

Commission communication on the Community marketing authorisation procedures for medicinal products

(98/C 229/03)

INTRODUCTION

As part of the overall strategy for building a single market for pharmaceuticals, a series of new procedures for granting marketing authorisations were introduced. On 1 January 1995, two new procedures for the authorisation of medicinal products for human and veterinary use came into effect. Council Regulation (EEC) No 2309/93 laid down procedures for a Community authorisation of medicinal products for human and veterinary use (i.e. the 'centralised' procedure) and established a European Agency for the Evaluation of Medicinal Products (EMA)⁽¹⁾. In addition, three Directives⁽²⁾ amended the existing Community pharmaceutical legislation to create a new 'mutual recognition' procedure for the authorisation of human and veterinary⁽³⁾ medicinal products based on the principle of mutual recognition of national authorisations, with binding Community arbitration in the event of disagreement between Member States.

The three year period of transition for the mutual recognition procedure which was foreseen in 1995 ended on 1 January 1998. Thereafter, access to the Community market follows either the centralised or mutual recognition route.

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

Now that the transition period for mutual recognition is over, and in order to ensure the continued successful operation of the new Community marketing authorisation systems, examination of a number of further issues is due. Therefore the Commission wishes to clarify its position on certain aspects relating to the implementation of the centralised and mutual recognition procedures.

A. SCOPE OF APPLICATION OF COUNCIL REGULATION (EEC) No 2309/93

According to Article 3(1) of Regulation (EEC) No 2309/93, no medicinal product referred to in Part A of the Annex may be placed on the market within the Community unless a marketing authorisation has been granted by the Community in accordance with the provisions of this Regulation (obligatory use of the centralised procedure).

Article 3(2) of this Regulation provides for the possibility that the person responsible for placing on the market a medicinal product referred to in Part B of the Annex may request that the authorisation to place the medicinal product on the market be granted by the Community in accordance with the provisions of this Regulation (voluntary use of the centralised procedure).

In order to be able to determine the scope of application of the centralised procedure, it is essential to have clear criteria to determine whether a medicinal product falls under the category of products for which a Community marketing authorisation is obligatory ('List A products') or under the category for which the centralised procedure is optional ('List B products').

1. Part A of the Annex — biotechnology derived products

The centralised procedure is mandatory for medicinal products derived from the biotechnological processes described in Part A of the Annex to Regulation (EEC) No 2309/93. Initially biotechnology was seen as an opportunity to develop new medicinal products which would otherwise not be possible. Now, however, biotechnology techniques can also be incorporated into the manufacture of existing medicinal products in order to enhance yields, improve quality or reduce environmental impact.

Part A of the Annex to the abovementioned Regulation covers medicinal products developed by means of the following biotechnological processes:

- recombinant DNA technology,
- controlled expression of genes coded for biologically active proteins in prokaryotes and eukaryotes, including transformed mammalian cells,

⁽¹⁾ OJ L 214, 24.8.1993, p. 1.

⁽²⁾ Council Directives 93/39/EEC, 93/40/EEC and 93/41/EEC, OJ L 214, 24.8.1993, pp. 22, 31 and 40.

⁽³⁾ For the readability and the clarity of the Communication, only the references to Directives concerning medicinal products for human use will be made in the text; the references to Directives regarding veterinary products will be given in footnotes.

— hybridoma and monoclonal antibody methods.

In Commission communication 94/C 82/4 (⁴), some practical examples of medicinal products covered by Part A had already been given:

- products intended for gene therapy,
- vaccines from strains developed by means of recombinant DNA technology, including gene deletion,
- any medicinal product for which a monoclonal antibody is used at any stage in the manufacturing process.

(a) *Medicinal product developed by means of recombinant DNA technology*

Since questions continue to arise in respect of the meaning of 'medicinal product developed by means of recombinant DNA technology', the Commission wishes to clarify its interpretation of these terms and thus make precise the scope of part A of the Annex to Regulation (EEC) No 2309/93.

As a preliminary remark, it has to be kept in mind that the main aims of the creation of the centralised procedure were the improvement of the functioning of the Single Market as far as medicinal products are concerned, the avoidance of duplication of scientific evaluation and the reduction of administrative burden and as a consequence, the promotion of the European pharmaceutical industry. Medicinal products developed by means of biotechnological processes were considered to be an appropriate and promising starting point for the centralised procedure. It is also important to stress that, according to Community pharmaceutical legislation, the quality, safety and efficacy of any medicinal product have to be equally ensured through the centralised and the decentralised procedures, the protection of public health being the ultimate aim of Community legislation in this matter.

To ensure an efficient and smooth functioning of these procedures, it is particularly important to determine which categories of substances developed by means of recombinant DNA technology represent, when used as constituents of medicinal products, an essential element of a medicinal product to be considered in the choice of the procedure to be followed.

The Commission considers that the definition in the European Pharmacopoeia monograph of products of recombinant DNA technology (monograph No 1997,784), which is already part of Community pharmaceutical legislation due to references in Directive 75/318/EEC (⁵), has to be applied in this context.

Thus any medicinal product in the composition of which there is a proteinaceous constituent obtained by means of recombinant DNA technology, falls under the scope of Part A of Regulation (EEC) No 2309/93, irrespective of whether or not the constituent is an active substance of the medicinal product.

(b) *Products intended for gene therapy*

Gene therapy corresponds to a set of processes aimed at the transfer of a gene, basically a piece of DNA, to human tissues and its subsequent expression *in vivo*. The systems for therapeutic gene transfer and expression involve a therapeutic gene and an expression system that is contained in a delivery system, known as a vector. The delivery system can use either viral vectors (retroviral or adenoviral vectors for example) as well as non-viral vectors (such as cationic liposomes or molecular conjugates). The vectors themselves, regardless of their physical nature, have to be considered as part of the 'product intended for gene therapy' which is a medicinal product in the meaning of the Community pharmaceutical legislation. Indeed the vectors represent an intrinsic part of this product endowed with a therapeutic effect.

