REVIEW ARTICLE

Herbal products: Marketing strategies and legislation

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Marketing of herbal products in the European Union (EU) has been regulated under national legislation for years, leading to differences in legal status of these herbal products. In one member state, a product may be regulated as a food supplement, while in the other member state the same product is considered a medicinal product, thereby subjected to medicinal law. To provide free movement of these products in the inner market, new legislation has been set to improve harmonization. This raises the question what the appropriate positioning and marketing strategy for a herbal product will be under this new EU legislation. This review describes the legal status and registration procedures of different categories of herbal products, taking into account technical requirements and interesting market perspectives. Information was collected from legislation, guidance and official documents published by the European Commission, European Food Safety Authority and the European Medicines Agency. In addition, information was found in conference presentations and the scientific literature from Medline and Scopus. The EU market of herbal products will change considerably in the near future. Many products now marketed as food supplements will be expected to be registered as traditional herbal medicinal product in the future. However, it will take years for the EU to fully implement the new rules for harmonization.

Key words: Herbal medicinal products, food supplements, harmonization of European legislation

INTRODUCTION

Herbal medicines have been used for thousands of years. In the European Union (EU), these products are currently marketed either as herbal medicines or as food supplements, according to the national regulations. The European Commission (EC) has taken measures to harmonize legislation for herbal products in the EU and to provide free movement in the inner EU market. In principle, the new European legislation on traditional herbal medicinal products permits the registration as a medicinal product in all member states. However, for a number of cases some hurdles still need to be taken. This review discusses the present and future situation for herbal products, taking into account legislation, technical requirements and marketing perspectives.

METHODS

This review provides for an overview of application procedures and technical requirements according to appropriate legislation. Information has been found in the legal documents published in the Official Journal of the European Communities and reports from the European Commission. Technical requirements were found in guidance documents provided by the European Food Safety Authority (EFSA), European Medicines Agency (EMEA) and European Federation of Associations for Health Product Manufacturers (EHPM). In addition, information has been found in conference presentations and websites of the competent authorities of member states. PubMed and Scopus were researched for articles on this topic.

HERBAL MEDICINAL PRODUCTS

Herbal products have a long history of medicinal use in many parts of the world. Especially in Asian and African countries, there is not only an old and rich tradition of herbal products, but plants continue to form a major source of medical treatment until today. Examples are Traditional Chinese Medicine, Ayurvedic and many other systems in different regions of the world. Often, these 'holistic' medicinal systems are based on a philosophy and an approach to diseases and treatment that differs from conventional medicine in the Western countries. Traditional medicine generally aims to improve the overall health and well-being of an individual person or patient, not merely focusing on the primary causative mechanism of a disease. This approach has shown efficacy in treating patients, especially in chronic multifactorial diseases. These results are often explained by the fact that traditional herbal medicines may contain multiple active ingredients acting in synergy in restoring the body's balance or preventing potential side effects.

A herbal product has to be classified as a medicinal product based on its presentation (indications that refer

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to treatment or prevention of a disease) or on its function (pharmacological, immunological or metabolic action). Herbal medicinal products can be categorized into three groups: New herbal medicinal products, herbal medicinal products with a bibliographical application (well-established use) and traditional herbal medicinal products. For these groups, different requirements are set to prove safety and efficacy, depending on the history of use, the proposed indicated use and the available amount of data.

EUROPEAN UNION LEGISLATION

Like all other medicinal products, herbal medicinal products need marketing authorization which requires a full dossier with preclinical and clinical data to prove safety and efficacy. Many herbal medicinal products, however, have a long history of use and may have (pre)clinical data available. Legislation for medicinal products is set in Directive 2001/83.[1,2]

New Herbal Medicinal Products

Herbal products without a documented history of use need to undergo a full development programme comparable to conventional drugs. This includes preclinical safety testing and clinical trials to prove efficacy and safety in humans. Also herbal medicinal with historic use, but with a new proposed indication, need full investigation to prove efficacy. In some cases, well-documented safety data are available and no additional preclinical safety testing is required.

Herbal Medicinal Products with a Well-established Use

Products with a long history of use often have been subject of scientific investigation. When the product has a recognized efficacy and an acceptable level of safety, the applicant may apply for marketing authorization under the precondition of well-established use according to 2001/83 article 10. In this situation, the applicant may not have to perform additional safety or efficacy tests. In addition to scientific evidence supporting the well-established use, it is required that the herbal product is in medicinal use in the EU for at least 10 years.

