislation and in particular can be considered as a starting point for the purposes of data exclusivity/market protection in the EU.

Further, in application of a bilateral agreement[5] between Switzerland and Liechtenstein, a Swiss marketing authorisation is automatically effective in Liechtenstein. This recognition has no effects outside the customs union between Switzerland and Liechtenstein. Consequently a marketing authorisation granted by the Swiss authorities and recognised by Liechtenstein, while Switzerland does not apply the EU pharmaceutical acquis, cannot be considered as a marketing authorisation granted in accordance with the pharmaceutical acquis for the purpose of EU legislation and in particular cannot be considered as a starting point for the purposes of data exclusivity/market protection in the EU (see part 6 on data exclusivity/market protection).

**Monaco**

An agreement between the Union 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[6]. 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

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[4]1Abkommen zwischen der Österreichischen Bundesregierung und der Regierung des Fürstentums Liechtenstein betreffend die automatische Anerkennung von in Österreich zugelassenen bzw. registrierten Human- und Tierarzneimitteln in Liechtenstein (Federal Law Gazette BGBl. III Nr. 126/2010)

[5] Website Liechtenstein: http://www.llv.li/amtsstellen/llv-ag-heilmittel-2/llv-ag-arzneimittel-2/llv-ag-arzneimittel zugelassene_arzneimittel.htm

[6] O.J. 19.12.03 L 332/42

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 manufacturing 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 ("Union 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[7] 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 must 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 Union, 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.

The marketing authorisation must 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 Union authorisations

The Union 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);

7 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).*

- 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 Union authorisation would be in the interest of patients or animal health at Union level. The applicant has to request confirmation that the product is eligible for evaluation through the centralised procedure (optional scope) and the EMA 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

Scientific aspects and working definitions for the mandatory scope of the centralised procedure drawn up by EMA are available at http://www.ema.europa.eu/pdfs/human/regaffair/12194407en.pdf

In order to obtain a Union authorisation, an application must be submitted to the EMA. 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 EMA, 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 Union 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 must contain the summary of product characteristics according to Article 11 of Directive 2001/83/EC and the labelling and the package leaflet according to Title V of Directive 2001/83/EC.

Once a central marketing authorisation has been issued, the maintenance of existing national marketing authorisation or the issuing of new national marketing authorisations for the same medicinal product could be envisaged only as long as the therapeutic indications are different in national and central marketing authorisations.

Indeed, if a product falls under the optional scope of the centralised procedure (Article 3(2) of Regulation (EC) No. 726/2004), the applicant has the choice of using either the centralised or the national (decentralised/mutual recognition) procedure for the same medicinal product. The "Communication on the Community marketing authorisation procedures for medicinal products"[8] clarifies that this choice does not allow both a central and a national marketing authorisation to co-exist simultaneously for the same product and that once a central marketing authorisation has been issued, there is no room for an additional scientific evaluation and regulatory decision for the same medicinal product (see in particular point A.2 and conclusion of the Communication). If such situation would occur the Commission would consider the need for a referral procedure.

8 Commission Communication 98/C229/03

The only exception for possible co-existence of central and national marketing authorisation that the Communication provides concern cases where there are different therapeutic indications (see point A.2.b).

## 2.3 Notion of 'global marketing authorisation'[9]

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 must also be granted an authorisation or be included in the initial marketing authorisation. All these marketing authorisations are considered as belonging to the same global marketing authorisation, in particular for the purpose of the application of Article 10 of the directive, which lays down rules on data exclusivity and market protection 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, including in different Member States within the EU, 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 is also part of the same global marketing authorisation.

To determine the notion of same marketing authorisation holder or applicant in this context, see section 2.8.

1. If the medicinal product being assessed contains a modification of an existing active substance, it should be clarified during the marketing authorisation procedure whether the product contains a new active substance or not. This clarification impacts on the existence or not of a global marketing authorisation if the medicinal products belong to the same marketing authorisation holder. Request for a new active substance claim should be submitted within the initial marketing authorisation application for medicinal product containing the modified substance and will not be considered retroactively. This assessment is to be done in accordance with the criteria of Annex I at the end of this Chapter and the conclusion should be reflected at least in the assessment report. If the assessment report does not indicate that the product contains a new active substance, it will be considered that the product at stake contains the same active substance and belongs to the global marketing authorisation of the already authorised medicinal product(s) as described in Article 6(1) of Directive 2001/83/EC.

   Example: Active substance A in MP 1→ active substance A' in MP 2

9 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'.

2. If the medicinal product being assessed contains within the same pharmaceutical form a combination of active substances, it will form a new and unique medicinal product requiring a separate marketing authorisation, regardless whether all of the active substances contained therein were already authorised in a medicinal product or not. In its application for the new combination, the applicant must demonstrate that each active substance has a documented therapeutic contribution within the combination and therefore all compounds are different active substance[10]. The authorisation for this new combination medicinal product is not considered to fall within the scope of the global marketing authorisations of the already authorised medicinal product(s) as described in Article 6(1) of Directive 2001/83/EC.

   Examples:

   Active substance A in MP1, active substance B in MP2 → Active substances A+B in MP3

   Active substances A+B in MP1, Active substances C+D in MP2→ Active substances A+C in MP3

   Active substances A+B in MP1, Active substance C in MP2 → Active substances A+C in MP3

   Active substances A+B in MP1→ Active substance A+C in MP2

3. If the medicinal product being assessed contains only one active substance which was part of an authorised combination product, the new medicinal product will form a new and unique medicinal product requiring a separate marketing authorisation. Considering that during the assessment procedure of the already authorised combination product, the marketing authorisation holder had demonstrated that each substance of the fixed combination has a documented therapeutic contribution within the combination and therefore all compounds are different active substances[11], the authorisation for the new medicinal product is not considered to fall within the scope of the global marketing authorisations of the already authorised combination medicinal product as described in Article 6(1) of Directive 2001/83/EC.

   Example: Active substances A+B in MP 1 → Active substance A in MP2

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

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

10 See DRAFT Reflection paper on the chemical structure and properties criteria to be considered for the evaluation of New Active 5 Substance (NAS) status of chemical substances [http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2015/04/WC500186193.pdf].