(c) *Cell therapy*

Cell therapy consists of the administration to humans of autologous living cells (i.e., emanating from the patient himself), or allogeneic cells (therefore coming from another human being) or even xenogeneic cells (coming from an animal). To some extent, these selected cells may have been manipulated or processed to change their biological characteristics, prior to their administration. This definition includes the expansion and activation of autologous

(⁴) OJ C 82, 19.3.1994, p. 4.

(⁵) OJ L 147, 9.6.1975, p. 1, Directive as last amended by Directive 93/39/EEC. For veterinary medicinal products: Directive 81/852/EEC (OJ L 317, 6.11.1981, p. 16), as last amended by Directive 93/40/EEC.

cell populations *ex vivo* (adoptive immunotherapy, for example) and the use of allogeneic or xenogeneic cells contained in microcapsules for protein drug replacement.

Cell therapy products have to be considered as medicinal products needing a marketing authorisation if they are industrially manufactured. If cell therapy products are the result of any biotechnology process referred to in Part A of the Annex to Regulation (EEC) No 2309/93, they will have to be authorised by the Community.

2. Part B of the Annex — high technology products and products containing new active substances

The centralised procedure is optional for the medicinal products referred to in Part B of the same Annex. Despite the optional nature of the procedure in such a context, its legal effects and in particular the legal characteristics of the Community marketing authorisation issued are developed to full effect. This is why it has to be stressed that, once granted with a Community marketing authorisation based on Part B of the Annex, a medicinal product can no longer be the subject of a subsequent (or previous) national marketing authorisation.

(a) *Conditions of implementation of Article 4(3)(8a) of Directive 65/65/EEC* ⁽⁶⁾

This Article grants certain derogations to applicants relating to the need to provide the results of pharmacological and toxicological tests or the results of clinical trials. An applicant can make use of these derogations in the centralised procedure only if the specific conditions set out in the relevant provisions are fully complied with.

1. Abridged applications

The text of Article 4(3)(8a)(i) and (iii) implies that the abridged application can only be lodged with the authority that evaluated and authorised

the original product as this authority holds the dossier on the medicinal product which is essentially similar to that of the second applicant. This means in the context of the centralised procedure that abridged applications can only be lodged with the EMEA.

— In the case of Article 4(3)(8a)(i) ('informed consent'), the product to which essential similarity ⁽⁷⁾ is claimed has to be centrally authorised and essential similarity has to be demonstrated by the applicant. Moreover, the consent of the marketing authorisation holder of the original product has to cover the use of the references being used for examining the application in question.

— In the case of Article 4(3)(8a)(iii) ('generic application'), the product to which essential similarity is claimed has to be authorised by the Community and essential similarity has to be demonstrated by the applicant. Moreover, the product to which essential similarity is claimed has to be marketed in the Community for not less than 10 years.

As stated before, for an abridged application concerning a medicinal product essentially similar to one already covered by a Community authorisation, the centralised route must be used in all cases. Therefore generic applications referring to Community marketing authorisation dossier for medicinal products which are essentially similar to Community authorised products falling under the scope of Part B of the Annex to Regulation (EEC) No 2309/93, must follow the centralised procedure.

2. Bibliographical applications

In the case of Article 4(3)(8a)(ii) ('bibliographical application') the well established use of the constituent(s) of the medicinal product has to be demonstrated and the applicant has to provide the EMEA with a complete set of detailed

⁽⁶⁾ OJ 22, 9.2.1965, p. 369/5, Directive as last amended by Directive 93/39/EEC. For veterinary medicinal products any reference to this Article has to be understood: Article 5(3) (10a)(i), (ii) and (iii) of Directive 81/851/EEC (OJ L 317, 6.11.1981, p. 1), Directive as last amended by Directive 93/40/EEC.

⁽⁷⁾ The exact meaning of the term 'essential similarity', as described in of the 'Notice to Applicants' (Volume 2A and Volume 6A of 'The rules governing medicinal products in the European Union') is: 'the same qualitative and quantitative composition in terms of active principles, and the pharmaceutical form is the same; and where necessary, appropriate bioavailability studies have been carried out; by extension, the concept of essentially similar also applies to different oral forms (e.g. tablets and capsules) with the same active substance for immediate release'.

references to published scientific literature presented in accordance with Directive 75/318/EEC⁽⁸⁾. It also has to be stressed that all requirements laid down in this Directive have to be addressed in the application.

(b) *Medicinal products containing the same active substance(s) as a Community authorised product*

In order to maintain coherence and transparency, and to preserve the unity of the Community Single Market, where the same marketing authorisation holder wishes to place on the market another medicinal product with the active substance which is already the subject of a Community authorisation, the Commission considers that the centralised procedure should be used, in particular when the therapeutic indication is within the third level of the ATC code. In cases where the applicant does not apply for a Community authorisation as described above, the therapeutic indication(s) authorised by the Community should not be part of the national authorisation. In such a context, the Commission will consider the benefit of referring the case to the EMEA through an arbitration procedure in accordance with Articles 11 or 12 of Directive 75/319/EEC⁽⁹⁾ in order to preserve the abovementioned coherence and transparency.

B. INTRODUCTION OF A BIOTECHNOLOGY MANUFACTURING STEP AFTER THE GRANTING OF A MARKETING AUTHORISATION

The new Community marketing authorisation system foresees that the centralised procedure has to be used for applications for medicinal products developed by biotechnology. However, the position of medicinal products already on the market and authorised by Member States, where one or more biotechnology steps are introduced into the manufacturing process after the marketing authorisation has been granted needs to be clarified. Hundreds of products are concerned by such a modification.

