

CHAPTER

1

Classification of Herbal (Medicinal) Products

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Introduction

Herbal products may be medicines, food or cosmetics. The decision tree shown in Figure 1.1 later in this chapter may assist in deciding in what category to fit your product. This chapter focuses on traditional herbal medicinal products (THMPs) but also gives additional information on the classification of borderline products.

The basis of all legislation regarding any pharmaceutical product is European directives. There are a number of these. Each directive contains subsections called articles. Some articles have been amended by a later directive or directives. Therefore there is more than one place to look when considering all the current legislation.

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Key milestones on the way to the European Union (EU) definition of a THMP were as follows:

- Directive 1999/83/EC of 8 September 1999 which gave clarification on provisions for well-established use (WEU)
- Directive 2003/63/EC of 25 June 2003 (an updated Annex I to Directive 2001/83/EC) with specific provisions for herbal medicinal products (HMPs) on WEU
- Directive 2004/24/EC of 31 March 2004 which determines the conditions for simplified registration of THMPs
- Regulation 726/2004/EC of 31 March 2004 which established the Committee on Herbal Medicinal Products (HMPC) within the framework of Directive 2004/24/EC. HMPC held its inaugural meeting in September 2004 with nominated members of all member states.

Food and cosmetics are otherwise regulated and not directly involved in the harmonisation process of HMPs. Definitions and regulatory frameworks concerning (herbal) medicinal products, food including food supplements, novel food as well as cosmetic products will be given in the following sections of this chapter.

Classification as a medicine

Article 1 of Directive 2001/83/EC as amended defines a ‘medicinal product’ as follows:

Any substance or combination of substances presented for treating or preventing disease in human beings.

Any substance or combination of substances which may be administered to human beings with a view to making a medical diagnosis or to restoring, correcting or modifying physiological functions in human beings is likewise considered a medicinal product.

Medicines come in a variety of pharmaceutical forms depending on the condition to be treated and the various alternative modes of treatment. The purpose of these various forms of medication is to carry the active constituent (the drug) to the area where it is most needed and in so doing to avoid, or keep to a minimum, any unwanted effects on other areas of the body.

Characteristics of medicinal products are thus:

- interference with normal bodily functions
- treatment or prevention of diseases
- diagnostic
- variety of pharmaceutical forms.

Detailed guidance on what is a medicine is available in the ‘borderline products’ section of the Medicines and Healthcare products Regulatory Agency (MHRA) website. This may help to determine whether your product is medicinal or not. Some key issues will be looked at in more detail in the following sections.

Herbal medicinal products

Directive 2001/83/EC as amended by Directive 2004/24/EC defines an HMP as follows:

Any medicinal product, exclusively containing as active ingredients one or more herbal substances or one or more herbal preparations, or one or more such herbal substances in combination with one or more such herbal preparations.

Thus, an HMP may consist of one or more herbal ingredients of different levels of modification (processing). The conditioning, handling or processing of the herb is, per definition, responsible for whether a product is a herbal substance or a herbal preparation.

A plant part used without a specific processing is defined as a herbal substance. This could be the whole, fragmented or cut plant or parts of the plants as well as certain exudates. The herbal substance is characterised by the plant part used and the botanical name according to the binomial system and may be specified, for example, whether it is fresh or dried (e.g. dried, whole or fragmented bark).

If a herb is processed, e.g. by extraction, distillation, expression, fractionation, purification, concentration or fermentation, it is called a herbal preparation. Powdered herbal substances, tinctures, extracts, essential oils, expressed juices and processed exudates are included. Examples of herbal substances are predominantly herbal teas (infusions) where the patient turns the herbal substance into a herbal preparation by adding boiling water and preparing an infusion.

HOW HERBAL MEDICINES CAN REACH THE MARKET

In the UK, there are three possible regulatory routes by which a herbal medicine can be placed on to the market. It is necessary to ensure that a product complies with the necessary requirements as outlined by the MHRA as follows.

Unlicensed herbal remedies

Most herbal medicines in the UK currently reach the consumer as unlicensed herbal remedies. However, since 30 April 2004 unlicensed manufactured herbal medicines can no longer be placed on the market under Section 12 (2) of the Medicines Act 1968. They now need to comply with the requirements of the registration as THMP or alternatively obtain a full marketing authorisation. Unlicensed manufactured herbal medicines placed on the market under Section 12(2) of the Medicines Act before 30 April 2004 will need to comply with the requirements of the registration as THMP by April 2011 or obtain a full marketing authorisation.

Guidance on how a herbal product can be registered with the MHRA as a THMP is the prime purpose of this book. Detailed information is also given on the MHRA homepage (www.mhra.org.uk).

Thus, since 30 April 2004 the possibility of placing a herbal remedy on the UK market as an unlicensed herbal product has clearly been reduced; however, Section 12(1) of the Medicines Act 1968 still permits unlicensed herbal remedies to be supplied to individual patients following a face-to-face consultation.

Registered traditional herbal medicines

Directive 2004/24/EC introduced a new pathway for marketing THMPs, the 'simplified registration'. The date 30 October 2005 marked the introduction of a new scheme, the Traditional Herbal Medicines Registration Scheme, which, it was claimed, would help protect public health by requiring specific standards of safety and quality for traditional herbal medicines in contrast to unlicensed products.