## 2.4 Validity of the marketing authorisation

### 2.4.1 Renewal

Marketing authorisations granted in the Union 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 must provide the EMA 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 nine 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 is 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).

While the submission of the file should take place at least 9 months prior to the expiry of the marketing authorisation, premature submissions should be avoided. In this regard, it is noted that the renewal should take place upon the expiry of the period of five years and that such decision will be based on the consolidated file submitted by the marketing authorisation holder for this purpose, demonstrating that the benefit-risk is positive. A submission that is made too prematurely may not be sufficiently up to date for the Commission/Competent Authorities to adopt a decision on the renewal.

Recommendations regarding the content of the consolidated file for the renewal are provided in the EMA Guideline on the Processing of Renewals in the Centralised Procedure [11] and CMDh Best Practice Guide on the processing of renewals in the MRP/DCP [12].

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

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 Union market will cease to be valid. When an authorised product previously placed on the market in the authorising Member State or in the Union is no longer actually present on the market for a period of three consecutive years, the authorisation for that product will cease to be valid. The competent authority may, in exceptional circumstances and on public health grounds grant exemptions. Such exemptions must be duly justified.

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11 http://ec.europa.eu/health/files/eudralex/vol-2/2012-06_gpr.pdf

12 http://www.hma.eu/fileadmin/dateien/Human_Medicines/CMD_h_/procedural_guidance/Renewal/CMDh_004_2005_Rev.9_cl.pdf

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 protection and other protection rules which have to be respected.

The absence of the medicinal product from the market must be of three consecutive years, therefore in case the medicinal product would be put back on the market, the period of three years would restart. This situation may occur several times.

The marketing authorisation will remain valid if at least one presentation of the medicinal product 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 comprises 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 Union market" means that the medicinal product is at least marketed in one Member State of the Union. 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).

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 must inform the competent authority of the authorising Member State or the EMA of the date of actual marketing of the medicinal product in that Member State or in the Union, taking into account the various presentations authorised. The holder must also notify the national competent authority or the EMA if the product ceases to be placed on the market, either temporarily or permanently. Such notification must, otherwise than in exceptional circumstances, be made no less than 2 months before the interruption in the placing on the market of the product. The marketing authorisation holder must inform the national competent authorities or the EMA of the reasons for such action. Upon request by the national competent authority or the EMA, particularly in the context of pharmacovigilance, the marketing authorisation holder must provide the national competent authority or the EMA 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.

### 2.4.3 Suspension or withdrawal of medicinal product and voluntary withdrawal of marketing authorisation

A marketing authorisation holder must notify respectively the Member States concerned/EMA of any action taken to suspend the marketing or to withdraw a medicinal product from the market, to request the withdrawal or to not request the renewal of a marketing authorisation together with the reasons for such action. He must in particular declare if his action concerns the efficacy of the medicinal product or the protection of public health.

## 2.5 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, delivered through centralised, national or decentralised/mutual recognition procedure, must contain the name of the medicinal product, which may be either an 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 Union authorisations granted following applications through the centralised procedure, it is important that applicants identify at an early stage a name which would be valid throughout the Union when using the centralised procedure. However, in exceptional cases, the Commission may authorise the use of a different name in a Member State where the proposed name has been cancelled, opposed or objected to under trade-mark law (Article 6(1) of Regulation (EC) No 726/2004).

See also the EMA 'Guideline on the acceptability of name for human medicinal products processed through centralised procedure' available at http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2009/10/WC500004142.pdf

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 is 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 available the decision granting the marketing authorisation together with the package leaflet, the summary of the product

characteristics and any possible conditions to the marketing authorisation. In addition, they must draw up an 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 should be provided separately for each indication applied for.

As regards products authorised through the centralised procedure, notification of the marketing authorisation must be published in the Official Journal of the European Union and the EMA must 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).

## 2.7 Multiple applications

In the framework of the centralised procedure only one marketing authorisation may be granted to an applicant for a specific medicinal product.

However, according to Article 82(1) 2nd subparagraph of Regulation (EC) 726/2004 the same applicant can submit more than one application for the same medicinal product 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. In such case, the Commission will inform the applicant whether the conditions are met before he submits his application to the EMA. For further details see the Commission services note on the handling of Duplicate Marketing Authorisation Application,
http://ec.europa.eu/health/files/latest_news/2011_09_upd.pdf

There are no corresponding provisions in Directive 2001/83/EC that apply to the mutual recognition and decentralised procedures. In such circumstances, the acceptance of multiple applications in mutual recognition and decentralised procedures should, however, not be used to undermine harmonisation at Union level or to circumvent the application of Union legislation. In particular, multiple applications should not lead to applications for the same medicinal product being submitted in different Member States and handled outside the principles of mutual recognition laid down in chapter IV of Directive 2001/83/EC. To avoid such an effect, the following principles should be observed:

- reference to any authorisation obtained for that medicinal product should be provided with the application for a marketing authorisation;
- as far as possible, the same reference Member State should be used in case of multiple applications;
- Article 18 should be relied on to avoid that multiple applications are used to obtain marketing authorisations for the same medicinal product in different Member States outside the procedural framework of chapter IV of Directive 2001/83/EC;
- the applicant may decide whether the mutual recognition procedure or the decentralised procedure is used for obtaining the multiple marketing authorisations.

See CMDh Recommendations on Multiple Applications in Mutual Recognition and Decentralised Procedures (June 2007) available at http://www.hma.eu/fileadmin/dateien/Human_Medicines/CMD_h_/procedural_guidance/Application_for_MA/Multi_App_MRP_DCP_2007_06_Rev3.pdf

## 2.8 Concept of "applicant" and "marketing authorisation holder"

The concept of "applicant" and "marketing authorisation holder" are important for the application of the global marketing authorisation definition and also in other contexts, such as the submission of applications under Directive 2001/83/EC, the submission of variations under work-sharing procedures or the submission of multiple marketing authorisations under Article 82(1) of Regulation (EC) No 726/2004. The definition of "applicant" provided for in the 1998 Commission Communication[13] should be clarified in the light of the experience gathered.

