COMMISSION OF THE EUROPEAN COMMUNITIES

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COMMUNICATION FROM THE COMMISSION TO THE COUNCIL AND THE EUROPEAN PARLIAMENT

concerning the

Report on the experience acquired as a result of the application of the provisions of Chapter 2a of Directive 2001/83/EC, as amended by Directive 2004/24/EC, on specific provisions applicable to traditional herbal medicinal products

Document on the basis of Article 16i of Directive 2001/83/EC

1. INTRODUCTION

1.1. Background to the report

In order to overcome the difficulties encountered by Member States in applying the pharmaceutical legislation to herbal medicinal products in a uniform manner, specific provisions for traditional herbal medicinal products have been introduced in the Community code relating to medicinal products for human use (Directive 2001/83/EC).

Under Articles 16a to 16i of Directive 2001/83/EC, introduced by Directive 2004/24/EC, a specific registration procedure is to be used by the Member States for herbal medicinal products that meet the criteria for a traditional herbal medicinal product. Herbal medicinal products are defined as any medicinal product exclusively containing as active ingredients one or more herbal substances, one or more herbal preparations, or one or more such herbal substances in combination with one or more such herbal preparations.

Article 16i requires the Commission to submit a report to the European Parliament and to the Council concerning the application of the simplified registration procedure and including an assessment of the possible extension of traditional-use registration to other categories of medicinal products. This document was prepared in consultation with the European Medicines Agency and the Committee on Herbal Medicinal Products (HMPC) and was submitted for consultation to the Member States and interested parties. As a major source of information, the Commission welcomed the HMPC report of 31 October 2006 (Doc.Ref.EMEA/HMPC/187219/2006) presenting the views of the EMEA and the HMPC.

1.2. Current situation

The simplified registration procedure is intended for herbal medicinal products that have a long tradition, but do not fulfil the requirements for a marketing authorisation, in particular the requirement for applicants to demonstrate by detailed references to published scientific literature that the constituent or constituents of the medicinal products has or have a well-established medicinal use with recognised efficacy and an acceptable level of safety (‘well established use’).

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

The application for a simplified registration procedure should thus be accompanied by bibliographical or expert evidence to the effect that the medicinal product in question or a corresponding product has been in medicinal use the relevant period. With regard to the manufacturing of these products and their quality, applications have to fulfil the same requirements as applications for a marketing authorisation. However, a long tradition of use may remove the need for clinical data, if 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.

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

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

In view of the particularities of herbal medicinal products, a Committee for Herbal Medicinal Products (HMPC) has been established at the EMEA.

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 of these for use in traditional herbal medicinal products will be established by the Commission following a proposal by the HMPC. In order to promote harmonisation, Member States will recognise the registration of traditional herbal medicinal products based on Community monographs.

For the application of both the traditional-use and the well-established use provisions, Community herbal monographs will also be established by the HMPC to serve as a basis for simplified registration or bibliographical marketing authorisation applications.

When this new simplified registration procedure was introduced, it seemed appropriate to limit its scope in a first step to traditional herbal medicinal products. It also seemed appropriate to evaluate in due course the application of this new procedure, together with an assessment of the possible extension of the scope of traditional-use registration to other categories of medicinal products.

2. EXPERIENCE ACQUIRED WITH THE SIMPLIFIED REGISTRATION PROCEDURE

2.1. Transposition of Directive 2001/83/EC

Directive 2004/24/EC had to be transposed by 30 October 2005. By 10 March 2008, it had been fully transposed in 25 Member States. Two Member States have still not transposed Directive 2004/24/EC and infringement procedures have been initiated by the European Commission.

2.2. Applications in Member States

On 30 June 2007, 110 applications had been introduced in 17 Member States. The number of applications is very unevenly distributed, with more than 20 applications having been made in some Member States. In most Member States, however, no or very few applications have so far been introduced. A total of 23 applications have been finalised.

2.3. Referrals to the HMPC

Directive 2004/24/EC amending Directive 2001/83/EC introduced several provisions allowing referral to the HMPC for an opinion on certain matters relating to herbal medicinal products. Up to March 2008, one referral had been made to the HMPC under Article 16c(1)(c).