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Licensed herbal medicines

Several hundred herbal medicines hold a marketing authorisation (a product licence) throughout the EU. In order to obtain a marketing authorisation a product needs to meet standards of safety, quality and efficacy/effectiveness (Figure 1.1).

When seeking to license herbal medicines, manufacturers have had difficulty meeting requirements to prove efficacy employing classical means (e.g. double-blind placebo-controlled clinical studies). This was one factor that led to the introduction of the Traditional Herbal Medicines Registration Scheme and many products are likely to follow this regulatory route. It will remain possible to obtain full marketing authorisation for herbal medicines where the required levels of efficacy as well as safety and quality can be demonstrated.

Following European Commission (EC) guidelines, a marketing authorisation for HMPs can be obtained in different ways depending on the substance, indication and intended claim. Levels of evidence to prove efficacy were defined by the Final Concept Paper on the Implementation of Different Levels of Scientific Evidence in Core Data for Herbal Medicinal Drugs (EMEA, 2004) as follows:

- *Grade A: Evidence Ia, Ib: Requires at least one randomised controlled trial as part of the body of literature of overall good and consistency addressing the specific recommendation*
- *Grade B: Evidence IIa, IIb, III: Requires availability of well-conducted clinical studies but no randomised clinical trials on the topic of recommendation*
- *Grade C: Evidence IV: Requires evidence from expert committee reports or opinions and/or clinical experience of respected authorities. Indicates absence of directly applicable studies of good quality.*

Thus the possibilities to obtain marketing authorisation for HMPs are:

- full marketing authorisation: procedure with full documentation with new tests and trials
- marketing authorisation of WEU HMPs: full bibliographic documentation
- mixed application: including existing bibliographic evidence, supplemented by the applicant's own research
- registration as traditional HMPs: simplified dossier for THMPs.

An overview of the legal framework for HMPs within the EU is given in Figure 1.2 (Vlietinck, 2006).

Traditional herbal medicinal product (THMP)

The usual requirement for medicines to be proven efficacious (as required under Directive 2001/83/EC) is replaced for THMPs by a requirement to demonstrate 30 years' traditional use for the required medicinal indication. The HMPC plays a central role in the evaluation of THMP.

COMMITTEE ON HERBAL MEDICINAL PRODUCTS (HMPC)

The HMPC was established in September 2004, replacing the Committee for Proprietary Medicinal Products (CPMP) Working Party on Herbal Medicinal Products. The Committee was established in accordance with Regulation (EC) no. 726/2004 and Directive 2004/24/EC.

The main task of the Committee is to establish Community herbal monographs and profiles of herbal substances, preparations and combinations thereof for use in traditional medicinal products. For this purpose the Working Party on Community Monographs and Community List (MLWP) was established in January 2006 (operational from March 2006), replacing the temporary HMPC Safety