An "applicant" and "marketing authorisation holder" can be a physical or legal entity. However, for the purposes of the application of the pharmaceuticals rules, having a distinct legal personality does not necessarily entail that each entity can be considered as a distinct applicant or marketing authorisation holder to the other one. In particular, it is noted:

- Applicants and marketing authorisation holders belonging to the same company group or that are controlled by the same physical or legal entity are to be considered as one entity.

- Applicants and marketing authorisation holders that do not belong to the same company group and are not controlled by the same physical or legal entity are to be considered as one applicant/marketing authorisation holder if they have concluded tacit or explicit agreements concerning the marketing of the same medicinal product for the purposes of the application of the pharmaceuticals rules regarding that medicinal product. This includes cases of joint marketing but also cases where one party licenses to the other party the right to market the same medicinal product in exchange for fees or other considerations.

This concept applies, *mutatis mutandis*, to the definition of "sponsor" in the context of orphan designations.

# 3. MARKETING AUTHORISATION PROCEDURES

## 3.1 Centralised procedure

A marketing authorisation granted under the centralised procedure is valid for the entire EU market, which means the medicinal product may be put on the market in all Member States. For medicinal products which fall within the mandatory scope of the

13 OJ C 229, 22/7/1998, p.4

centralised procedure in accordance with the Annex to Regulation (EC) No 726/2004, the application is submitted to the EMA. An application may likewise be submitted to the EMA 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 Union marketing authorisation.

In particular, applications on the basis of Article 10, where the reference medicinal products is centrally authorised may be submitted via the centralised procedure. Alternatively, they may be authorised by the competent authorities of the Member States through a national, mutual recognition procedure or decentralised procedure provided that the conditions, laid down in Article 3(3) of the Regulation are met (e.g. same summary of product characteristics, same name in all the Member States).

Those Similar biological ("biosimilar") medicinal products which are developed by means of one of the biotechnological processes listed in the Annex to Regulation(EC) No 726/2004 must however be authorised via the centralised procedure.

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

When a marketing authorisation application is submitted for a product which is of major public health interest, in particular from the viewpoint of therapeutic innovation, the applicant may request an accelerated assessment procedure in accordance with Article 14(9) of Regulation (EC) 726/2004. The applicant should justify their expectation that the medicinal product is of major public health interest particularly from the point of view of therapeutic innovation.

For further details on the documentation required to substantiate a request for accelerated assessment and on the reduced timetable, reference is made to the EMA website.

### 3.1.1 Conditional marketing authorisation, marketing authorisation granted under exceptional circumstances and marketing authorisation subject to conditions

The conditional marketing authorisation is only provided for the centralised procedure (Article 14(7) of Regulation (EC) No 726/2004. Commission regulation (EC) No 507/2006 is laying down the rules on the granting of such marketing authorisation.

It must be distinguished from the marketing authorisation under exceptional circumstances (Article 14(8) of Regulation (EC) No 726/2004 and Article 22 of Directive 2001/83/EC) and the marketing authorisation subject to conditions (Article 9.4 b, c, ca, cb, cc. of Regulation No 726/2004 and Article 21a of Directive 2001/83/EC) which are possible under centralised and National/DCP/MRP procedures

### 3.1.2 Orphan medicinal products

There are two EU Regulations covering orphan medicinal products: Regulation (EC) No 141/2000 and its implementing regulation, Commission Regulation (EC) No 847/2000[14].

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 Union and Member State initiatives which support research and development of orphan medicinal products, and the possibility to request fee reductions from the EMA.

### 3.1.3 Advanced Therapy Medicinal Products

Regulation (EC) No 1394/2007 of the European Parliament and of the Council of 13 November 2007 on Advanced Therapy Medicinal Products (ATMP) applies in the European Union from 30 December 2008.

3.1.4 Transfer of a Union marketing authorisation

The transfer of a marketing authorisation granted under the centralised procedure is regulated in Commission Regulation (EC) No. 2141/96, of 7 November 1996.

In accordance with that Regulation, the marketing authorisation holder should submit an application to the EMA with supported documents.

When transferring the marketing authorisation of a designated Orphan medicinal product, the marketing authorisation holder must also transfer the Orphan designation of the product concerned in accordance with Article 5(11) of Regulation (EC) No 141/2000.

## 3.2 Decentralised procedure and mutual recognition procedure

Both the decentralised and the mutual recognition procedures are based on the recognition by national competent authorities of an assessment performed by the authorities of one Member State. According to the European Court of Justice, "[…] *Article 28 of Directive 2001/83/EC* […] *confers a Member State in receipt of an application for mutual recognition only a very limited discretion in relation to the reasons for which that Member State is entitled to refuse to recognise the marketing authorisation in question. In particular, as regards any assessment going beyond the verification of the validity of the application with regard to the conditions laid down in Article 28, the Member State concerned, except where there is a risk to public*

14 OJ L 103, 28.4.2000, p. 5.

*health, must rely on the assessments and scientific evaluations carried out by the reference Member State*"[15]. Although the facts of the case relate to a MRP, the ECJ is interpreting Article 28 (4) which applies both to MRP and DCP[16].

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 (SmPC), 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 SmPC, 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 1234/2008 for the examination of variations and the use of the decentralised and mutual recognition procedures for extensions.

For further details see chapter 2.

### 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 1234/2008 for the examination of variations and the use of the decentralised and mutual recognition procedures for extensions and renewals.

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15 §41 of ECJ C-452/06

16 ECJ C-145/11, (cf. para. 39).

For further details see chapter 2.

## 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 Union are either registered according to Articles 14 and 15 or authorised according to Article 16 of that directive.[17]

It follows from Article 1(5) of Directive 2001/83/EC that a homeopathic medicinal product is any medicinal product prepared from substances called homeopathic stocks in accordance with a homeopathic manufacturing procedure described by the European Pharmacopoeia[18] or, in the absence thereof, by the pharmacopoeias currently used officially in the Member States. A homeopathic medicinal product may contain a number of principles.