These medicinal products have, by virtue of the granting of a marketing authorisation, demonstrated quality, safety and efficacy and are being used by patients, in many cases for a long time.

According to Community pharmaceutical legislation, the marketing authorisation holder shall inform the competent authorities of any change in the manufacturing process. This also includes the introduction of a biotechnology manufacturing step. If an active substance from the same supplier is common to more than one marketing authorisation, combining these cases will avoid unnecessary duplication of work.

The Commission considers that the appropriate rules to deal with these cases are the following:

1. **The constituent concerned by the introduction of recombinant DNA technology is of a proteinaceous nature**

According to Regulation (EEC) No 2309/93 and the interpretation already mentioned (see point A.1) of 'medicinal product developed by means of recombinant DNA technology', a medicinal product will fall under Part A of the Annex to this Regulation if the constituent concerned by the introduction of this recombinant DNA technology step is of a proteinaceous nature. Therefore this product has to be authorised through the centralised procedure.

2. **Other cases**

— The medicinal products are not covered by Commission Regulations (EC) No 541/95 or (EC) No 542/95⁽¹⁰⁾ (i.e. products that have not been subject to any Community procedure).

For products not covered by Commission Regulations (EC) No 541/95 or (EC) No 542/95, the marketing authorisation holders should just notify the change to the competent authorities of the concerned Member States if they can provide these authorities with a certificate of suitability from the European Pharmacopoeia establishing that the constituent concerned by the introduction of the biotechnology step still complies with monographs from the European Pharmacopoeia. If this constituent does not comply with monographs and a certificate of suitability is therefore not available, the marketing authorisation holder should lodge an application for a variation to the original marketing authorisation according to the nationally applicable rules.

However when, in the case of a constituent described in the European Pharmacopoeia, the introduction of the biotechnology step is liable to leave

⁽⁸⁾ For veterinary medicinal products: Directive 81/852/EEC.

⁽⁹⁾ OJ L 147, 9.6.1975, p. 13, Directive as last amended by Directive 93/39/EEC. For veterinary medicinal products any reference to these Articles has to be understood: Articles 19 or 20 of Directive 81/851/EEC.

⁽¹⁰⁾ OJ L 55, 11.3.1995, pp. 7 and 15.

impurities not controlled in a monograph from the European Pharmacopoeia, these impurities must be declared and a suitable test procedure must be described. If a certificate of suitability from the European Pharmacopoeia is available which specifies the supplementary test(s), the notification procedure should be followed.

- The medicinal products are covered by Regulation (EC) No 541/95 (i.e. products covered by marketing authorisations which have undergone a Community procedure) or by Regulation (EC) No 542/95 (i.e. products covered by Community marketing authorisation).

For products covered by Regulations (EC) No 541/95 and (EC) No 542/95 which fall under the scope of Regulation (EEC) NO 2309/93, the marketing authorisation holders must lodge an application with the appropriate competent authority (authorities of the concerned Member States or EMEA). Where the marketing authorisation holder can demonstrate that the specified conditions of a Type I variation are met and in particular can provide a certificate of suitability from the European Pharmacopoeia establishing that the constituent concerned by the introduction of the biotechnology step still complies with a monograph from the European Pharmacopoeia, a Type I variation procedure within the meaning of the abovementioned Commission Regulations will be accepted. If these conditions are not met, the marketing authorisation holder has to lodge an application for a Type II variation procedure within the meaning of the abovementioned Commission Regulations.

C. NAME OF A MEDICINAL PRODUCT

Member States grant a marketing authorisation to a single authorisation holder who is responsible for placing the medicinal product on the market. The marketing authorisation includes, when available, the INN (International Non-Proprietary Name) and when branded, a single invented name (brand name). Only one brand name should normally be approved per marketing authorisation granted.

This also applies in the case of a Community authorisation for which there is a single summary of product characteristics (SPC), a single leaflet and a single label approved⁽¹¹⁾. It is advisable for applicants using the

centralised procedure to identify at an early stage, and before lodging the application, one brand name which can be used throughout the Community while keeping fall-back options (brand name(s)) in reserve.

However, in exceptional cases, in particular where the proposed brand name has been cancelled, opposed or objected to under trade mark law in a Member State, the Commission will address the issue in order not to disadvantage patients and their access to the concerned medicinal product in that Member State. If sufficient evidence is given by the marketing authorisation holder that, in spite of all its efforts, the chosen or foreseen trade mark cannot be used in a Member State, the Commission will — exceptionally — authorise the use of a different trade mark in that Member State. Should a derogation be granted, it will affect neither the legal obligations of the marketing authorisation holder, nor the validity of the marketing authorisation throughout the Community and shall not be used to introduce any partitioning of the European market, i.e. to restrict or prevent the free movement of the concerned medicinal product.

D. PARALLEL DISTRIBUTION OF COMMUNITY AUTHORISED MEDICINES

A Community marketing authorisation is, by definition, valid in all Member States. Therefore products put on the market of one Member State can be marketed in any other part of the Community by a distributor, independent of the marketing authorisation holder ('parallel distributor'). In such circumstances, the marketing authorisation holder remains unchanged and retains, of course, the responsibility incumbent on him/her under Community law.

In this context, which is very different from the parallel importation of medicines authorised nationally because of differences which can exist between the marketing authorisation granted by the Member State of origin and the one granted by the Member State of destination, the only changes to the product which can be required in order to allow parallel distribution are changes in the language of the labelling and package leaflet to comply with Article 4(2) and Article 8 of Directive 92/27/EEC⁽¹²⁾, and/or, more rarely, changes in the size of the package (repackaging).

⁽¹¹⁾ For medicinal products for human use: see answer given by Mr Bangemann on behalf of the Commission to a Parliamentary written question from Mr K. Collins (written question No E-2553/96; OJ C 83, 14.3.1997, p. 26).