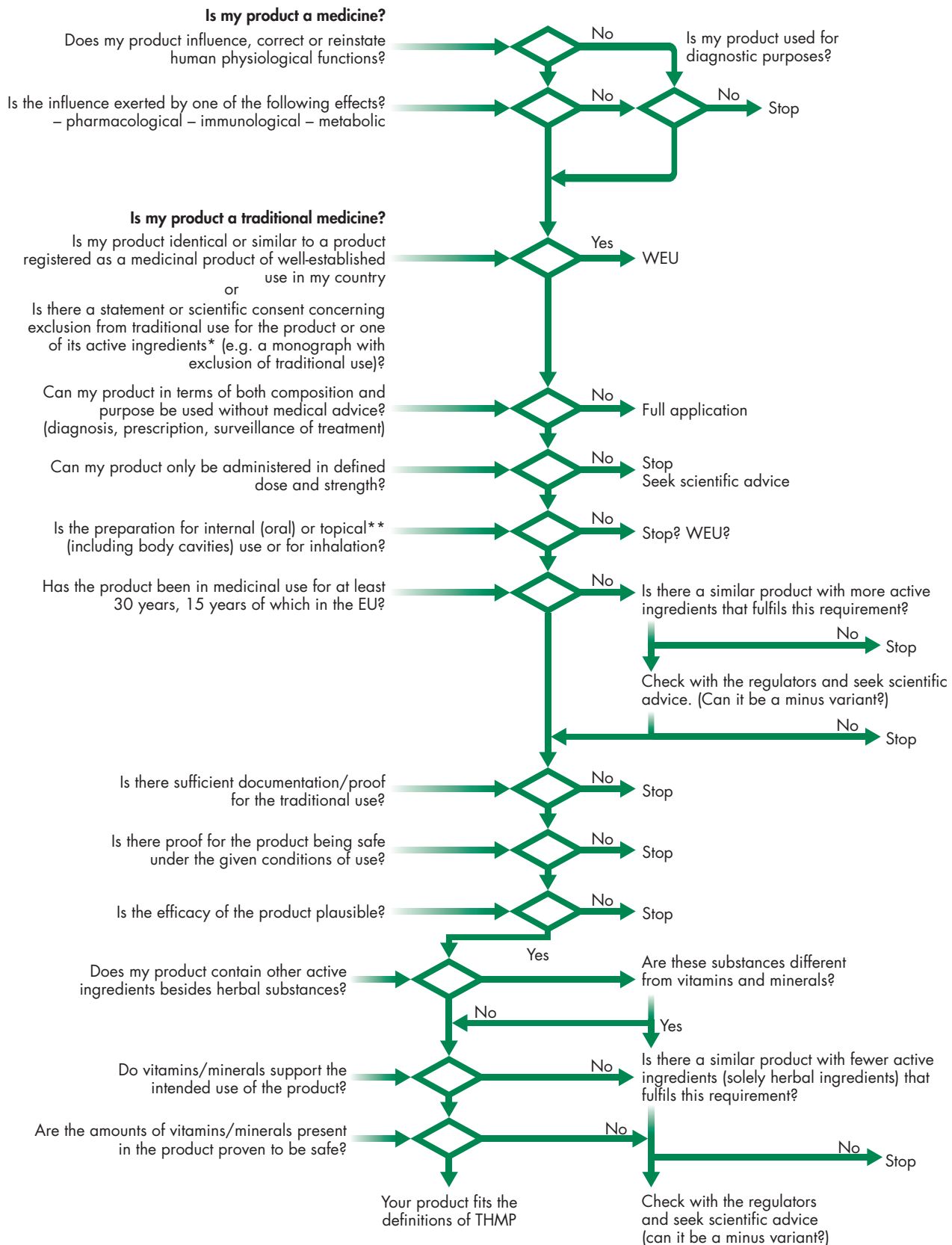


FIGURE 1.1 Decision tree.

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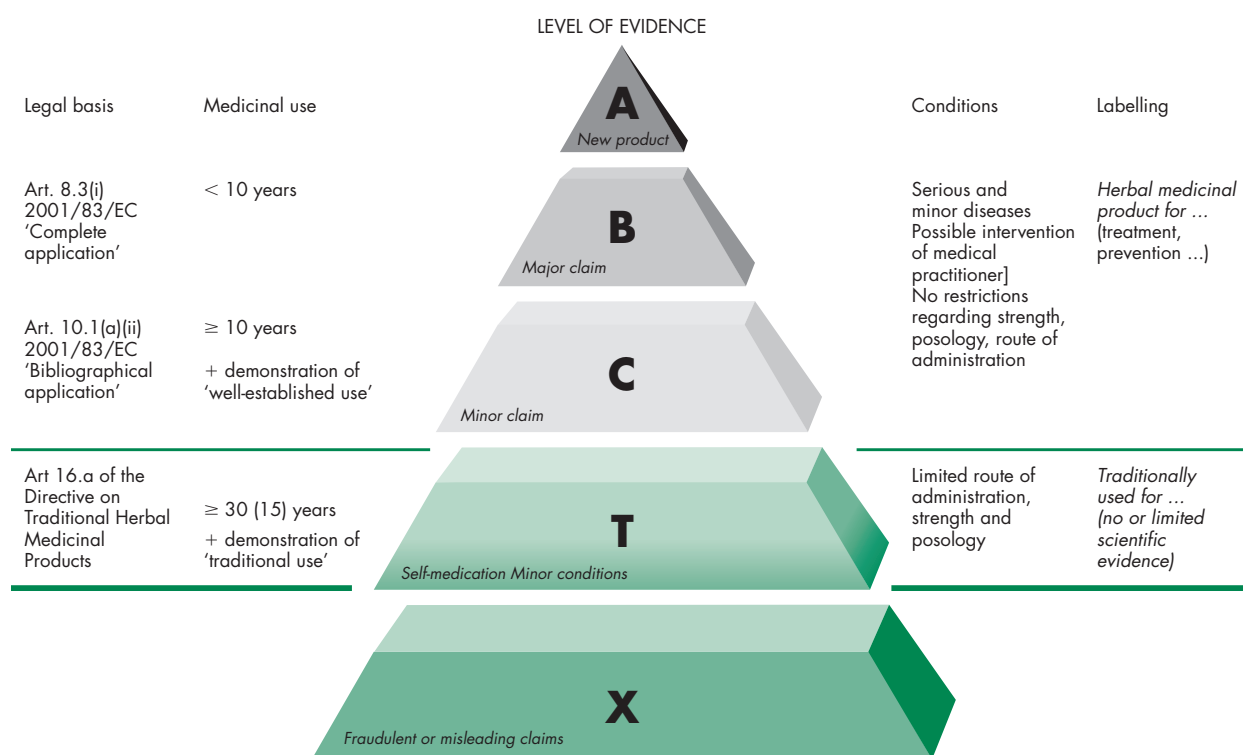


FIGURE 1.2 Overview: legal framework for herbal medicinal products in the EU. (Reproduced with permission from Vlietinck (2006)).

and Efficacy Drafting Group. To fulfil this objective, the MLWP works with a short-term priority list of 45 plants which was established by the Safety and Efficacy Drafting Group.

In addition, the MLWP is responsible for developing guidance relating to WEU and traditional-use applications, as well as addressing safety issues arising in the area of HMPs. Where appropriate, the MLWP coordinates its work with the Committee for Medicinal Products for Human Use (CHMP) Safety Working Party.

HERBAL MEDICINAL PRODUCTS WORKING PARTY (HMPWP)

Up to 2004 the HMPWP served as a forum for exchange of experience in the field of HMPs. The Working Party prepared a number of documents providing member states and applicants with guidance and common criteria for interpretation on how to prove the quality, safety and efficacy of HMPs adequately. The HMPWP became a working party of the CPMP in 2002. The views presented in these documents are those of the HMPWP alone. The documents are released for the purposes of transparency and have no legal force with respect to Directive 2001/83/EC. The HMPWP ceased operation in 2004.