A bibliographical application may be sufficient for marketing authorization. Scientific evidence to support well-established use may come from scientific literature databases, historical textbooks and monographs. It is especially recommended to use information provided in a community monograph (if available) or monographs from the European Scientific Cooperative On Phytotherapy[3] or World Health Organization.[4-6] Requirements on data submission to substantiate well-established use are set out in Directive 1999/83.[7]

Traditional Herbal Medicinal Products

Herbal medicinal products that have a history of use do not always fulfil the requirements for well-established use. In particular, the evidence may not be sufficiently documented. To allow these products on the market, herbal medicinal products may have access to the market under the registration procedure as traditional herbal medicinal products. While medicinal products need to have market authorization, traditional herbal medicinal products only need registration. Traditional herbal medicinal products have to be in medicinal use for 30 years, of which at least 15 years in the EU. The historical use has to be substantiated with references to sales information, textbooks, expert reports of pharmacists, herbal experts and medicals or historically used national pharmacopoeias.[8] The product's safety and efficacy are exclusively based on the traditional use. The applicant has to state that the product's strength and posology are in line with the traditional use and information in herbal monographs. No additional data on safety and efficacy have to be submitted.

Traditional herbal medicinal products may only claim mild indications that comply with the traditional use. Retailing is licensed only as over-the-counter (OTC) product without supervision of a medical practitioner. The safety and efficacy of traditional herbal medicinal products is substantiated by the long history of medicinal use. The claim of these types of products should therefore contain the phrase: Traditional herbal medicine for use in … [indication]…, exclusively based on long standing use.

The Herbal Medicinal Product Committee (HMPC) of EMEA is working on community monographs and the community list to improve the harmonization of scientific evidence in the EU. This will facilitate the free movement of herbal medicinal products in Europe by the mutual recognition procedure.

The community monographs will contain information about traditional use and/or well-established use. These monographs should be used in the assessment of marketing authorization (well-established use) or registration (traditional use). In addition to the community monographs, the HMPC is also working on the community list entries. The community list contains the HMPC's opinion of a herb in regard to strength, posology, permitted indications, known contraindications and known herb–drug interactions. Community monographs will be published by the HMPC on the website of EMEA. List entries will be published by the EC. Recently, the first list entries have been adopted by the EC.[9]

IMPLEMENTATION OF THE NEW LEGISLATION

The new legislation for traditional herbal medicinal products (2004/24) will come into force on 1st April 2011. This will improve the free movement of products marketed under the EU legislation as herbal medicinal products with well-established use, or as traditional herbal medicinal

products. However, the regulation and classification of herbal products currently differs between member states. Therefore, the implementation and transition from national to EU regulation will probably still be accompanied with difficulties in harmonization.

THE SITUATION IN GERMANY

In Germany, the majority of the herbal medicinal products in the market are currently authorized as herbal medicinal product with well-established use 90% in 2004.[10] However, this well-established use is based on reference to herbal monographs of the German Commission E. The European definition of well-established use is much more difficult to substantiate and many herbal products currently on the German market will not meet these requirements. However, it is expected that herbal medicinal products with well-established use with reference to Commission E monographs will remain.[11] This is not in line with the required substantiation level in other European countries and these products therefore hinder the European harmonization process of herbal medicinal products.

A second group of herbal medicinal products is that of the traditional medicinal products. These products were on the market before 1978 and were therefore considered to be safe based on traditional use. These products have to apply for a new registration as traditional herbal medicinal product according to EU Directive 2004/24. Not all of these products will survive the transition to traditional herbal medicinal product following EU legislation, but many will. At the moment, about 1.000 traditional herbal medicinal products may apply for a new registration in the next year. According to a conference presentation, it seems likely that German organizations for the pharmaceutical industry are lobbying for the possibility to carry more solid claims for traditional herbal medicinal products, just to distinguish between herbal medicinal products and food supplements.[12]

THE SITUATION IN THE NETHERLANDS

In general, herbal products are marketed in The Netherlands as food supplements and sometimes as homeopathic medicines. Substantiation of well-established use according to the EU legislation seems not feasible for the majority of herbal medicinal products. In The Netherlands, the Medicine Evaluation Board CBG seems to direct merely to registration as traditional herbal medicinal products. As a result, no information on efficacy should be included in the dossier.