2.4. Herbal Medicinal Products Committee (HMPC)

The HMPC was established in 2004 and has held regular meetings. It has also established temporary working parties and developed a number of guidance documents.

22 monographs have been adopted and published and another 17 are in public consultation. According to the HMPC, the full application of the Directive would require the publication of approximately 200-300 monographs.

Two draft entries for the list have been proposed by the HMPC to the Commission so far.

In its contribution to the European Commission for the preparation of this report, the HMPC stated that drafting proposals for entries in the Community list or Community monographs required significant resources. Moreover, the monographs adopted by the HMPC need to be periodically updated. The HMPC has stated that it does not have sufficient resources to carry out these tasks.

2.5. Genotoxicity data issue

Under Article 16c(1)(d) of Directive 2001/83/EC, an application for simplified registration must be accompanied by a bibliographic review of safety data together with an expert report. In addition, the competent authority may ask for any further data necessary to assess the safety of the medicinal products.

The introduction of the simplified registration procedure was based on the assumption that safety and efficacy could be adequately substantiated by long-standing use without requiring additional testing and systematic documentation on all points of Annex I of Directive 2001/83/EC regarding safety. If an application relates to a herbal substance, preparation or combination contained in the list, the safety data do not need to be provided and the competent authority cannot ask for additional data.

In its guideline on non-clinical documentation for herbal medicinal products in applications for a marketing authorisation (bibliographical and mixed applications) and in applications for simplified registrations, the HMPC is of the view that the genotoxic potential of herbal preparations should always be assessed. The guideline further states that genotoxic data are available for many active substances, but their quality is often inadequate for a safety assessment. When such an assessment cannot be made, further genotoxicity testing is thus required.

Similarly, in its report, the HMPC identified major issues concerning the availability and quality of genotoxicity data for herbal substances when developing the first series of draft list entries. The HMPC is of the view that if relevant questions regarding genotoxicity data remain unanswered, even after a comprehensive literature search has been performed, a positive opinion on a Community list entry cannot be given. In order to obtain these data, further genotoxicity testing would have to be conducted.

In order to ensure the successful application of the Directive, the issues relating to genotoxicity demand careful scientific and legal consideration. As stated in the HMPC report, the systematic request for genotoxicity data has made the proposal of list entries difficult since these data are generally not available. It has probably also contributed to the small number of applications received so far. Consequently, a request for genotoxicity data to assess traditional herbal medicinal products should be made on a case-by-case basis when there is a specific concern for safety, as required by the relevant provisions in the legislation. This ensures the protection of public health while allowing the registration of traditional herbal medicinal products. A more restrictive approach would create the risk that the products concerned will end up being marketed under another classification (and not as medicinal

products), without the necessary quality, safety and efficacy controls applicable under pharmaceutical legislation.

3. EXTENDING TRADITIONAL-USE REGISTRATION TO OTHER CATEGORIES OF MEDICINAL PRODUCTS

3.1. Current situation

Directive 2004/24/EC was intended to address the specific situation of traditional herbal medicinal products. In order to gain experience, the scope of the Directive was deliberately limited to these products. However, other products may face a similar situation and have a long tradition as medicinal products but do not fulfil the requirements for a full marketing authorisation or a well-established use authorisation. This applies to several traditional forms of medicine, which include, for example, the following:

Anthroposophic medicine has been established in Europe since 1920. It is practised in Germany, the Netherlands, the UK, Italy, Spain, Poland and France, among others. It follows a global therapeutic approach that embraces the individual as a whole taking into consideration both the personality and the body. Anthroposophic products are designed to stimulate the patient's powers of self-healing and use mineral, vegetable, metal and animal-based raw materials. They can be used in every form of dosage and administration, including the external, internal and parenteral routes.[1]

Traditional medicines from other parts of the world include Ayurveda (traditional Indian medicine) and Chinese traditional medicine. These systems of medicine have existed for centuries in other parts of the world and have their own specific remedies. Some of these remedies could qualify as traditional herbal medicinal products, but other traditional medicinal products do not qualify for the simplified registration procedure.