⁽¹²⁾ For veterinary medicinal products: Article 47 and Article 48(1) of Directive 81/851/EEC.

In the context of medicinal products authorised by the Community, it must be remembered that, by definition, the Community marketing authorisation encompasses all linguistic versions of the labelling and package leaflet and all available, authorised pack sizes.

In any case, the original condition of the product inside the packaging must not be directly or indirectly affected and any changes in the size of the package must be duly justified, i.e. it must be demonstrated that they are strictly necessary to market the product distributed in parallel in the Member State of destination in the same conditions as the product distributed by the marketing authorisation holder.

Although no further authorisation is required, the Community (in practice the EMEA) and national authorities (authorities of the Member States in which the medicinal product will be distributed in parallel) shall be informed that such parallel distribution will take place in order to enable the EMEA to check compliance with the terms of the Community marketing authorisation and the national authorities to monitor the market (batch identification, pharmacovigilance, etc.) and to carry out post-marketing surveillance.

1. Information to be submitted by the parallel distributor

The parallel distributor must send to the competent authorities the following information:

- (a) the (brand and INN) name(s) of the medicine(s) concerned and its/their authorisation number(s) in the Community register of medicinal products;
- (b) name or business name of the parallel distributor;
- (c) one or more mock-ups of the medicines as they will be marketed in the Member State of destination, including the package leaflets;
- (d) a copy of the wholesale distribution authorisation within the meaning of Article 3 of Directive 92/25/EEC ⁽¹³⁾ (if not already provided to the authorities) and/or a manufacturing authorisation within

the meaning of Article 16 of Directive 75/319/EEC ⁽¹⁴⁾ (if not already provided to the authorities) if there is a change of pack size in conformity with the already authorised pack sizes;

- (e) as the case may be, a comprehensive justification if there is a change of pack size in conformity with the already authorised pack sizes.

2. Procedure

In the Commission's view, any objection from the competent authority shall be notified within 30 days and shall state in detail the reasons on which it is based. Obviously, a parallel distributor has to fulfil, as a wholesale distributor, the obligations incumbent on him under the terms of Articles 5 and 8 of Directive 92/25/EEC ⁽¹⁵⁾.

According to the current case-law of the Court of Justice of the European Communities, the trade mark owner must be given advance notice by the parallel distributor that the repackaged product is to be put on sale. The owner may also require the parallel distributor to supply him with a specimen of the repackaged product before it goes on sale, to enable him to check that the presentation after repackaging is not such as to damage the reputation of the trade mark.

E. MUTUAL RECOGNITION PROCEDURE

Whilst safeguarding the protection of public health, the Community procedure of mutual recognition in the new system has as one of its main objectives the harmonisation of national marketing authorisations and the avoidance of duplicative evaluation. In addition, it introduces the possibility of Community referral (the arbitration procedure) in the event of disagreement between Member States. Regardless of the basis for harmonisation (e.g. mutual recognition at the request of the company, or by the Member State, or arising from divergent decisions between Member States or in cases of Community interest), once this harmonisation has been achieved, it is maintained by further procedures relating to variations and pharmacovigilance.

⁽¹³⁾ OJ L 113, 30.4.1992, p. 1; for veterinary medicinal products: Article 50a of Directive 81/851/EEC.

⁽¹⁴⁾ For veterinary medicinal products: Article 24 of Directive 81/851/EEC.

⁽¹⁵⁾ For veterinary medicinal products: Article 50a and Article 50b of Directive 81/851/EEC.

1. Legal provisions

Council Directive (EEC) No 93/39⁽¹⁶⁾ introduced provisions into Community pharmaceutical legislation which determine the scope of application and the application modalities of the mutual recognition procedure. The provisions which are most relevant for determining the scope and the operation of the mutual recognition procedure are:

- Article 4(11) of Council Directive 65/65/EEC⁽¹⁷⁾ which imposes an obligation to provide information to the competent authority. (Even though this provision is not directly linked to mutual recognition, it has a particularly important role for the mutual recognition procedure),
- applications for products already authorised in another Member State, i.e. mutual recognition at the request of an applicant (Article 9 of Directive 75/319/EEC)⁽¹⁸⁾ and obligatory mutual recognition by the competent authorities of the Member States (Article 7a of Directive 65/65/EEC)⁽¹⁹⁾,
- simultaneous applications for products as yet not authorised in a Member State (Article 7(2) of Directive 65/65/EEC)⁽²⁰⁾.

2. End of the transition period

When adopting these provisions, a transition period of three years (1995 to 1998) was foreseen, so that both Member States and industry could gradually become familiar with the operation of this new system before it became obligatory. Thus applicants wishing to access more than one Member State market had a choice between the mutual recognition procedure or independent national applications.

This transition period ended on 31 December 1997. Therefore, the method of access (other than by the centralised procedure) to the Community market is now by mutual recognition. This means that from now on, any medicinal product which is to be placed on the market of more than one other Member State has to be processed through the mutual recognition procedure only.

As a consequence, from 1 January 1998, any application⁽²¹⁾ regarding the authorisation of a medicinal product which is already the subject of an existing marketing authorisation in another Member State will have to follow the Community mutual recognition procedure, thus guaranteeing uniform marketing authorisation decisions throughout the single European market.

In such a context, it is worth mentioning the particular case where an applicant withdraws an application regarding a medicinal product in one Member State during a mutual recognition procedure in order to avoid an arbitration (according to Article 10 of Directive 75/319/EEC⁽²²⁾) being triggered by that Member State. The transitional period being over, this applicant no longer has any possibility of accessing the market of the Member State where the application has been withdrawn with the concerned product, an independent national marketing authorisation for a product already authorised in another Member State being illegal.