The differences in regulation for Germany compared to countries as The Netherlands reduce the chances for mutual recognition and free movement of these products. The establishment of community monographs will provide a base for the mutual recognition procedure, but do not completely remove its barriers. In addition, the establishment of community monographs and community list entries is progressing slowly. In December 2008, 45 community monographs have been adopted and 15 more are about to be published. It is estimated that 200-300 community monographs are necessary to fully implement the Directive on traditional herbal medicinal products.[13]

HERBAL FOOD SUPPLEMENTS

Food supplements are products for use by the consumer to supplement the normal diet in order to promote health. Food supplements should not be classified as medicinal products, although the line between these categories can be thin. Medicinal claims are thus prohibited for food supplements. Classification is based on the presentation and function of the product. Food supplements are subject of the general food law Regulation 178/2002.[14] Specific legislation on food supplements and health claims is set out in Directive 2002/46[15] and in Directive 1924/2006.[16] Health claims are now divided in generic health claims (1924/2006, article 13) and disease risk reduction claims and claims referring to children's development (both in 1924/2006, article 14).

Generic Health Claims refer to:

1. The role of a nutrient or other substance in growth, development and the functions of the body,
2. Psychological or behavioural functions and
3. Slimming or weight control, or a nutrient effecting hunger, satiety senses and energy uptake from the diet.

Generic health claims (with generally accepted scientific evidence) are being listed by EFSA, after evaluation of dossiers submitted by the member states. EFSA list will have the status of advice to the EC that will decide on the definitive list with permitted article 13 generic health claims. The list should be available at last January 2010. When an applicant wants to use a health claim that is not on the positive list (and is not a disease risk reduction claim or children's development claim), the applicant may apply for inclusion of that specific claim in the positive list. New article 13 claims may be submitted with protection of scientific data, thereby strengthening the market position for the product.

Claims that refer to a reduction of disease risk (1924/2006, article 14) are subject of a rigorous authorization procedure based on an extensive dossier. EFSA evaluates these claims, together with new article 13 claims according to the highest standards. In the mean time, several health claims have been rejected because of the lack of scientific evidence. Dossiers for the application of a new article 13, or an article 14 claim

will be submitted to the national competent authority that will send it to EFSA. After 5 months, the EFSA will adopt or reject the claim and the EC will publish this in the Community Register for consultation by the member states.

In addition to the regulations on health claims, substances used in food supplements should meet the requirements of the novel food law. This means that substances used in food supplements need to have a history of use as food in Europe. Food products not used in the EU for a significant time and in a significant amount before May 1997 need to have marketing authorization according to the novel food law. A full registration procedure as a novel food will make the total development programme more expensive and therefore not attractive.

Recently, the EC published a report on the harmonization procedures of, among others, herbal food supplements.[17] This report concludes that it is not feasible to establish harmonized rules to herbal products, because of the lack of scientific data. In addition, it is not necessary to set harmonized measures as a result of regulation 764/2008 on the mutual recognition of products on the inner EU market.[18] This regulation forces member states to accept an application of a product already lawfully marketed in another member state, unless acceptance of the product could lead to concerns about protection of health and life of humans, animals or plants. The rejection of the application should be accompanied with reasons that are 'in proportionality' and are seen in the light of national nutritional habits and in the light of the results of international scientific research.

DOSSIER REQUIREMENTS

The dossier requirements for medicinal products are listed in the EMEA Directive 2003/63, the Annexes as an amendment to Directive 2001/83.[19] The dossier should comply with the requirements listed in the Annexes, in order to support harmonization of dossiers in the European community. The format for the Common Technical Document (CTD) for the application of a herbal medicinal product is set out in a document by EMEA and in Figure 1.[20] A full dossier consists of modules 1-5. This holds for all conventional (synthetic) medicines as well as for new herbal medicinal products. Herbal medicinal products with a well-established use or traditional herbal medicinal products may include less information in the CTD. The requirements for modules 1-3 are equal for all herbal medicinal products.

Module 1 contains administrative information, a summary of product characteristics, labelling and packaging information, information about the experts, specific requirements for different types of applications and environmental risk assessments. This is equal for all sorts of medicinal products.

Module 2 merely consists of summaries of module 3, 4 and 5. This module also contains an introduction to the product, background information and expert reports on genotoxicity assessment[21] and traditional use specific to traditional herbal medicinal products.