Based on the particular characteristics of homeopathic medicinal products, such as the very low level of active principles they contain and the difficulty of applying to them the conventional statistical methods relating to clinical trials, Articles 14 and 15 of Directive 2001/83/EC provide for a simplified registration procedure for those homeopathic medicinal products which are placed on the market without therapeutic indications in a pharmaceutical form and dosage which do not present a risk for the patient. Furthermore, according to Article 13(2) of Directive 2001/83/EC, the Member States are obliged to establish the abovementioned simplified registration procedure for the homeopathic medicinal products referred to in Article 14.

However, if a homeopathic medicinal product is not eligible for the simplified registration procedure, before placing the product on the market of a Member State, it has to be authorised, regardless of the marketing authorisation procedure in accordance with Articles 8, 10, 10a, 10b, 10c and 11 of Directive 2001/83/EC as appropriate.

Nevertheless, in accordance with Article 16(2) of Directive 2001/83/EC, in case of a national procedure, a Member State may introduce or retain in its territory specific rules for the pre-clinical tests and clinical trials of homeopathic medicinal products other than those referred to in Article 14(1) in accordance with the principles and characteristics of homeopathy as practised in that Member State. Accordingly, if the homeopathic medicinal product is eligible for the simplified registration procedure, the Member State cannot introduce other requirements than the ones following from Articles 14 and 15 of Directive 2001/83/EC.

An application under the simplified registration procedure may cover a series of medicinal products derived from the same homeopathic stock or stocks. The simplified registration procedure allows the registration of homeopathic medicinal

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17 As Directive 2001/83/EC provides for a complete harmonisation of national authorisation procedures for medicinal products, no other procedures can be set up for homeopathic medicinal products but the ones provided by Directive 2001/83/EC, see ECJ-Case C-84/06.

18 See section 5.1.2

products, provided that they are administered orally or externally, that no specific therapeutic indication appears on the labelling of the medicinal product or in any information relating thereto, and that there is a sufficient degree of dilution to guarantee the safety of the medicinal product.

In addition, in order to demonstrate, in particular, the pharmaceutical quality and the batch-to batch homogeneity of the products concerned, the applicant has to provide the documents set up by Article 15 of Directive 2001/83/EC.

According to Article 14(2) of Directive 2001/83/EC the criteria and rules of procedure provided for in Article 17(1) of that directive apply by analogy to the special, simplified registration procedure for homeopathic medicinal products. Hence, an application under the simplified registration procedure must be assessed within 210 days after the submission of a valid application.

However, it follows from Article 39 of Directive 2001/83/EC that Article 29(4), (5) and (6) and Articles 30 to 34 do not apply to the homeopathic medicinal products registered under the simplified registration procedure. Consequently, if a Member State cannot approve the assessment under the simplified registration procedure conducted by the reference member state, on the grounds of potential serious risk to public health, and the Member States fail to reach an agreement in the coordination group, the case will not be submitted to the EMA for arbitration. Each Member State will therefore take its own decision.

According to Article 68 of Directive 2001/83/EC, homeopathic medicinal products must be labelled in accordance with the provisions of title V of Directive 2001/83/EC on the labelling and package leaflet, and be identified by a reference on their labels, in clear and legible form, to their homeopathic nature. However, it follows from Article 69 of Directive 2001/83/EC that in addition to the clear mention of the words "homeopathic medicinal product", the labelling and, where appropriate, the package leaflet for homeopathic medicinal products authorised under the simplified registration procedure must *bear no other information* than those mentioned in Article 69 of that Directive.

However, the principles and the procedural rules of title V of Directive 2001/83/EC will apply to those products. Hence, according to Article 56, the particulars referred to in Article 69 must be easily legible, clearly comprehensible and indelible. Furthermore, as there is no waiver from the Braille requirements laid down by Article 56a of the Directive with regard to homeopathic medicinal products registered through the simplified procedure, these requirements apply also to homeopathic medicinal products. However, this requirement has to be read in conjunction with Article 69(1) of Directive 2001/83/EC, which provides that the labelling and, where appropriate, the package leaflet for the homeopathic medicinal products registered through the simplified procedure, must bear only the information provided by that article. Accordingly, the scientific name of the stock or stocks followed by the degree of dilution should be put in Braille format on the packaging of the product. If the scientific names of the stocks on the labelling are supplemented by an invented name, this should also be put in Braille format.

According to Article 58 of Directive 2001/83/EC, the inclusion in the packaging of all medicinal products of a package leaflet is obligatory, unless all the information required is directly conveyed on the outer packaging or on the immediate packaging. Furthermore, according to Article 56a of the said directive, the marketing authorisation holder hall ensure that the package leaflet is made available on request from patients' organisations, in formats appropriate for the blind and partially sighted. Consequently, if package leaflets are needed for homeopathic medicinal products registered through the simplified procedure, they are also to be made available in formats appropriate for the blind and partially-sighted.

## 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 Union code relating to medicinal products for human use for traditional herbal medicinal products. According to Articles 16a to 16i of Directive 2001/83/EC, a specific registration procedure is foreseen for herbal medicinal products fulfilling the criteria of a traditional herbal medicinal product.

That registration procedure is intended for herbal medicinal products with a long tradition, which do not fulfil the requirements for a marketing authorisation, including those set out in Article 10a of Directive 2001/83/EC. In particular where an applicant cannot 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 Union.

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 Union. 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.

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. However, to prevent treatment of more serious pathologies with traditional herbal medicinal products, it is possible for the indications of traditional herbal medicinal products to refer to the use after exclusion of serious conditions by a medical doctor. In any case, the traditional herbal medicinal product still needs to be intended and designed for use without the supervision of a medical practitioner for diagnostic purposes or for prescription or monitoring of treatment. The traditional herbal medicinal product has to be a non-prescription medicinal product.