3. Application of Article 4(3)(11) of Directive 65/65/EEC in the context of the mutual recognition procedure (documents to be submitted by the applicant)

In order to place a medicinal product on the market, an applicant must submit an application for a marketing authorisation to the competent authorities of each of the Member States where the product is to be marketed. The provisions of Directive 65/65/EEC apply in respect of the data to be supplied to demonstrate the quality, safety and efficacy of the product and the administrative data. Further, to ensure the availability of the necessary information upon which mutual recognition is based, applicants are required to comply, at the time of submission and with regular updates, with the provisions of Article 4(3)(11) of Directive 65/65/EEC.

⁽¹⁶⁾ For veterinary medicinal products: Directive 93/40/EEC.

⁽¹⁷⁾ For veterinary medicinal products any reference to this Article has to be understood: Article 5(13) of Directive 81/851/EEC.

⁽¹⁸⁾ For veterinary medicinal products any reference to this Article has to be understood: Article 17 of Directive 81/851/EEC.

⁽¹⁹⁾ For veterinary medicinal products any reference to this Article has to be understood: Article 8a of Directive 81/851/EEC.

⁽²⁰⁾ For veterinary medicinal products any reference to this Article has to be understood: Article 8(2) of Directive 81/851/EEC.

⁽²¹⁾ To be more precise, any application validated from 1 January 1998.

⁽²²⁾ For veterinary medicinal products any reference to this Article has to be understood: Article 18(13) of Directive 81/851/EEC.

This Article lists the particulars and documents that have to accompany any application for a marketing authorisation (be it an application for a central authorisation or for a national authorisation or for the mutual recognition of a national authorisation). However, this provision has a particularly important role for the mutual recognition procedure. Its point 11 imposes an obligation on any applicant to provide the following information:

- copies of any authorisation obtained in another Member State or in a third country to place the relevant medicinal product on the market, together with a list of those Member States in which an application for authorisation submitted in accordance with the Directive 65/65/EEC is under examination,
- copies of the summary of the product characteristics proposed by the applicant or approved by the competent authorities of the Member State,
- copies of the package leaflet proposed in accordance with Article 6 of Directive 92/27/EEC or approved by the competent authorities of a Member State in accordance with Article 10 of the same Directive ⁽²³⁾,
- details of any decision to refuse authorisation, whether in the Community or in a third country, and the reasons for such decision.

According to Article 4(3)(11) the applicant shall submit 'copies of any authorisation obtained'. Legislation does not require the applicant to provide information on authorisations which have been granted to other persons. However, in order to avoid circumvention of this provision, applicants belonging to the same mother company or group of companies have to be taken as one entity. Applicants which, without belonging to the same mother company or group of companies, have concluded agreements (e.g. 'licensees') or which exercise concerted practices concerning the placing on the market of the relevant medicinal product in different Member States, also have to be taken as one for the purpose of Article 4(3)(11).

In such particular context, criteria to determine the meaning of the terms 'the relevant medicinal product'

are needed. The Commission considers that this wording has to be taken to encompass any medicinal product which has the same qualitative and quantitative composition in active substances (i.e. the same strength) and the same pharmaceutical form as the product for which a marketing authorisation is sought.

However, applicants are strongly advised to forward to the competent authority — pursuant to Article 4(3)(11) of Directive 65/65/EEC — all other available information on similar or related marketing authorisations they have been granted or applications they have lodged in other Member States or in third countries. The transmission of such information will help the competent authority to establish that legislative requirements are not circumvented. The transmission of such information to the competent authority is therefore also in the applicant's own interest and it will contribute to a smooth and swift procedure.

4. Mutual recognition procedure triggered by the applicant (Article 9 of Directive 75/319/EEC)

(a) *Normal procedure*

Article 9 of Directive 75/319/EEC refers to the mutual recognition by Member States ('concerned Member States') of a national marketing authorisation previously granted by a first Member State ('reference Member State'), the applicant having launched this procedure when applying in the concerned Member States. It explicitly covers only cases in which a marketing authorisation has already been issued in another Member State. Cases in which identical applications are pending in different Member States and in which an earlier authorisation was not yet granted in another Member State are not covered by this Article.

In accordance with the provisions of Article 9, the applicant must fulfil the following conditions:

- the application for marketing authorisation must conform to the requirements of the pharmaceutical legislation, i.e. be a valid application and be accompanied, as appropriate, by the information and particulars referred to in Articles 4, 4a and 4b of Directive 65/65/EEC,
- the applicant must certify that the dossier submitted is identical to that accepted by the first Member State and he shall certify that the summary of the product characteristics proposed

⁽²³⁾ For veterinary medicinal products: Article 48 of Directive 81/851/EEC.

by him is identical to that accepted by the first Member State. Moreover he shall certify that all the dossiers filed as part of the procedure are identical.

Where an applicant fulfils these conditions the first marketing authorisation has to be recognised, in particular the SPC as approved by the first Member State. In cases where a Member State cannot recognise the marketing authorisation of the first Member State, then the matter is referred for arbitration (Article 10 of Directive 75/319/EEC) ⁽²⁴⁾.

(b) *Identical SPC and identical dossiers*

Article 9 requires explicitly that the 'summary of the product characteristics proposed by the applicant in accordance with Article 4a of Directive 65/65/EEC is identical to that accepted by the first Member State'. This provision states clearly that the SPCs of medicinal products undergoing the mutual recognition procedure have to be identical. The only parts of the SPC which need not be identical are:

- the 'name of the medicinal product' ⁽²⁵⁾ (because the name constitutes a formal and not a substantive element of the identity of a product), and
- the 'name of the marketing authorisation holder' (because applicants belonging to the same mother company or group of companies and applicants having concluded agreements or exercising concerted practices concerning the placing on the market of the relevant medicinal product have to be taken as one entity).

Applicants should be aware however that normally an identical name should be chosen for an identical product, unless there are compelling reasons not to do so.