Ayurveda literally means 'science of life' in Sanskrit. It is not only a medical system but a way of life that aims for the holistic management of health and diseases. Ayurvedic medicinal products include ingredients of plant, animal and mineral origin. Most contain only herbal ingredients. The substances included in the products are described in the monographs of the Ayurveda Pharmacopoeia. [2]

A variety of dosage forms and presentations of Ayurvedic formulations are used, ranging from food-like presentations to pharmaceutical forms. There is no significant use of parenteral formulations, with non-invasive techniques predominating.

Within the Ayurvedic tradition, no particular distinction is made as regards the legal classification (prescription or non-prescription) of products. They are typically prescribed by practitioners following examination and diagnosis of the patient and their administration is followed up throughout use, normally in healthcare settings.

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1 *Anthroposophic Medicines, their origin, production and application, Medical section of the School of Spiritual Science, 4143 Dornach, Switzerland. Anthroposophic Pharmaceutical Codex, APC, The International Association of Anthroposophic Pharmacists, Dornach, Switzerland, 11.2007, available at http://www.iaap.org.uk/downloads/codex.pdf, 4.12.07.*

2 Mission Report, Fact-Finding Mission of the European Commission to India 15-18 January 2007.

Traditional Chinese medicine theory asserts that processes of the human body are interrelated and in constant interaction with the environment. It is largely based on the philosophical concept that the human body is a small universe with a set of complete and sophisticated interconnected systems. Traditional Chinese medicinal products, which can also take the form of injections, are often combined products of herbal origin but also may contain animal, mineral and metal ingredients.[3]

The major reasons why the above products may not be able to obtain a marketing authorisation or a simplified registration under the current Community legal framework are as follows:

– Composition of the product

Directive 2001/83/EC requires traditional herbal medicinal products to be composed **exclusively** of herbal substances or preparations, with the exception of vitamins and minerals having an ancillary action. Some traditional products are mostly but not exclusively composed of herbal substances. They may also include mineral components, animal products, metal products or herbal constituents.

– Route of administration

Traditional herbal medicinal products must be administrated orally, externally or via inhalation. According to the public statement of the HMPC on the interpretation of the term 'external use' for use in the field of traditional herbal medicinal products, the term 'external' means mainly application on the skin, but includes topical, oral, nasal, rectal, vaginal, ocular or auricular use. The route of administration for certain medicinal products in other traditions can also be by injection.

– Unsupervised use and indications

According to Directive 2004/24/EC, traditional herbal medicinal products must be intended and designed for use without the supervision of a medical practitioner. This would cover minor disorders or symptoms that are benign. However, some traditional medicinal products do not fulfil these criteria and are not suitable for administration without the supervision of a qualified practitioner. Traditional medicinal products with therapeutic indications that involve diseases such as cancer, psychiatric diseases, infectious diseases such as hepatitis or influenza, cardiovascular diseases or metabolic diseases such as diabetes are not suitable for administration without the supervision of a medical practitioner. In some traditions, moreover, the therapy is integrated within a global approach as part of a general diagnosis by a duly qualified practitioner. However, this does not necessarily mean that certain of the products used could not be considered, under Community pharmaceutical legislation, as non-prescription products.

– Proof of traditional use in the Community

The traditional use of traditional herbal medicinal products is demonstrated by bibliographic and expert evidence that the medicinal product in question or a corresponding product has

[3] International traditional Chinese medicine programme for cooperation in science and technology, Ministry of Science and Technology, People's Republic of China and various contacts with the Chinese delegation and Chinese medicine practitioners.

been in medicinal use throughout a period of at least 30 years, including at least 15 years within the Community. The rationale behind this requirement is the difficulty of verifying whether information on use outside the Community provides a reliable basis to assess the efficacy and, especially, safety of a product. However, it is difficult for traditional medicinal products from other parts of the world to meet the requirement of at least 15 years use within the Community. In such cases, the product must be referred to the HMPC for an opinion to assess whether all the other conditions for simplified registration as set out in Article 16a of Directive 2001/83/EC are met. This situation can prevent access to the European market for some traditional herbal medicinal products from third countries.