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 EMA in accordance with Article 16h of Directive 2001/83/EC. The HMPC is responsible for various tasks concerning the simplified registration and authorisation of medicinal products as provided for in Directive 2001/83/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 Union 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. When monographs have been established, they must be taken into account by the Member State when examining an application. Accordingly, even though the Member States are not obliged to follow the monograph, any decisions to not accept the content of the monograph as adopted by the HMPC should be duly justified taking into account the important role of monographs to bring harmonisation to this field, and to facilitate the use of the simplified registration procedure.

If an EU herbal monograph exists for a herbal substance and the application for the herbal medicinal product is based on Article 10a of Directive 2001/83/EC (well

established use), the submission of non-clinical and clinical overview/summaries is necessary to explain the relevance of the monograph and/or additional literature for the given application. However it is not necessary to provide all the articles referred in the List of References supporting the monograph.

In order to promote harmonisation, Member States should recognise registrations of traditional herbal medicinal products granted by another Member State based on Union 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 Paediatric requirements for medicinal products

Regulation (EC) No. 1901/2006[19] of the European Parliament and of the Council on medicinal products for pediatric use entered into force on 26 January 2007. It aims to facilitate the development and availability of medicinal products for use in the paediatric population[20]. To attain this goal, the Regulation places on applicants certain obligations, the main one being submission of data on the use of a medicinal product in children obtained in accordance with an agreed paediatric investigation plan (PIP) by EMA. Provided that the requirements of Regulation 1901/2006 are fulfilled, the applicants may be then eligible for a reward, as provided in Title V of this Regulation, that may be an extension of the supplementary protection certificate (SPC), extension of market exclusivity, or data/market protection, as the case may be.

For further detail, please refer to the Commission's Guideline on the format and content of applications for agreement or modification of a paediatric investigation plan and requests for waivers or deferrals and concerning the operation of the compliance check and on criteria for assessing significant studies[21], available at http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:C:2008:243:0001:0012:EN:PDF

Additionally, Regulation 1901/2009 provides for a specific authorisation for medicinal products developed exclusively for use in the paediatric population: the paediatric use marketing authorisation – PUMA as defined in Article 2.4 of the Regulation. This authorisation can be requested for a medicinal product no longer covered by intellectual property rights and may retain the existing brand name of the corresponding adult product. Medicinal products that have received a PUMA will benefit from the data and marketing protection periods set out in Directive 2001/83/EC (Article 38(2) of Regulation (EC) 1901/2006).

For information on guidelines developed by the CMDh, see http://www.hma.eu/216.html. For information on guidelines developed by the EMA, see section “Special Topics-Medicines for children on the EMA website

[19] OJ L 378, 27.12.2006, p. 1

[20] *'paediatric population' means that part of the population aged between birth and 18 years*", Article 2, point 1 of Regulation 1901/2006.

[21] OJ C 243 of 24/09/ 2008, p. 1.

http://www.ema.europa.eu/ema/index.jsp?curl=pages/special_topics/general/general_content_000302.jsp&murl=menus/special_topics/special_topics.jsp&mid=WC0b01ac058002d4ea

## 3.6 Independent national procedures

Independent national procedures will continue, but are strictly limited 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 Union is to be promoted via a coordinated approach for referring medicinal products, for which divergent decisions have been adopted, to the EMA 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 7 of this chapter).

## 3.7 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 State 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 must 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. .

The register of the medicinal products authorised under Article 126a is available at the Commission web-site: http://ec.europa.eu/health/documents/community-register/html/except_index.htm

For medicinal products authorised in accordance with Article 126a of Directive 2001/83/EC, marketing authorisation holders do not qualify for the rewards in the sense of Regulation 1901/2006 as described in section 3.5 above.

# 4. UNION REFERRALS

In certain circumstances in the framework of marketing authorisations granted by the competent authorities of the Member States, a Union procedure, involving a scientific opinion by, as appropriate, the CHMP/Pharmacovigilance Risk Assessment Committee (PRAC) can be triggered. This procedure is commonly called Union "referral", which may be triggered in the cases listed below and which are further described in chapter 3 of volume 2A of the Notice to applicant:

i) in accordance with Article 29 of Directive 2001/83/EC, where one or more concerned Member States cannot agree on the recognition of an authorisation already granted in a mutual recognition procedure or a final assessment and product information prepared by the Reference Member State in view of granting the marketing authorisation in a decentralised procedure due to a potential serious risk to public health[22], the points of disagreement must be referred to the coordination group provided by Article 27 of that Directive..

   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 EMA. The expression 'potential serious risk to public health' is defined in the Commission's Guideline on the definition of a potential serious risk to public health in the context of Article 29(1) and (2) of Directive 2001/83/EC [23], available at http://ec.europa.eu/enterprise/sectors/pharmaceuticals/files/eudralex/vol-1/com_2006_133/com_2006_133_en.pdf

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 of that Directive 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 Union, Member States must, each year, forward to the coordination group a list of medicinal products for which a harmonised summary of product

[22] See ECJ C-452/06.

[23] OJ C 133, 8/6/2006 p. 5 - 7

characteristics should be drawn up. The coordination group must lay down a list taking into account the proposals from all Member States and will 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[24], the Member States or the Commission or the applicant or the marketing authorisation holder must, in specific cases where the interests of the Union 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. Where the referral results from the evaluation of data relating to pharmacovigilance the matter must be referred to the PRAC. Its final recommendation will be forwarded to the CHMP or the coordination group, as appropriate. . However when one of the criteria listed in Article 107i(1) is met, the procedure laid down in Articles 107i to 107k must apply. Where the referral concerns a range of medicinal products or a therapeutic class, the Agency may limit the procedure to certain specific parts of the authorisation. In such case, Article 35 must 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 107i of Directive 2001/83/EC[25] A Member State or the Commission, as appropriate, must, on the basis of concerns resulting from the evaluation of data from pharmacovigilance activities:

   a) initiate the procedure provided for in the section by informing the other Member States, the Agency and the Commission where it considers suspending or revoking a marketing authorisation, prohibiting the supply of a medicinal product, refusing the renewal of a marketing authorisation, or it is informed that the marketing authorisation holder, on the basis of safety concerns, has interrupted the placing on the market of a medicinal product or has taken action to have a marketing authorisation withdrawn, or intends to take such action or has not applied for the renewal of a marketing authorisation.

   b) inform the other Member States, the Agency and the Commission where it considers that a new contraindication, a reduction in the recommended dose or a restriction to the indications of a medicinal product is necessary. The information must outline the action considered and the reasons therefor.

   c) initiate the procedure in any of the cases referred in the paragraph b above, when urgent action is considered necessary.