When planning to apply for a traditional-use registration, it will therefore be required to demonstrate that the herbal medicine or 'corresponding' (that is, comparable) product(s) has been in medicinal use for 30 years preceding the date of the application. Normally at least 15 years of this usage must have been within the EU. THMPs already on the market in the member states must comply with the new scheme within at least 7 years (April 2011) but timelines are different and may be earlier in certain member states (e.g. for Germany it is December 2008).

According to Directive 2004/24/EC, 'corresponding products' are those that have the same active ingredients, the same or similar intended purpose, the same or similar route of administration and

equivalent strength. The MHRA runs a preapplication notification scheme. Companies can submit outline information about likely registrations and receive feedback. Moreover, the MHRA publishes UK public assessment reports of registered THMPs. MHRA also provides a Traditional Herbal Medicines Registration Scheme on its website (MHRA, 2007b). The scheme was launched in October 2005 in the UK and the first traditional herbal registration (THR) was granted 1 year later. To comply with the scheme, the MHRA recommends (Woodfield, 2007):

- to be clear on regulatory status of products
- to check that you have expertise to pursue THMP registration
- to remember that the 210-day timeline does not include ‘clock stops’
- to remember the time needed for stability testing, etc.
- to take a realistic view on how many registrations can be progressed at once
- not to start with the most complex product of the range.

THMPs may exist as monoproducts but also as combinations of several herbal substances/preparations and/or vitamins and minerals.

MONOPRODUCTS

Monoproducts are THMPs with one single herbal substance or a herbal preparation that is listed as a Community herbal monograph and/or on the list of herbal substances, preparations and combinations thereof for use in traditional medicinal products.

COMBINATIONS

THMPs often contain a large number of active substances formulated in accordance with good medical practice 30 years ago or more. In the last decades pharmacological and scientific knowledge has increased and requirements on fixed combinations have changed. A herbal combination used in a THMP must show plausibility with respect to the claimed traditional indication. As a result more monopreparations or combinations with only a few components have been accepted for WEU and THMP registration. Plausibility and therapeutic efficacy may be increased by reducing the number of active substances in herbal combinations (minus variants).

Minus variants

The traditional use of herbal combinations may be documented with HMPs which may contain more herbal substances than the product that is to be licensed. With regard to THMPs, Directive 2004/24/EC stated that a corresponding product:

... is characterised by having the same active ingredients, irrespective of the excipients used, the same or similar intended purpose, equivalent strength and posology and the same or similar route of administration as the medicinal product applied for.

Moreover, Article 16c (3) outlined that the requirements to show medicinal use throughout the period of 30 years is satisfied:

... if the number or quantity of ingredients of the medicinal product has been reduced during that period.

Thus, traditional use of a herbal combination can be documented with reference to corresponding products that contain more active ingredients than the product applied for. For example, a product may be referred to which contained or still contains substances in homeopathic dilutions if the product to be

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licensed does not contain these substances, or reference may be made to a product comprising three herbal substances while the product to be licensed only contains two, where the third (omitted) substance does not contribute to the combination's efficacy or has since been identified as carrying a safety risk. The product to be licensed would then be a 'minus variant' of the corresponding product.

Products with a well-established medicinal use (WEU)

Definition of and guidance on well-established medicinal use are given in Annex 1 Part II of Council Directive 2003/63/EC (25.06.2003) as follows:

1. (a) Factors important to establish whether a product should be classified under the well-established medicinal use category are:
 - the time over which a substance has been used, not less than 10 years from first and systematic use as a medicinal product
 - quantitative aspects of the use of the substance
 - the degree of scientific interest in the use of the substance
 - the coherence of scientific assessments.

Therefore different periods of time may be necessary for establishing well-established use of different substances. In any case, however, the period of time required for establishing a well-established medicinal use of a constituent of a medicinal product must not be less than one decade from the first systematic and documented use of that substance as a medicinal product in the Community.

1. (b) Bibliography

... should cover all aspects of the safety and/or efficacy assessment and must include or refer to a review of the relevant literature, taking into account pre- and post-marketing studies and published scientific literature concerning experience in the form of epidemiological studies and in particular of comparative epidemiological studies. All documentation, both favourable and unfavourable, must be communicated.

1. (c) Concerning missing information: justification must be given why demonstration of an acceptable level of safety and/or efficacy can be supported although some studies are lacking.
1. (d) Non-clinical and/or clinical overviews must explain relevance of any data submitted which concern a product different from the product intended for marketing.
1. (e) Postmarketing experience with other products containing the same constituents is of particular importance and applicants should put a special emphasis on this issue.

In view of the requirements for an application of a product with well-established medicinal use it is to be decided whether a product meets the requirements for a full or WEU application or if sufficient scientific data are lacking and therefore a simplified registration is necessary.

The beneficial effects of an HMP being classified under WEU must be evaluated against the possible harmful effects. Evaluation takes into account the nature of the active ingredients, the dosage form (for example, tablet or liquid), the nature of the disease or condition to be treated, the effective dose that needs to be given, the type of patient (for example, age, sex) and the duration of treatment. For example, a high risk-to-benefit ratio may be acceptable in the treatment of terminally ill patients where

the quality of life might be enhanced, whereas a very low risk-to-benefit ratio is expected in the treatment of patients with self-limiting diseases, for the purpose of prophylaxis and for those requiring lifelong treatment for their illnesses. The latter applies for the vast majority of HMPs.