3.2. Extending the scope of the simplified registration procedure

The rationale behind the current simplified registration procedure is to enable products that have been in long-standing traditional medicinal use to be registered under a simplified procedure **because their safety and efficacy can be deduced from their long-standing use under the specified conditions of use**. The vast majority of medicinal products with a sufficiently long and coherent tradition are based on herbal substances. It therefore seemed appropriate to limit the scope of the simplified registration in a first step to traditional herbal medicinal products. There are several conditions to be met for a product to be eligible for registration. Taken together, these conditions guarantee that only traditional herbal medicinal products have access to the simplified registration procedure, where it is appropriate and justified to depart from the strict requirements of Chapter I of Title III of Directive 2001/83/EC.

The purpose of this report is to evaluate whether there are other medicinal products that could meet the conditions for simplified registration. In view of the different aspects noted above, the following conclusions can be drawn regarding the extension of scope:

– Composition of the product

Registration of traditional use could be extended to encompass substances that are not herbal substances or herbal preparations but which also have a long-standing tradition with well-documented safety and plausible evidence of efficacy or pharmacological effects. These substances may be used on their own or in association with herbal products. They may include substances of animal, mineral or metallic origin and micro-organisms. These substances should be assessed under the same conditions and procedures as herbal medicinal products and their long-standing use would be documented under the same conditions as for traditional herbal products. As already provided for in Directive 2004/24/EC, in order to substantiate quality, the applicant would have to provide the same particulars and documents as for an application under Chapter I of Title III of Directive 2001/83/EC, including the results of physico-chemical, biological or microbiological tests. In particular, for products of animal origin, the relevant provisions of Module 3 of Directive 2003/63/EC will apply, including specific measures for the prevention of the transmission of animal spongiform encephalopathy. For starting material of animal origin, the history and origin of the starting material must be described and documented.

As already provided for in Directive 2004/24/EC, where the safety of the product is concerned, the applicant would have to prove a well-documented traditional use under the existing rules with relevant proof of the product's safety. In cases of doubt as to the safety of the traditional use, additional data may be required by the competent authority before the simplified registration can be granted.

As already provided for in Directive 2004/24/EC, where efficacy is concerned, the applicant would have to document the pharmacological effects or the plausibility of efficacy on the basis of long-term use and experience.

– Route of administration

Traditional-use registration is limited to certain routes of administration because these are the safest ways of administration. In addition, since the simplified registration procedure is intended for products that, by virtue of their purpose, are intended to be used without the supervision of a medical practitioner, it is not appropriate to extend the procedure to include other routes that would generally require the supervision of a practitioner. Injection products should therefore continue to follow the normal marketing authorisation procedure.

– Unsupervised use and indications

Since simplified registration does not require clinical trials of safety and efficacy, as a lighter procedure compared with the marketing authorisation procedure, it appears appropriate to limit the scope of simplified registration to products aimed at minor diseases that can be treated without the intervention of a practitioner.

– Proof of long-standing use in a third country

In the simplified registration procedure, applicants need to prove 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 application, including at least 15 years within the Community. The requirement for at least 15 years traditional use in the Community was introduced as it was considered more difficult to gather information on the traditional use of a product from other parts of the world, especially data on safety, since pharmacovigilance systems vary widely across the world. However, use in the Community may be accepted for this requirement if evidence can be supplied of the same use for which registration is sought even if this use was without registration or authorisation as a medicinal product.

More experience with the requirement for at least 15 years use in the Community has to be gathered with a view to assessing its necessity. Pending this assessment the requirement should be maintained.

– Procedure

The current procedure for assessment of traditional medicinal products would remain unchanged. This means that the assessment would be performed by the national competent authorities, which would have to evaluate whether all the conditions for simplified registration are met, including documented safe use. As already provided for in Article 16c(1)(c) of Directive 2001/83/EC, referral to the HMPC for an opinion on the adequacy of the long-standing use would continue to be an option. Extending the scope of the simplified registration procedure should thus not lead to an unduly high increase in the workload of the HMPC after an initial phase.

3.3. Results of the public consultation

A draft of this report was published for consultation on the website of DG Enterprise and Industry's Pharmaceuticals Unit on 30 May 2007. Comments on the document were invited by 10 August 2007. During the consultation, DG ENTR received 53 contributions. A

summary of the responses was published on the pharmaceuticals website[4]. All the responses were carefully analysed and taken into consideration whenever possible.