According to Article 9, the applicant for mutual recognition 'shall testify that the dossier is identical

to that accepted by the first Member State, or shall identify any additions or amendments it may contain'. Identical products with an identical SPC should be based on identical dossiers because any variation introduced between the granting of the first marketing authorisation and an application for mutual recognition should at least have been notified to the competent authority and should already be taken up in the existing dossier for the product. In order to make sure that a full harmonisation is achieved in the mutual recognition procedure, legislation explicitly addresses this issue and asks the applicant to identify any need for updating the dossier on the occasion of a planned mutual recognition.

(c) *Content of the dossier*

The fact that the applicant for mutual recognition is explicitly required by legislation to submit an application together with all relevant information and particulars illustrates a general principle of the mutual recognition procedure for medicinal products: 'every concerned Member State shall have a complete dossier at its disposal'. A situation in which just one Member State has the complete dossier while other concerned Member States merely rely on the dossier in another Member State, is therefore not the situation envisaged by legislation. This fact has, as will be addressed below, important repercussions particularly for the mutual recognition of generic medicines.

As previously underlined, the holder of the authorisation shall submit — together with the application for mutual recognition — all the information and particulars referred to in Articles 4 and 4a of Directive 65/65/EEC.

Article 4(3)(8a) grants certain derogations to applicants concerning the need to provide the results of pharmacological and toxicological tests or the results of clinical trials. According to the principle established above that 'every concerned Member State should have a complete dossier at its disposal', an applicant may make use of these derogations in the mutual recognition process only if the specific conditions outlined in Article 4(3)(8a) ⁽²⁶⁾ are also met in the Member State(s) in which mutual recog-

⁽²⁴⁾ For veterinary medicinal products any reference to this Article has to be understood: Article 18 of Directive 81/851/EEC.

⁽²⁵⁾ At the end of the mutual recognition procedure, there will be only one brand name approved per marketing authorisation granted (national marketing authorisations) which is consistent with the current provisions of Community law as underlined under point C.

⁽²⁶⁾ It has to be pointed out that these specific conditions have remained unchanged in spite of the setting out of the mutual recognition procedure (and of the centralised one).

dition is applied for (the concerned Member State(s)). This means specifically:

— In the case of Article 4(3)(8a)(i) ('informed consent'), the product to which essential similarity is claimed has to be authorised both in the reference and the concerned Member State(s) and essential similarity has to be demonstrated by the applicant in all these Member States (except for cases in which the 'original product' has already undergone mutual recognition in the concerned Member States. In such cases the criteria of essential similarity are automatically met). Moreover, the consent of the marketing authorisation holder of the original product has to cover the use of the pharmacological, toxicological or clinical references contained in the file of the original medicinal product in each Member State concerned by the procedure.

— In the case of Article 4(3)(8a)(ii) ('bibliographical application') the applicant has to provide the Member State involved in the mutual recognition procedure with a complete dossier including the proof of the well-established use of the constituent(s) of the product through detailed references to published scientific literature presented in accordance with Directive 75/318/EEC. It must also be stressed that all requirements laid down in this Directive have to be addressed in the application. The applicant had of course the choice of the bibliographical data on which it based the application in the reference Member State. The acceptance of these bibliographical data by the reference Member State gives the framework for the issuing of the marketing authorisation subject later on to mutual recognition. According to the abovementioned Article, the data submitted have to prove recognised efficacy and an acceptable level of safety as far as the constituent(s) of the medicinal product on evaluation is concerned. Applications filed in this context are and have to stay, by definition, complete and independent ('stand alone applications').

— In the case of Article 4(3)(8a)(iii) ('generic application'), the product to which essential similarity is claimed has to be authorised both in the reference and the concerned Member State(s) and essential similarity has to be demonstrated by the applicant in all concerned Member States, except for cases in which the 'original product' has already undergone a Community procedure; in such cases the criteria of essential similarity are

automatically met in the concerned Member States when demonstrated in the reference Member State.

Moreover, the product to which essential similarity is claimed must have been authorised within the Community, in accordance with Community provisions in force for not less than six (or 10) years. If the protection period is equal in all the concerned Member States, no problem will arise; if, however, the protection period in the 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 10-year period.

(d) *Specific cases regarding generic products*

Community legislation has not foreseen any kind of derogation as regards the eligibility of generic products to the mutual recognition procedure and the implementation of this procedure as far as they are concerned.

Due to the peculiarities of these products, the Commission would like to emphasise the following points.

For applications for mutual recognition of marketing authorisations of generic medicinal products in Member States in which the summary of product characteristics of the original product to which essential similarity is claimed is not harmonised, essential similarity has to be demonstrated by the applicant in all concerned Member States. It is particularly required that all the indications in the SPC proposed by the generic application (as authorised by the reference Member State) must be in the SPC of the original product, which may have, at least in some of the concerned Member States, additional ones.

The proof of essential similarity can include the need to produce appropriate bioavailability studies. However, even in cases where the original products (or, to be more precise: the SPCs of the original products) are not (yet) harmonised, Member States have to take into account — as far as possible and relevant — the results of bioavailability studies used in the reference Member State.

Difficulties could be encountered arising from the mutual recognition of a 'generic' medicinal product's marketing authorisation because in some cases mutual recognition would result in (horizontal) harmonisation across Member States of the SPC of a generic product but (vertical) disharmony within individual Member States between the harmonised generic SPC and the SPC of the original product in the same Member States. This is due to the fact that the 'original' product, i.e. the first marketing authorisation granted to the inventor company, and against which 'essential similarity' is claimed, does not always have the same summary of product characteristics across all Member States. This situation can be tolerated insofar as it does not lead to a public health problem. In cases where it presents a serious risk to public health (mainly as regards contra-indications, undesirable effects, precautions of use, etc.), the matter will have to be referred to arbitration pursuant to Article 10 of Directive 75/319/EEC as far as the generic product is concerned and a procedure based on Article 11 of the same Directive will ensure a parallel harmonisation of the national SPCs of the original product.