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24 Article 1.2 of Directive 2012/26/EU amending Article 31 of Directive 2001/83/EC, applicable as from 28 October 2013.

25 Article 1.7 of Directive 2012/26/EU amending Article 31 of Directive 2001/83/EC, applicable as from 28 October 2013.

vi) Variations to marketing authorisations as foreseen in Regulation 1234/2008.

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

viii) in accordance with article 29 of Regulation 1901/2006 in the case of medicinal products authorised under Directive 2001/83/EC, an application as referred to in Article 8 of this Regulation may be submitted, in accordance with the procedure laid down in Articles 32, 33 and 34 of Directive 2001/83/EC, for authorisation of a new indication, including the extension of an authorisation for use in the paediatric population, a new pharmaceutical form or a new route of administration. That application must comply with the requirement laid down in point (a) of Article 7(1). The procedure is limited to the assessment of the specific sections of the summary of product characteristics to be varied.

## 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, "hybrid" 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 of active substances in a medicinal product;
- 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 Union 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 must be promptly supplied. In this regard, marketing authorisation holders of marketing authorisations granted in accordance with Article 10 or 10c of Directive 2001/83/EC should introduce variations swiftly whenever the marketing authorisation of the reference medicinal product or of the "original" medicinal product is changed to address a safety or efficacy concern.

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.

### 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 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

Article 8(3)(ca) of Directive 2001/83/EC requires the evaluation of the potential environmental risks posed by the medicinal product. In fulfilling this requirement, all applicants/marketing authorisation holders should take into account the CHMP Guideline ‘On Environmental Risk Assessment of Medicinal Products for Human Use’ available at http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/10/WC500003978.pdf .

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

5.2.1 Stand alone application

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 must 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.

5.2.2 "Mixed application"

Where Module 4 and/or 5 of the application for marketing authorisation 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 7 on mixed marketing authorisation application.

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

### 5.3.1 General concepts

#### 5.3.1.1 Reference medicinal product

For data exclusivity and market protection period of the reference medicinal product, see section 6.

A definition of reference medicinal product is given in Article 10(2)(a) of Directive 2001/83/EC, which provides that the reference medicinal product means 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 authorisation has been issued. In turn, Article 8 provides that in order to obtain a marketing authorisation an application must be made to the competent authority by an applicant established in the Union 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 medicinal product

Reference can be made to the dossier of a reference medicinal product for which a marketing authorisation has been granted in the Union in accordance with Articles 8(3), 10a[26], 10b or 10c of Directive 2001/83/EC. The application form in Module 1 of the dossier for an Article 10 application should clearly identify the reference product in order for the reference Member State, in case of MRP/DCP, to prepare the assessment report.

On the contrary, reference cannot be made to the dossier of a medicinal product for which a marketing authorisation has been granted in the Union in accordance with Article 10(1).

However, in those cases where a medicinal product has been developed through an application submitted in accordance with Article 10(3) of Directive 2001/83/EC leading to a new indication, strength, pharmaceutical form, a marketing authorisation application of a subsequent generic of this medicinal product can include the new indication, strength, pharmaceutical form, etc. To this effect, it will also be possible to refer to the data submitted to support the development.

Reference must be made to a product which is or has been authorised in the Union, (i.e. a marketing authorisation has been granted for the reference medicinal product, but it may have ceased to exist) and in accordance with the Union law[27].

In case, the reference medicinal product is no more produced and placed on the Union market , demonstration of the bioequivalence with the reference medicinal product through bioavailability studies should however be performed on batches which have been authorised within the Union.

Application in accordance with Article 10 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. These authorisations for these 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. However, where the reference medicinal product has been withdrawn, it is noted that public health concerns linked for instance to the lack of pharmacovigilance data may prevent the granting of such marketing authorisation. (case C-223/01, AstraZeneca, judgment of the European Court of Justice of 16 October 2003).

An application according to Article 10 of Directive 2001/83/EC cannot be filed simultaneously with an application for a reference product (case C-223/01, AstraZeneca, judgment of the European Court of Justice of 16 October 2003).

The marketing authorisation holder of the reference medicinal product can file an application on the basis of Article 10 to his own medicinal product, provided that the requirements of Article 10 are fulfilled, for example the data exclusivity period has expired. It should be noted that in case of centralised application, Article 82(1) of Regulation 726/2004 applies (see section 2.7) For National/DC/MR procedures, see section 2.7.

[26] Case C-104-13, ECJ 23/10/2014

[27] Case C-527/07, ECJ 18/06/2009

#### 5.3.1.2 “European reference medicinal product”

According to Article 10(1), third subparagraph of Directive 2001/83/EC a generic application can also be submitted in a Member State although the reference medicinal product has never been authorised in that Member State. In that case, a reference medicinal product in another Member State should be identified, so-called the European reference medicinal product.

In these cases, 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).

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 should 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 application submitted on the basis of Article 10 (see CMD(h) working document - information to be submitted by the Member State of the European reference medicinal product at http://www.hma.eu/uploads/media/ERP_information.pdf)

### 5.3.2 Particularities for application according to Article 10

Article 10 constitutes a single legal base for the submission of applications. The content of such applications must comply with the requirements set out therein.

#### 5.3.2.1 Application in accordance with paragraph 1 of Article 10 (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 medicinal 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 must 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. 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 would be necessary to submit the results of appropriate pre-clinical tests and clinical trials in accordance with the requirements of Article 10(3) (see section 5.3.5). To the extent that the active substance may be considered as a new active substance as defined in Annex III at the end of this Chapter, the applicant may consider the submission of an application in accordance with Article 8(3) of Directive 2001/83/EC.