For more information on the differences between WEU and THMP registration, requirements and permitted indications, HPMC's community monographs may be consulted. A bibliographic application will be possible only if the published data are in a form that gives good clinical evidence. It is very important to note that any bibliographic application as WEU must be backed, for example, by an HPMC monograph covering WEU use.

While the Directive states that the simplified registration (THMP) should only be used for products where there is a notified lack of sufficient scientific data,

... this simplified procedure should be used only where no marketing authorisation can be obtained pursuant to Directive 2001/83/EC, in particular because of a lack of sufficient scientific literature demonstrating a well-established medicinal use with recognised efficacy and an acceptable level of safety.

It is quite feasible to register products as THMP in one EU market which may have WEU status and a full market authorisation in another EU state, provided that they meet THMP requirements (traditional use) in the country in question.

Alternative marketing opportunities

Herbal products may also be marketed as food, food supplements or ingredients of functional foods or cosmetics if they are not medicines.

FOODS, FOOD (DIETARY) SUPPLEMENTS AND NOVEL FOOD

Herbal substances marketed as food can be marketed as:

- normal foods as defined in the UK Food Safety Act 1990
- food (dietary) supplements covered by Directive 2002/46/EC of the European Parliament and of the Council on food supplements
- novel food, including genetically modified (GM) food covered by Novel Food Regulation (EC) 258/97.

Food

The definition of food in the UK Food Safety Act 1990 is that used in Article 2 of EC Regulation 172/2002:

... food (or foodstuff) means any substance or product, whether processed, partially processed or unprocessed, intended to be, or reasonably expected to be ingested by humans

Food shall not include medicinal products within the meaning of Council Directive 2001/83/EC. Information on what is a food is provided by the UK Food Standard Agency (www.food.gov.uk). The Food Standards Agency is an independent government department set up by an Act of Parliament in 2000 to protect the public's health and consumer interests in relation to food.

The MHRA published Guidance Note 8: A Guide to What is a Medicinal Product (MHRA, 2007a). Therein, food is defined as follows:

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'Food' includes any food, drink or food supplement that is part of the diet. Any ingested product which is not a medicinal product is a 'food', including articles and substances of no nutritional value. A product which the average consumer would regard as something to be eaten, drunk or chewed as part of his/her diet for example, because of its taste, flavour, or nutritional value is unlikely to be classified by the MHRA as a medicinal product unless it contains one or more ingredients generally regarded as medicinal and indicative of a medicinal purpose. If the MHRA determines that such a product is not a medicine, it will be regulated under food law. A product which satisfies equally well the conditions for classification as a food and the conditions for classification as a medicinal product will be classified as a medicinal product.

Claims to treat, prevent or cure disease are prohibited for food.

An MHRA determination that a product is not a medicine does not amount to an approval that the product may legally be sold under food law and vice versa. Also, a Food Agency determination that a product is not a food does not amount to an approval that the product may legally be sold as a medicine. Manufacturers and individuals intending to place a product on the market as a food should seek confirmation from the Trading Standards Service of their local authority.

Food supplements

The EU defines a food supplement as:

Foodstuffs the purpose of which is to supplement the normal diet and which are concentrated sources of nutrients or other substances with a nutritional or physiological effect, alone or in combination, marketed in dose form, namely forms such as capsules, pastilles, tablets, pills and other similar forms, sachets of powder, ampoules of liquids, drop-dispensing bottles, and other similar forms of liquids and powders designed to be taken in measured small unit quantities.

The definition developed by the Proprietary Association of Great Britain (PAGB), British Herbal Manufacturers' Association (BHMA) and the Health Food Manufacturers' Association (HFMA) is:

Foods in unit dosage form, e.g. tablets, capsules and elixirs, taken to supplement the diet. Most are products containing nutrients normally present in foods which are used by the body to develop cells, bone, muscle etc., to replace co-enzymes depleted by infection and illness, and generally to maintain good health.

According to Mason (2007), dietary supplements fall into several categories in relation to ingredients:

1. multivitamins and minerals, single vitamins and minerals, combinations of vitamins and minerals, combinations of vitamins and minerals with other substances
2. vitamins and minerals, for which a requirement and a deficiency disorder in humans have not, so far, been recognised
3. natural oils containing fatty acids for which there is some evidence of beneficial effects
4. natural substances containing 'herbal' ingredients with recognised pharmacological actions but whose composition and effects have not been fully defined
5. natural substances whose composition and effects are not well defined but which may have beneficial effects
6. enzymes with known physiological effects, but of doubtful efficacy when taken orally
7. amino acids or amino acid derivatives.

The majority of dietary supplements in the UK are classified legally as foods, and sold under food law. Thus, most supplements are not controlled by the Medicines Act 1968.

Food supplements must comply with the requirements of the food supplements Directive 2002/46/EC. This directive came into force in July 2002 and was implemented in the UK by the Food Supplements (England) Regulations 2003. Separate, equivalent legislation has been made in Scotland, Wales and Northern Ireland. The directive and these regulations have applied in full since 1 August 2005.