5. Mutual recognition, procedure triggered by a Member State (Article 7a of Directive 65/65/EEC)

Article 7a of Directive 65/65/EEC (which became binding as of 1 January 1998) creates an obligation on Member States to initiate, each time it is applicable, a mutual recognition procedure independently of the course of action chosen by an applicant. This binding provision refers to all applications validated as of 1 January 1998. Therefore, from 1 January 1998 onwards, any application regarding a medicinal product which is already covered by an existing marketing authorisation in another Member State will have to be considered in the context of the mutual recognition procedure.

This procedure has thus to be considered as a 'catch-all' provision given to the Member States in order to secure an efficient implementation of Community law provisions dealing with the mutual recognition of national marketing authorisations.

In this context, the Commission considers that differences between the SPC already approved in one

Member State and the proposed SPC, part of the application under consideration in another Member State, do not automatically prevent the latter from triggering a mutual recognition procedure⁽²⁷⁾. If these differences have no therapeutic implications⁽²⁸⁾, i.e. both products have the same qualitative and quantitative composition in active substances (i.e. the same strength) and the same pharmaceutical form, they have to be considered as being the same and a mutual recognition procedure has to be followed.

However, in the case of a medicinal product with a well-established use demonstrated in accordance with Article 4(3)(8)(a)(ii) of Directive 65/65/EEC ('bibliographical application'), this well-established use being based on data referring to an existing group of products with different SPCs in the Member States, national independent procedures could continue to be followed as far as no Community harmonisation of the use of the constituent(s) of the said product exists; the purposes of Article 7a of Directive 75/319/EEC being not to provide harmonisation of an entire therapeutic class or a complete group of products. In any case, Article 11 of the same Directive remains, of course, applicable.

6. Simultaneous applications (Article 7(2) of Directive 65/65/EEC)

Article 7(2) of Directive 65/65/EEC offers Member States the possibility to start a mutual recognition procedure, where an application lodged in one Member

⁽²⁷⁾ This of course applies if the applicant is the same in the concerned Member States. However applicants belonging to the same mother company or group of companies have to be taken as one entity. Applicants which, without belonging to the same mother company or group of companies, have concluded agreements (e.g. 'licensees') or which exercise concerted practices concerning the placing on the market of the relevant medicinal product in different Member States, also have to be taken as one (see also point E.3).

⁽²⁸⁾ The same approach has been followed already by the ECJ in the context of parallel imports to determine if the imported product is the same as the one already marketed in the country of import and thus can be covered by the same marketing authorisation (e.g. see Case C-201/94 *The Queen v. the Medicines Control Agency ex parte Smith & Nephew Pharmaceuticals Ltd* [1996] ECR I-5846).

State is already under active examination in another Member State.

This provision explicitly covers only cases in which identical applications are pending in different Member States and in which an earlier authorisation was not yet granted in another Member State. Cases in which a marketing authorisation has already been issued in another Member State are not covered by this Article. In such cases Article 7a of Directive 65/65/EEC applies.

The wording 'may' in Article 7(2) implies that the concerned Member State has an option to choose whether to suspend the authorisation procedure and await the assessment report prepared by the other Member State or to proceed with the application. This provision is applicable and remains applicable for all applications submitted after 1 January 1995. The entering into force of Article 7a on 1 January 1998 has no direct effect on the applicability of this provision. Different Member States 'may' therefore go on in parallel with simultaneous and identical applications under Article 7(2) even after 1 January 1998. However, this possibility is only theoretical, because as soon as one of the two Member States actually grants a marketing authorisation, Article 7a of Directive 65/65/EEC becomes applicable and the Member State which has not yet granted an authorisation must start a mutual recognition procedure in accordance with this Article.

Since the application must be under active examination in the other Member State, this mechanism requires Member States to actively cooperate. Having determined that the application is under active examination, the Member State which has suspended its evaluation informs the other (reference) Member State and the applicant of its decision to suspend detailed examination of the application in question.

Within 90 days of the receipt of the assessment report which has been prepared during the examination of the application, the Member State which suspended the examination shall either recognise the decision of the other (reference) Member State and the summary of the product characteristics as approved by it, or, if it considers that there are grounds for supposing that the authorisation of the medicinal product concerned may present a risk to public health, it shall apply the procedures set out in Articles 10, 11 and 12 of Directive 75/319/EEC ('arbitration procedure').

7. Maintenance of achieved harmonisation

As already stressed above, the mutual recognition of marketing authorisations for medicinal products is based on the principle that the SPCs for products that have undergone the mutual recognition procedure shall be identical and remain identical in all concerned Member States. This principle, enshrined in Article 15 of Directive 75/319/EEC, clearly covers all marketing authorisations which have been granted following the procedures foreseen in Article 9 of Directive 75/319/EEC and Articles 7 and 7a of Directive 65/65/EEC.

The principle that achieved harmonisation has to be maintained is, however, not limited to products which have undergone mutual recognition. As already mentioned above, it also covers all other cases in which a SPC was fully or partly harmonised through any Community procedure.

The following list indicates the cases in which authorisations have to be considered in any case as being harmonised in all the concerned Member States:

- medicinal products which have been considered within the scope of application of Directive 87/22/EEC ⁽²⁹⁾ (ex-concertation products),
- medicinal products which have benefited from the procedures of mutual recognition foreseen in Articles 7 and 7a of Directive 65/65/EEC,
- medicinal products authorised according to Article 9(4) of Directive 75/319/EEC,
- medicinal products which have been the subject of a referral to the procedures foreseen by Articles 11 and 12 of Directive 75/319/EEC ⁽³⁰⁾.