The various immediate-release oral pharmaceutical forms are 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 on the investigation of bioequivalence' [28](see also annex I 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.

**‘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 taking into consideration 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

[28]http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2010/01/WC500070039.pdf

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, are considered to be 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, and which after mixing form different solutions to be administrated, as for example a macroemulsion and a microemulsion, 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 CHMP 'guidelines on the investigation of bioequivalence' available at http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2010/01/WC500070039.pdf

Article 10(2)b last sentence of Directive 2001/83/EC states: "[…]*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 appropriate detailed guidelines".*

Such exemptions from the need to demonstrate bioequivalence should be justified in module 1 of the dossier and in the clinical overviews.

Where bioequivalence cannot be demonstrated through bioavailability studies Article 10(3) requires that the results of appropriate pre-clinical tests or clinical trials will be provided.

#### 5.3.2.2 Application in accordance with paragraph 3 of Article 10 ("hybrid"medicinal product)

Article 10(3) of Directive 2001/83/EC 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.

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 II at the end of this Chapter.

#### 5.3.2.3 Application in accordance with paragraph 4 of Article 10 (" Similar biological medicinal product")

Article 10(4) of Directive 2001/83/EC requires that in the framework of an application under Article 10, 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 must not be provided. Guidance is available at the website of the EMA http://www.ema.europa.eu.

## 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 Union 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 must be provided in accordance with Article 8(3)(i), but it is not 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’.

A key principle of the *acquis* is that there must be a marketing authorisation for each medicinal product that is put on the EU market. Therefore, the fixed combination definition is limited to active substances contained in a same pharmaceutical form of administration, the so-called 'fixed-combination'. The combination of active substances, where active substances are included in separate pharmaceutical forms and presented in a combination pack cannot be considered as fixed combination.

In very exceptional circumstances, which must be considered on a case by case basis, the marketing of distinct medicinal products in the same package may be indispensable for public health reasons. Such reasons cannot be related to convenience or commercial purposes.

Marketing authorisations for medicinal products containing more than one active substance in a single pharmaceutical form can be granted on different legal basis. In case of an application on the basis of Article 10b of Directive 2001/83/EC the applicant does not have to provide scientific references relating to each individual active substance.

For impact on the global marketing authorisations as described in Article 6(1) of Directive 2001/83/EC see section 2.3.

Applications for fixed-combination medicinal products under Article 10b are conditioned to the fact that the individual substances have been the object of a marketing authorisation in the EEA via a Union or national procedure, even though it is not in the same Member State.

It follows from the wording of Article 10b as well as from Part II.5 of Annex I to Directive 2001/83/EC that a full dossier comprising all the information of modules 1 to 5 has to be provided in relation to the fixed-combination. The guideline on clinical development of fixed combination medicinal products[29] provides guidance on the clinical elements of such dossier. As with any application for a new medicinal product such a full dossier can be either a dossier based solely on own pre-clinical tests and/or clinical trials or on a mixed dossier taking into account data exclusivity rules.

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.

In case the dossier is only composed of references to published scientific literature, the legal basis would not be Article 10b of Directive 2001/83/EC, but possibly 10a if all requirements are fulfilled (see section 5.4).

## 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."

As Article 11 of Directive 2001/83/EC refers only to application on the basis of Article 10, an informed consent application does not have to cover all presentations/indications of the medicinal product with regard to which consent is given. Consent may be given to use the documentation contained in the file of the relevant medicinal product for a given presentation/indication provided that the application relies on that consent as regards all three modules of the dossier. It is a

29 DRAFT Guideline on clinical development of fixed combination medicinal products http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2015/05/WC500186840.pdf

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).

An informed consent application cannot cover more presentations or indications that the medicinal product with regard to which consent is given.

The concept of "European reference medicinal product" is laid down by Article 10 and is applicable in case of application in accordance with Article 10 (see section 5.3.1.2). It does not apply in the context of applications under Article 10c. In addition, it should be noted that an informed consent application is only possible if there is still a valid marketing authorisation to which consent is given.

Furthermore, informed consent applications need to respect the following:

- for a central marketing authorisation the informed consent application has to follow the centralised procedure;
- for a national marketing authorisation the informed consent application has to follow a national procedure (either pure national or MRP or DCP). A prerequisite is, that the marketing authorisation is granted in this/these MS.

It follows that an application under Article 10c can only be submitted to a Member State where the medicinal product with regard to which consent is given is authorised. 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 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, but the marketing authorisation holder is to take appropriate steps having regard to the requirement of permanent access to the file.

# 6. DATA EXCLUSIVITY AND MARKET PROTECTION

## 6.1 Data exclusivity and market protection period for reference medicinal products

### 6.1.1 Principles on data exclusivity and market protection of 'reference medicinal product'

The medicinal product, once authorised on the basis of Article 10, can however only be placed on the market 10 or 11 years after the authorisation of the reference medicinal product, depending on the protection period applicable for the reference medicinal product. The protection period in the concerned Member State must also be taken into consideration before placing the medicinal product on its market.

It should be noted, however, that these periods of protection will only apply to applications for reference medicinal products submitted once the provisions of Directive 2004/27/EC and Regulation (EC) No 726/2004 start to apply; see section 6.1.2.

### 6.1.2 Data exclusivity and market protection 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 is not 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 Union.

According to the second subparagraph of Article 10(1), generic products authorised in this way must 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 protection” 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.

### 6.1.3 Data exclusivity and market protection 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 (except in Croatia where the new periods of protection apply for all products) 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, Bulgaria, Romania 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.