One of the provisions of this directive is an approved list of nutrients and their chemical sources that can legally be included in food supplements. The first list covers the vitamins and minerals that may be used in food supplements (such as vitamin C, calcium, iron). It excludes six minerals (tin, silicon, nickel, boron, cobalt and vanadium) that are currently used in food supplements on sale in the UK.

The second list covers the chemical forms (sources) of those vitamins and minerals that may be used. These lists can be added to following a favourable opinion on individual nutrients or nutrient sources from the European Food Safety Authority (EFSA) after consideration of a dossier containing safety data.

Only vitamins and minerals in the forms listed in the directive may be used in the manufacture of food supplements after 31 December 2009.

Several dossiers have been submitted to the EC under Article 4(6) of Directive 2002/46/EC for approval as a food supplement. Some are not appropriate to be sold as food supplements as the regulatory authorities consider them to be medicines. Several substances, for which dossiers were originally submitted, have been classified as medicinal by the MHRA and may no longer be sold in the form of food supplements in the UK. These substances have hence been withdrawn from the food supplements market.

Companies that wish to market particular nutrients or nutrient sources in other member states should check with the relevant competent authority on requirements with respect to current derogation.

According to Directive 2002/46/EC:

There is a wide range of nutrients and other ingredients that might be present in food supplements including, but not limited to, vitamins, minerals, amino acids, essential fatty acids, fibre and various plants and herbal extracts.

The Directive has laid down specific rules for vitamins and minerals and stated that:

Specific rules concerning nutrients, other than vitamins and minerals, or other substances with a nutritional or physiological effect used as ingredients of food supplements should be laid down at a later stage, provided that adequate and appropriate scientific data about them become available.

With respect to the use of herbal substances/preparations in food supplements, new regulations are to be expected in the future in the context of Directive 2002/46/EC, but:

... until such specific Community rules are adopted and without prejudice to the provisions of the Treaty, national rules concerning nutrients or other substances with nutritional or physiological effect used as ingredients of food supplements, for which no Community-specific rules have been adopted, may be applicable.

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Health claims will be regulated by the proposed Health and Nutrition Claims Regulation. Advertising of dietary supplements is regulated by various advertising laws.

Genetically modified (GM) and novel foods

If your herbal product is placed on the market as food or food ingredients you must be sure that it is not a novel or GM food. Otherwise it has to undergo novel food approval.

Ingredients that do not have a history of significant consumption within the EU prior to 15 May 1997 may be subject to the controls of Novel Food Regulation (EC) 258/97. All novel foods are subject to a premarket safety assessment under Novel Food Regulation (EC) 258/97. The Novel Food Regulation is presently undergoing substantial revision. The main objective is to separate foods that have been traditionally used, but not within the EU, from foods that are entirely new in origin, such as GM products.

In the UK the Advisory Committee on Novel Foods and Processes (ACNFP) carries out all novel food assessments. Advice on this point should be sought from the Food Standards Agency.

COSMETICS

The Cosmetics Directive 76/768/EC (implemented in the UK by the Cosmetic Products (Safety) Regulations 2004 (SI 2004/2152)) as amended, harmonises the requirements for cosmetics in the European Community to achieve free trade in cosmetics while ensuring that the products are safe and consumers are not misled. It prohibits, or places restrictions on, certain ingredients and defines a cosmetic product.

The Annexes to the Cosmetics Directive list substances that must not be used in cosmetics and substances whose use is regulated. Under this system, cosmetic products must meet various safety requirements, but, unlike medicinal products, they do not require a licence.

Article 1(1) of the Cosmetic Directive (Council Directive 76/768/EEC of 27 July 1976) defines a cosmetic product as:

... any substance or preparation intended to be placed in contact with the various external parts of the human body (epidermis, hair system, nails, lips and external genital organs) or with the teeth and the mucous membranes of the oral cavity with a view exclusively or mainly to cleaning them, perfuming them, changing their appearance and/or correcting body odours and/or protecting them or keeping them in good condition.

Thus the principal purpose and characteristics of a cosmetic product are:

- cleaning
- perfuming
- changing the appearance
- correcting body odours
- protecting
- keeping in good condition

and refer to external parts of the body, oral mucous membrane or teeth.

The European Council and the Commission agree that the expression 'protecting or keeping in good condition' does not cover prevention of disease or protection against contamination.

However, products may be on the borderline between cosmetics and medicines and guidance is given in the MHRA Guidance Note 8: A Guide to What is a Medicinal Product (MHRA, 2007a) and the EC Guidance Document on the Demarcation Between the Cosmetic Products Directive 76/768 and the Medicinal Products Directive 2001/83 as Agreed Between the Commission Services and the Competent Authorities of Member States (European Commission, 2005).

Borderline products

Most human medicines are clearly identifiable as such and are subject to EC marketing authorisation procedures. However, there are some products where it is not so easy to distinguish a medicine from, for example, cosmetics or food supplements. These are known as borderline products.

A minority of products may potentially satisfy the definition of a medicinal product and simultaneously the definition of another type of product. The MHRA will decide whether to classify such a product as a medicinal product on a case-by-case basis, taking into account all relevant factors in relation to its presentation and function. However, in accordance with Article 2(2) of the directive, where doubt remains as to its classification as a medicine or another type of product, it will be classified as a medicinal product (MHRA, 2007a).

MHRA provided guidance on borderline products (MHRA, 2001) that should be read in conjunction with Guidance Note 8: A Guide to What is a Medicinal Product (MHRA, 2007a).