⁽²⁹⁾ OJ L 15, 17.1.1987, p. 38, repealed by Directive 93/41/EEC.

⁽³⁰⁾ For veterinary medicinal products any references to this Article has to be understood: Article 19 or 20 of Directive 81/851/EEC.

8. Fixed combination of products

Questions may arise concerning the procedure applicable for the authorisation of 'combination products' (i.e. products containing two or more medicinal products — like vaccines — in a fixed combination) when the SPCs of one or more products contained in the combination product are already harmonised. Strictly speaking, any combination product is a separate and unique product, requiring a separate authorisation and separate SPC. The combination product can therefore never be seen as 'the same' or as an 'identical product' to a product encompassed in the combination. Nevertheless, a competent authority is obliged — in the situation described above — to take into account and to respect the harmonisation already achieved as far as the assessment of one or more parts of the combination product is concerned. Otherwise there would be a clear case for making use of the provision of Article 12 of Directive 75/319/EEC in order to maintain harmonisation.

9. Application of the mutual recognition provisions to 'line extensions' of non-harmonised national marketing authorisations

Some fundamental changes (e.g. changes to the therapeutic indications or changes to strength, pharmaceutical form and route of administration) to a marketing authorisation require an application for a new marketing authorisation to be made.

The fact that applications for such changes have to be made through the scientific evaluation procedure normally required for new applications and not through a more simplified procedure ('variations procedure') must not disguise the fact that, from the point of view of the Commission, the applicant, in such cases, applies for a change to an existing marketing authorisation and not for a completely new one. When such changes regard new strengths, new pharmaceutical forms or new indications, they are called deliberately line extensions of an existing marketing authorisation.

It is worth mentioning in this context the case where an applicant initially was granted for the same medicinal product two different and purely national authorisations in different Member States. If, afterwards, the same applicant wished — by lodging applications for changes or variations of the national marketing authorisations — to obtain harmonised national authorisations in different

Member States, it would clearly not be possible to exclude such a case from the scope of application of the mutual recognition procedure.

In such a case, the application for the relevant change or variation will have to be considered as an application for an authorisation for the same product within the meaning of Article 9 of Directive 75/319/EEC with the resulting legal consequences.

It goes without saying that — as in any other case of mutual recognition — the criteria concerning the identity of the product and the identity and completeness of the dossier have to be fulfilled. In other terms, prior to any mutual recognition procedure for 'line extensions', the applicant will have to harmonise the already approved national SPC in order to support his applications in all the concerned Member States with the same dossier. This *a priori* harmonisation can be achieved either through a set of coordinated national variation procedures⁽³¹⁾ or through the Community procedure foreseen in Article 11 of Directive 75/319/EEC. If the applicant chooses to submit a completely new dossier without any cross-references to the dossiers supporting the existing national authorisations, such prerequisite harmonisation is, of course, not needed.

CONCLUSION

The new Community system for marketing authorisations was set out in 1993 to provide harmonisation and coherence in a very specific market, which was still deeply heterogeneous and partitioned in spite of nearly 30 years of elaboration of common technical standards and criteria. Since 1995 and even more since 1 January 1998 with the end of the transitional arrangements in the mutual recognition procedure, a new European legal environment exists which has to be used to ensure a gradual, continuous and sustained harmonisation of all medicinal products accessing the Community market.

While providing such harmonisation, the new Community system for marketing authorisation serves three separate interests. To the citizens of Europe, it guarantees that new medicinal products marketed in the Community have been independently evaluated to a high scientific standard of quality, safety, and efficacy and it aims at assuring that the same medicinal products will be used under the same conditions throughout the European Union. To the pharmaceutical industry, it offers fast access to the Single European Market, either through a single Community authorisation or through

⁽³¹⁾ Commission Regulation (EC) No 541/95 is not applicable to independent national marketing authorisations which have not benefited from any Community procedures.

the effect of mutual recognition. Lastly, but not least, it makes for more rational use of the resources needed for authorisation and monitoring of medicinal products by eliminating the duplication of evaluation that characterised the former system.

However, the role of public authorities at national and Community level is confined to creating appropriate economic and regulatory conditions, and it is therefore up to economic operators to make the most of the Single Market. In such a context it is of the utmost importance that the pharmaceutical companies become fully integrated into the new legal and regulatory environment and duly take into account in their different projects and commercial strategies, the new 'rules of the game'.

The Member States have been diligent in putting into place Single Market legislation and applying Community guidelines on the development of medicinal products.

However, divergent interpretations within national administrations, a certain unwillingness to rely on other Member States' scientific evaluation and additional lengthy national administrative procedures (issuance of administrative decisions) have prevented the full benefit of the new procedures from being realised. These delays at national level continue to limit the Single Market's positive contribution to public and patient access to medicinal products.

In order to remedy this situation and more generally to improve the functioning of the procedures, modifications of the current legal texts could be needed and this will have to be addressed in the course of the overall review of the new system which is due to take place in the year 2000. In order to prepare this exercise, the Commission looks forward to receiving contributions from the national administrations, from the EMEA and all other interested parties (consumers' and patients' associations, pharmaceutical companies, industry federations, etc.).

Non-opposition to a notified concentration

(Case No IV/M.1218 — Packaging International BV/NV Koninklijke KNP BT)

(98/C 229/04)

(Text with EEA relevance)

On 3 July 1998, the Commission decided not to oppose the above notified concentration and to declare it compatible with the common market. This decision is based on Article 6(1)(b) of Council Regulation (EEC) No 4064/89. The full text of the decision is only available in English and will be made public after it is cleared of any business secrets it may contain. It will be available:

- as a paper version through the sales offices of the Office for Official Publications of the European Communities (see list on the last page),
- in electronic form in the 'CEN' version of the CELEX database, under document number 398M1218. CELEX is the computerised documentation system of European Community law; for more information concerning subscriptions please contact:

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