Module 3 is the most important for the application of herbal medicinal products. The requirements set out in this module 3 shall apply to all herbal medicinal products. The quality of the herbal medicinal products and the manufacturing process should be secured by adherence to the guidelines for Good Agricultural Practices and Good Manufacturing Practices. In this module, the following should be described: Characteristics of the raw herbal material, plant parts used compliance with the (European) pharmacopoeia, extraction methods, tests to control for stability of the raw materials and methods to control for the concentration of active constituents and the absence of impurities (e.g. NMR analysis). In addition, the following should be described for the finished product: Components of the medicinal product control for consistency of the final product, validation of analytical procedures and stability controls. This list is not complete, all requirements are found in Directive 2003/63 and other EMEA guidelines for the production of herbal medicinal products.[22,23]

Module 4 includes all information regarding preclinical data. The registration of a traditional herbal medicinal product does not need a specification of module 4. A herbal medicinal product with well-established use may sustain with a bibliographic review of data. This product may also apply for market authorization with a 'mixed application' and thus may include a preclinical report.[24] New herbal medicinal products need to fulfil the complete requirements of the CTD and a report on preclinical trials is needed in this module.

Module 5 includes all clinical results. This module is not required for the registration of traditional herbal medicinal products. Applications for a herbal medicinal products with a well-established use need to be submitted with sufficient available bibliographic data. Herbal medicinal products with a new indication or with no prior use need full reports of clinical trials.

The dossier requirements for food supplements are set out in the technical guidance for the preparation and presentation of the application for authorization of a health claim.[25] This dossier consists of four parts that contain the requirements for food/constituent characteristics and scientific data. The requirements for the quality and control methods set out are less strict than for herbal medicinal products. The substantiation of claims for food supplements should be based on peer-reviewed scientific data from

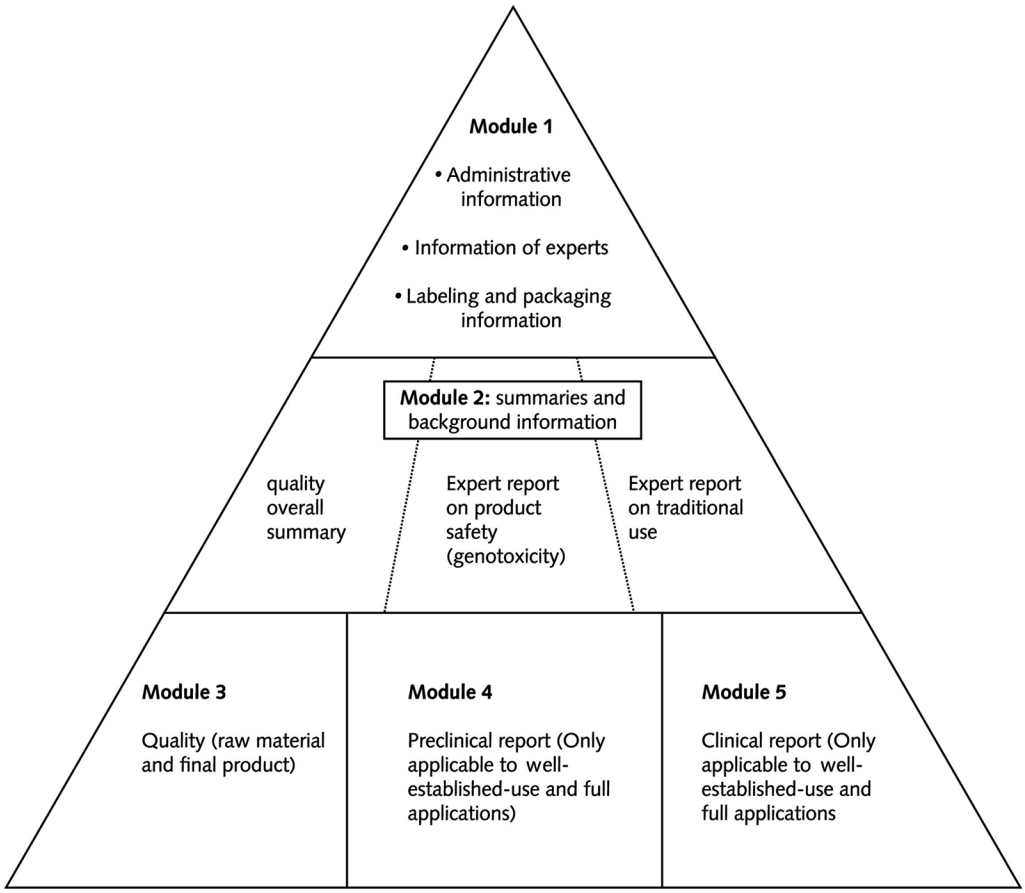

Figure 1: Common Technical Document relevant for the application of herbal medicinal products