The data exclusivity rules applicable before adoption of the current legislation allowed the coexistence of periods of six and ten years of protection in different Member States for the same product. In other words, the generic of a reference product was allowed access to the market at different points in time in different Member States.
The new harmonised data exclusivity and market protection periods in Article 10(1) of Directive 2001/83/EC do not apply retroactively. It follows that:

- An application in accordance with Article 10 of Directive 2001/83/EC can only be processed via the centralised procedure after expiry of the period of protection of the Member State where the reference medicinal product was authorised (e.g, if the reference product is authorised in a Member State where a ten-year period of protection applies, the application under the centralised procedure may only be submitted after the 10 year period);

- An application in accordance with Article 10 of Directive 2001/83/EC can only be submitted under the decentralised/mutual recognition procedure after expiry of the period of protection of the reference medicinal product in the Reference Member State and the Concerned Member States. It follows that, if the period of protection in the Reference Member State and in three Concerned Member States is six years, a decentralised procedure to obtain a marketing authorisation in accordance with Article 10 of Directive 2001/83/EC is only possible regarding these four Member States. A mutual recognition procedure can be triggered *a posteriori* to cover other Concerned Member States once the protection period therein expires also.

### 6.1.4 Relevant periods of protection in the case of the reference medicinal product/"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 exclusivity in the Member State where it is authorised.

A medicinal product could be used as reference medicinal product if three cumulative conditions are met:

- The reference medicinal product is (or has been) authorised in the EU (through a centralised or national procedure);

- The reference medicinal product is or has been authorised in accordance with the pharmaceutical *acquis*,

- The relevant data exclusivity period has expired.

Therefore, the starting date for calculating the data exclusivity period is the date of authorisation in accordance with the pharmaceutical *acquis* of the reference medicinal product in the territory of the European Union. The data exclusivity period must have expired in the Member States concerned on the date at which the application for the generic medicinal product is submitted (see in that respect section 6.1.2 and 6.1.3).

### 6.1.5. 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 are considered to be part of the same marketing authorisation for the purposes of applying the rules on data exclusivity and marketing protection.

This means that for a reference medicinal product, the start of the data exclusivity and market protection periods is the date when the first marketing authorisation was granted in the Union in accordance with the pharmaceutical *acquis*. 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 exclusivity and market protection 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, national or centralised procedure (see section 2.3), irrespective of the legal basis and under a different name[30].

This ten-year period can only be prolonged in the case of certain new indications, as described in section 6.2.

### 6.1.6 Reliance on pre-clinical and clinical data contained in the dossier of a reference medicinal product under data exclusivity

During the period of data exclusivity of a medicinal product, the data contained in the pre-clinical and clinical file of that product and obtained through access to documents or freedom of information legislation within the EU or in third countries, cannot be

30 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.

relied on by other applicants or the authorities in a subsequent application to ascertain the safety and efficacy of other products. As long as a product authorised in the EU is under data exclusivity, the reliance on published or unpublished pre-clinical and clinical data contained in the dossier of that product within the EU or in third countries by the competent authorities to grant a marketing authorisation would lead to a circumvention of the data exclusivity rules. Therefore, such application cannot be accepted.

## 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 has been granted. 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) applies 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.

Guidance on elements required to support the significant benefit in comparison with existing therapies of a new therapeutic indication in order to benefit from an extended (11 years) marketing protection period is available at http://ec.europa.eu/health/files/eudralex/vol-2/c/guideline_14-11-2007_en.pdf

## 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 will be granted, provided that significant pre-clinical or clinical studies were carried out in relation to the new indication.”

An applicant making reference to Article 10(5) must provide justification regarding the existence of a new indication, of a well-established substance and of significant pre-clinical or clinical studies. The new indication can be included either in the existing marketing authorisation via a type II variation or submitted with an application for a new marketing authorisation.

A well-established substance is an active substance included in the authorised 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.

The data exclusivity period is non-cumulative to other periods of protection: it refers exclusively to the data concerning the new indications. Therefore, the concerned medicinal product could be used as reference medicinal product with the exclusion of the indication(s) which is covered by this data exclusivity if the medicinal product fulfils the general requirements of reference medicinal product.

Such data exclusivity period is an incentive for development of new indications whilst data protection would not otherwise apply.

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.

Guidance on a new therapeutic indication for a well established substance is available at http://ec.europa.eu/health/files/eudralex/vol-2/c/10%20_5_%20guideline_11-2007_en.pdf

## 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.

For further guidance please refer to the Guideline on changing the classification for the supply of a medicinal product for human use, available at http://ec.europa.eu/health/files/eudralex/vol-2/c/switchguide_160106_en.pdf

# 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 changes to the product information or changes to the technical dossier submitted by the marketing authorisation holder. The procedures for the approval of such amendments have been set out in Commission Regulation (EC) No 1234/2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products.

Commission Guidelines on the details of the various categories of variations, on the operation of the procedures laid down in Chapters II, IIa, III and IV of Commission Regulation (EC) No 1234/2008 of 24 November 2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products and on the documentation to be submitted pursuant to those procedures provide additional information about procedures to amend marketing authorisations as well as the classification of variations.

## 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.

Where the marketing authorisation holder takes urgent safety restriction, he must forthwith inform the relevant national competent authority or the EMA (in the case of authorisations granted by the member States or the Union, respectively). If the national competent authority/EMA has not raised any objections within 24 hours of the receipt of that information, the urgent safety restriction is deemed accepted. The corresponding variation application reflecting the urgent safety restriction must be submitted immediately to the national competent authority/EMA 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 must be obliged to implement the urgent safety restrictions. The corresponding variation application reflecting the urgent safety restriction, must be submitted immediately to the national competent authority/EMA 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 must 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.[31].

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.
- Harmonising the data for a given plasma/antigen present in several medicinal products.
- Ensuring consistency throughout the European Union.

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 Union legislation, issued by the EMA. This certificate is valid throughout the European Union.

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 EMA website[32].

[31] 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).

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

# ANNEX I DEFINITION OF A NEW ACTIVE SUBSTANCE

A new chemical, biological or radiopharmaceutical active substance includes:

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

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

- a biological substance previously authorised in a medicinal product in the European Union, but differing significantly in properties with regard to safety and/or efficacy which is due to differences in one or a combination of the following: in molecular structure, nature of the source material or manufacturing process;

- a radiopharmaceutical substance which is a radionuclide, or a ligand not previously authorised in 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 II 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 significantly 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)<br><br>i) new route of administration<br>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<br>same route/ pharmaceutical form and posology | Bioavailability (cf. guideline) |
| d) | suprabioavailable products<br>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. |