A product that is for use only as a toilet preparation, disinfectant, food or beverage is not normally regarded as a medicinal product and therefore does not require a marketing authorisation before being sold in the UK. Similarly, dietary supplements, containing such familiar substances as vitamins, amino acids or minerals, are generally subject to food safety and food labelling legislation rather than medicines control. However, changes may occur due to new scientific knowledge and safety evaluations as described above in relation to the supplement Directive.

On the borderline between food and medicine are also some special products including food for a particular nutritional purpose, e.g. products to provide nutritional support to athletes and people who exercise (sports supplements) and products for individuals wishing to lose weight (slimming/dieting products). These would fall within the definition of a medicinal product if:

- they make medicinal claims
- they modify physiological functions by acting pharmacologically, immunologically or metabolically, or are marketed and used with a view to having such an effect.

HOW TO DETERMINE WHETHER A PRODUCT IS MEDICINAL

The MHRA's Borderline Section will offer advice on the status of a product in cases of doubt. In making a decision, the MHRA will consider each individual product's merits and any information that may have a bearing on the product's status, for example:

- the claims made for the product
- the pharmacological properties of the ingredients
- comparison with potentially similar licensed products in the market
- the presentation to the public through labelling, packaging, promotional literature and advertisements.

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In addition there is an Independent (Advisory) Review Panel which, on request, will consider written and oral representations against MHRA provisional classification determinations. Guidance on requesting a review of a provisional determination issued by the Borderline Section is available. Further information can be found in the demarcation paper provided by the EC between cosmetics and medicines (European Commission, 2005).

A good example of a borderline herbal product is bath salts:

Bath salts are used to counteract certain sensations such as heaviness in the legs and tiredness. Therefore, they would normally not fall under the definition of medicinal products. However, bath salts may be medicinal products if the product is presented as treating/preventing these symptoms as being of pathological origin and the product as a medicine to combat these symptoms. The same reasoning applies to foot care products.

Criteria to be considered regarding cosmetics and medicines include:

- the mode of application
- principal purpose
- all claims made for the product
- the context in which the claims are made, and the overall presentation
- how a product appears to the public, or to those to whom it is promoted
- the labelling, and packaging/package inserts, including any graphics
- the promotional literature, including testimonials and any literature issued by a third party on behalf of the supplier
- advertisements
- any particular target of the marketing information/advertising material, for example, population groups with, or particularly vulnerable to, specific diseases or adverse conditions.

There is also a definition by virtue of function (European Commission, 2005) to characterise a product as medicinal:

- restores, corrects or modifies physiological functions by exerting a pharmacological, immunological or metabolic action (Directive 2004/27/EC).

However, the ‘modification of physiological function’ criterion is not absolute, as has been stated for moisturising creams (European Commission, 2005):

Every moisturising cream affects the skin cells by adding water to the cell. Depilatories and anti-wrinkle products (cf. annex 1 to the Cosmetics Directive) modify physiological functions by exercising an effect on somatic (skin) cells.

Thus, pharmacological, immunological or metabolic actions may serve as criteria in those cases. They were defined as follows.

Pharmacological action

Interaction between the molecules of the substance in question and a cellular constituent, usually referred to as a receptor, which either results in a direct response, or which blocks the response to another agent. Although not a completely reliable criterion, the presence of a dose—response correlation is indicative of a pharmacological effect.

Key characteristics of pharmacological actions

- Interaction with a receptor
- Dose–response relationship

Immunological action

Action in or on the body by stimulation and/or mobilisation of cells and/or products involved in a specific immune reaction.

Key characteristic of immunological action

- Involved in specific immune reactions

Metabolic action

Action which involves an alteration, including stopping, starting or changing the speed of the normal chemical processes participating in, and available for, normal body function. The fact that a product is metabolised by the human body does not necessarily mean that the substance contained in the product has a metabolic action upon the body.

Key characteristic of metabolic action

- Modification of chemical (metabolic) processes (this is, for example, also characteristic for food)

Summary

Herbal products may be medicines, food or cosmetics. To assist companies make a decision in determining the likely status of their product the MHRA has compiled a list of herbal ingredient categories (MHRA, 2005). This list may help decide whether or not a herbal product can be placed on the market as a THMP.

The list gives the botanical and other names of various plants together with the known uses of those plants.

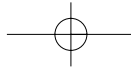
For instance, garlic is listed with uses recorded in medicine, food, aromatherapy and cosmetics, for Black Cohosh medicinal and cosmetic uses are recorded, while croton oil is listed in the prescription-only medicine order and a medicinal product containing it will therefore be controlled as a prescription-only medicine in the UK (MHRA, 2005).

The MHRA pointed out that the list is not exhaustive and the following points should always be considered:

- The list is for information only: the status of a product under medicines legislation is determined on an individual basis taking into account all the factors detailed in Guidance Note 8 (MHRA, 2007a).
- Products that contain an ingredient showing a ‘no’ in the medicinal uses column may none the less be classified as medicinal depending on the product’s presentation.
- The list has no legal status.
- If a product is not considered a medicinal product advice should be sought from the relevant regulatory body on the legality of that product.

The list gives the following information:

- botanical name
- common name



16 PRODUCT ELIGIBILITY

- any recorded medicinal uses
- any recorded food uses
- recorded use in aromatherapy
- recorded use in cosmetic products
- general comments
- the part(s) of the plant used medicinally.