published and unpublished studies. In general, the study group should be relevant for the proposed target group. Therefore, it is expected that EFSA will only accept data from clinical trials on healthy subjects, as otherwise the product would have a medicinal use. EFSA has established a new draft document that describes a rigorous set of tests for safety assessment.[26] These tests however are not obligatory. It is the responsibility of the manufacturer to market safe products. Food supplement companies, especially the larger ones, might take all measures to secure a safe product. This will include controls for concentrations of active constituents and impurities. Often herbal food supplements, like herbal medicinal products, are under active quality control with fingerprint analyses. The European Federation of Associations of Health Products Manufacturers (EHPM) has established a quality guide for the safe and consistent manufacturing of food supplements, mainly focusing on the procedures of Hazard Analysis Critical Control Point (HACCP). The implementation of the HACCP procedure however should be flexible, regarding the size and efforts of the manufacturer.[27]

CONCLUSIONS

Different marketing strategies for herbal products are possible. To start with, three main groups of products can be distinguished:

1. A product with a known effect and predefined indication. The advantage of such a product is that it can be marketed as a (traditional) medicinal product and therefore may easily find the target consumer.
2. A product with a new indication that needs a relatively small investment to develop. This product could be marketed as food supplement with a new article 13 claim, or with a disease risk reduction claim ('article 14'). Such a procedure may require additional clinical testing.
3. A product with a new indication having a medicinal claim. The disadvantage is that this development programme requires rigorous preclinical and clinical tests and is very expensive.

A herb with a known effect on health, either from traditional use or well-established use, described under 1 can be developed as a food supplement or as a (traditional) herbal medicinal product. These products can be in the EU market as food supplements, as well as (traditional) herbal medicinal product. It is an important question to determine whether the product is subject to food law or to medicines laws. This difference depends on the presentation and function of the product. No herb or ingredient can be

evaluated as medicinal product as such, but classification depends on the total of the end product's characteristics. In the next few years, it is expected that the European Court of Justice will judge on borderline products in cases of dispute. As an example, see case C-319/05 of the European Court of Justice.[28] These trials will help to determine the border between food supplements and medicinal products. In addition, the concentration of the herb may be a determinant for the classification as medicinal product or food supplement.[29] It is expected that a new committee of the EC will work on the boundaries between food supplements and herbal medicinal products.

It is expected that the market for herbal products will shift when the new legislation for herbal medicinal products (Directive 2004/24) is fully implemented. The interesting but difficult question is: What will be the impact on the herbal food supplement market? With the new Directive and the community monographs, it has become relatively easy to develop a herbal product as a medicinal product. The possibility of having a solid medicinal claim will weigh out the higher costs for the registration and manufacturing of medicinal products, compared to that of food supplements. It might therefore be expected that many food supplements will disappear because of competition and that the herbal food supplement market will become smaller. In addition, the EC reported that the Directive on traditional herbal medicinal products may be extended to other products, like traditional medicinal products derived from animal origin, medicinal honey, and certain amino acids and probiotics. Further extension, however, will not be started before the Directive on traditional herbal medicinal products is fully implemented.[13]

For traditional herbal products it may be wise to apply for registration. This decision, however, greatly depends on a number of factors related to legislation, technical requirements and marketing. In relation to marketing, one should think about their target population. Is the product intended to be delivered directly to the consumer? This product requires a clear, medicinal claim. When the product should be recommended by a physician practicing complementary medicine or a herbalist, the need for a medicinal claim is less, as the professional is able and willing to understand the scientific literature on the ingredients.

In addition, the economic perspectives should be taken into account. What investment is possible in product development? The possibilities for marketing protection by intellectual property and data protection should be taken into account. A new article 13 claim on a food supplement could give some marketing protection, while a traditional medicinal product can not be protected by intellectual property. Decisions on the marketing strategy for a herbal product should be evaluated on case-by-case basis. Finally, it is advisable to follow the developments and the future perspectives for herbal products in Europe closely, as this market will evolve rapidly in the coming years.

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