Most of the comments supported extending the scope of Directive 2004/24/EC based on the criterion of composition as proposed in the draft report. However, certain respondents reported obstacles to the registration of products through the simplified registration procedure, linked to the other criteria for registration or to implementation issues. The specificity of certain medical traditions as a whole was also raised as an issue in the consultation.

4. SUMMARY AND CONCLUSION

Directive 2004/24/EC was intended to address the specific situation of medicinal products that, despite their long tradition of use, do not fulfil the requirements for a marketing authorisation as set out in the Community pharmaceutical legislation. By introducing a simplified registration procedure with specific requirements, the Directive aimed to allow these products to be marketed under harmonised conditions and to ensure the protection of public health by making such products subject to the necessary guarantees of quality, safety and efficacy. During the public consultation on the draft of this report, numerous supportive views were expressed on the setting of harmonised safety standards for traditional products.

During the public consultation, some stakeholders referred to the experience with the application of the requirements of the simplified registration procedure. In particular, the issue of genotoxicity data needs careful consideration from a scientific and legal point of view. The requirement for genotoxicity data should be considered on a case by case basis in the framework of the simplified registration, because wrong interpretation of the legal requirements could possibly lead to the marketing of some products under another qualification that would not necessarily offer the same guarantees of quality, safety and efficacy. Such a result would be contrary to the public health and harmonisation objectives of Directive 2001/83/EC and Directive 2004/24/EC. In order to overcome this difficulty, a case-by-case decision, where specific concerns about safety exist, appears to be a proportionate and balanced approach and in line with the objectives of the Directive.

As regards the possible extension of the scope of the Directive, any such extension should be in line with the objectives of Directive 2004/24/EC, i.e. to have harmonised rules for the placing on the market of certain medicinal products with a long tradition of use but which do not generally satisfy the requirements for marketing authorisation, while ensuring the protection of public health by introducing specific requirements for proof of quality, safety and efficacy.

In this regard, the European Commission is prepared to consider extending the simplified registration procedure to products other than herbal substances with a long tradition of safe use. This proposal received general support during the public consultation on the draft of this report. On the other hand, the key requirements of the simplified registration procedure, based on public health considerations, such as the limitation to products with 15 years use in the Community, to certain routes of administration and to products that do not need the supervision of a medical practitioner, should be maintained. For certain requirements, more experience is needed before any change to the system can be proposed.

[4] http://ec.europa.eu/enterprise/pharmaceuticals/pharmacos/new.htm.

The proposed extension would enable certain medicinal products from specific European or non-European medicine systems (such as — in alphabetical order — anthroposophic, Ayurvedic, Chinese, Kampo Korean, Mongolian, Thai, Tibetan Unani, or Vietnamese medicine), as well as traditional products with a long-standing tradition in the European Union (such as honey, royal jelly, propolis, fish oils, minerals, micro-organisms and other substances) to be eligible for the simplified registration procedure with a view to placing them on the market as traditional medicinal products.

Many of these products are present in the Community market, and their inclusion under the simplified registration procedure will introduce harmonisation in a sector where differences currently exist between Member States as regards classification and placing on the market and will increase the protection of public health since the quality, safety and efficacy of the products concerned will be assessed during the simplified registration procedure.

On the other hand, it should be emphasised that Community legislation on medicinal products, in particular Directive 2001/83/EC laying down the procedures for placing products on the market, follows a product-specific approach and does not attempt to provide a framework for the regulation of traditions of medical practice.

During the public consultation, proponents of three traditional medical systems using products with a long-standing tradition expressed support for the global regulation of their traditions within the EU: anthroposophic, Ayurvedic and traditional Chinese medicine. It was suggested that proof of the plausibility of efficacy should not be by medicinal product, but by therapeutic approach.

Medical traditions such as those mentioned above are based on a holistic approach, and the set of requirements for the simplified registration procedure under Directive 2004/24/EC is not appropriate for a global regulation of such medical practices. The regulation of such traditions would demand a different approach from that introduced by Directive 2004/24/EC. Therefore, the Commission does not envisage extending the scope of the simplified registration procedure to cover traditional medical systems as such. Nevertheless, independently of this report, the suitability of a separate legal framework for products of certain traditions should be assessed.