The various ways of licensing and/or marketing a product are summarised below with regard to the respective requirements as well as advantages (or disadvantages) associated.

THMP

- Must have traditional use (30 years, 15 years within the EU)
- Safety information required
- Quality information required (manufacturing according to good manufacturing practice, analytical and stability data)
- No proof of efficacy required (traditional use sufficient)
- Reference to similar products can be made
- Minus variant possible
- Reference to Community monograph can be made
- Only 'weak' or general health claims can be made
- Development and registration comparatively inexpensive.

WEU

- Full dossier required (pharmaceutical and quality information)
- Bibliographic evidence for efficacy can be used
- Reference to similar products can be made
- Minus variant possible
- Reference to Community monograph can be made
- Stronger health claims can be made in accordance with clinically proven efficacy
- Wider array of marketing and advertising options available
- Development and registration relatively costly

FULL MARKETING AUTHORISATION

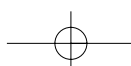
- Full drug development procedure required
- Full dossier required (pharmaceutical and quality information)
- Clinical evidence for efficacy required (trials)
- Strong health claims can be made in accordance with clinically proven efficacy
- Wider array of marketing and advertising options available
- Development and registration costly.

FOOD/FOOD SUPPLEMENT

- Must be a food
- Intended use must not be medicinal
- Only limited or no health claims can be made
- Less strict requirements as regards quality.

COSMETIC

- Intended use can be cosmetic only.



References

- Cosmetics Directive 76/768/EC as amended. Available online at: <http://europa.eu.int/eur-lex/lex/LexUriServ/LexUriServ.do?uri=CELEX:32001L0083:EN:HTML> (accessed 1 August 2008).
- Directive 1999/83/EC. Available online at: <http://europa.eu.int/eur-lex/lex/LexUriServ/LexUriServ.do?uri=CELEX:32001L0083:EN:HTML> (accessed 1 August 2008).
- Directive 2001/83/EC as amended. Available online at: <http://europa.eu.int/eur-lex/lex/LexUriServ/LexUriServ.do?uri=CELEX:32001L0083:EN:HTML> (accessed 1 August 2008).
- Directive 2002/46/EC. Available online at: <http://europa.eu.int/eur-lex/lex/LexUriServ/LexUriServ.do?uri=CELEX:32001L0083:EN:HTML> (accessed 1 August 2008).
- Directive 2003/63/EC. Available online at: <http://europa.eu.int/eur-lex/lex/LexUriServ/LexUriServ.do?uri=CELEX:32001L0083:EN:HTML> (accessed 1 August 2008).
- Directive 2004/24/EC. Available online at: Directive 2004/24/EC. Available online at: <http://europa.eu.int/eur-lex/lex/LexUriServ/LexUriServ.do?uri=CELEX:32001L0083:EN:HTML> (accessed 1 August 2008).
- Directive 2004/27/EC. Available online at: <http://europa.eu.int/eur-lex/lex/LexUriServ/LexUriServ.do?uri=CELEX:32001L0083:EN:HTML> (accessed 1 August 2008).
- EMEA (2004) EMEA/CPMP/HMPWP/1156/03. *Final Concept Paper on the Implementation of Different Levels of Scientific Evidence in Core Data for Herbal Medicinal Drugs*. London: EMEA.
- European Commission (2005) Guidance Document on the Demarcation Between the Cosmetic Products Directive 76/768 and the Medicinal Products Directive 2001/83 as Agreed Between the Commission Services and the Competent Authorities of Member States. Available online at: http://ec.europa.eu/enterprise/cosmetics/doc/guidance_doc_cosm-medicinal.pdf (accessed 1 August 2008).
- Mason P (2007) *Dietary Supplements*, 3rd edn. London: Pharmaceutical Press.
- Medicine and Healthcare products Regulatory Agency (2001) Guidance on Requesting a Review of a Provisional Determination Issued by the Borderline Section of the Medicines Control Agency. Available online at: www.mhra.gov.uk (accessed 1 August 2008).
- Medicine and Healthcare products Regulatory Agency (2005) List of Herbal Ingredients which are Prohibited or Restricted in Medicines. Available online at: www.mhra.gov.uk (accessed 1 August 2008).
- Medicine and Healthcare products Regulatory Agency (2007a) Guidance Note 8: A Guide to What is a Medicinal Product. Available online at: www.mhra.gov.uk (accessed 1 August 2008).
- Medicine and Healthcare products Regulatory Agency (2007b) Traditional Herbal Medicines Registration Scheme – Guidance for Retailers, Wholesalers, Importers and Manufacturers on the Requirements of the THMRS. Available online at: www.mhra.gov.uk (accessed 1 August 2008).
- Vlietinck AJ (2006) New European legislation for herbal medicinal products (HMPs) – new opportunities for African pharmaceutical industries? Presentation at Africa Herbal Antimalarial Meeting, Nairobi, Kenya 20–22 March.
- Woodfield R (2007) MHRA experience of operating the traditional herbal registration scheme – presentation at: The new Regulatory Framework for Herbal Medicinal Products; Vienna, 27–28 June.

Note: unless otherwise indicated, information referred to was provided by the MHRA (www.mhra.gov.uk) and Food Standard Agency websites (www.food.gov.uk).

