Herbal Medicines: Traditional Herbal Registration

In the UK, companies can only sell herbal medicines with the appropriate product licence, as follows:

- A full **marketing authorisation** based on the safety, quality and efficacy of the herbal product; or
- A **traditional herbal registration** based on the safety, quality and **evidence of traditional use** of the herbal product.

In this article, Dr Rosanna Cooper explores traditional herbal medicines and traditional herbal registrations.

Herbal Products – Are they Medicines, Food or Cosmetics?

Herbal products can be classified as medicines, food or cosmetics. The key is to assess your herbal products to ensure that they are correctly classified and therefore compliant under the law.

Traditional Herbal Medicinal Products

Article 1 of Directive 2001/83/EC (as amended) defines a '**traditional herbal medicinal product**' as a *"herbal medicinal product that fulfils the conditions laid down in Article 16a(1)"*.

The conditions laid down in Article 16a(1) are as follows:

"1. A simplified registration procedure (hereinafter "traditional- use registration") is hereby established for herbal medicinal products which fulfil all of the following criteria:

(a) they have indications exclusively appropriate to traditional herbal medicinal products which, by virtue of their composition and purpose, are intended and designed for use without the supervision of a medical practitioner for diagnostic purposes or for prescription or monitoring of treatment;

(b) they are exclusively for administration in accordance with a specified strength and posology;

(c) they are an oral, external and/or inhalation preparation;

(d) the period of traditional use as laid down in Article 16c(1)(c) has elapsed;

(e) the data on the traditional use of the medicinal product are sufficient; in particular the product proves not to be harmful in the specified conditions of

use and the pharmacological effects or efficacy of the medicinal product are plausible on the basis of long-standing use and experience."

A '**herbal medicinal product'** is defined in Article 1 of Directive 2001/83/EC (as amended) as *"**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."*

'**Herbal substances'** are defined as *"**all mainly whole, fragmented or cut plants, plant parts, algae, fungi, lichen in an unprocessed, usually dried, form, but sometimes fresh**. Certain exudates that have not been subjected to a specific treatment are also considered to be herbal substances. Herbal substances are precisely defined by the plant part used and the botanical name according to the binomial system (genus, species, variety and author)."*

Traditional Herbal Registration

A Traditional Herbal Registration is available, rather than a Marketing Authorisation, for placing **traditional herbal medicinal products on the market** or for their distribution by way of wholesale dealing in the UK.

Under Directive **2004/24/EC**:

"Recital 4 - Having regard to the particular characteristics of these medicinal products, especially their long tradition, it is desirable to provide a special, simplified registration procedure for certain traditional medicinal products. However, 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 should likewise not apply to homeopathic medicinal products eligible for marketing authorisation or for registration under Directive 2001/83/EC.

*(5) The long tradition of the medicinal product makes it possible to reduce the need for clinical trials, in so far as the efficacy of the medicinal product is plausible on the basis of long-standing use and experience. Pre-clinical tests do not seem necessary, where the medicinal product on the basis of the information on its traditional use proves not to be harmful in specified conditions of use. **However, even a long tradition does not exclude the possibility that there may be concerns with regard to the product's safety, and therefore the competent authorities should be entitled to ask for all data necessary for assessing the safety.** The quality aspect of the medicinal product is independent of its traditional use so that no derogation should be made with regard to the necessary physico-chemical, biological and microbiological tests. Products should comply with quality standards in relevant European Pharmacopoeia monographs or those in the pharmacopoeia of a Member State.*

(6) The vast majority of medicinal products with a sufficiently long and coherent tradition are based on herbal substances. It therefore seems appropriate to limit the scope of the simplified registration in a first step to traditional herbal medicinal products.

(7) The simplified registration should be acceptable only where the herbal medicinal product may rely on a sufficiently long medicinal use in the Community. Medicinal use outside the Community should be taken into account only if the medicinal product has been used within the Community for a certain time. Where there is limited evidence of use within the Community, it is necessary to assess carefully the validity and relevance of use outside the Community.

(8) With the objective of further facilitating the registration of certain traditional herbal medicinal products and of further enhancing harmonisation, there should be the possibility of establishing a Community list of herbal substances that fulfill certain criteria, such as having been in medicinal use for a sufficiently long time, and hence are considered not to be harmful under normal conditions of use."

Recital 4 of Directive 2004/24/EC provides that the simplified procedure of Traditional Herbal Registration is only available **where no marketing authorisation can be obtained for the product (pursuant to Directive 2001/83/EC) because of a lack of sufficient scientific literature demonstrating a well-established medicinal use with recognised efficacy and an acceptable level of safety**.

Marketing Authorisation

There is a general requirement under Article 6(1) of Directive 2001/83/EC (as amended), that a medicinal product must have a Marketing Authorisation before it can be placed on the market of a Member State, or be distributed by way of wholesale dealing in the UK.

"No medicinal product may be placed on the market of a Member State unless a marketing authorization has been issued by the competent authorities of that Member State in accordance with this Directive…"

For the purposes of this Directive, a 'medicinal product' relates to substances (or combination of substances) which are presented as being capable of preventing disease in human beings or **having an effect on the physiological functions of human beings** (Article 1 of Directive 2001/83/EC (as amended)).

"Medicinal product:
(a) Any substance or combination of substances presented as having properties for treating or preventing disease in human beings; or
(b) Any substance or combination of substances which may be used in or administered to human beings either with a view to restoring, correcting or

modifying physiological functions by exerting a pharmacological, immunological or metabolic action, or to making a medical diagnosis."

Applications for marketing authorisation of a herbal medicinal product must be accompanied by extensive supporting data, including results of physico-chemical, biological or microbiological tests, pharmacological tests, toxicological tests and clinical trials, in order to prove its **safety, quality and efficacy**. Where you can prove that there is sufficient scientific literature to demonstrate a well-established medicinal use with recognised efficacy and an acceptable level of safety, then you may not be required to provide the results of pre-clinical tests or clinical trials.

The Directive 2004/24/EC states that where the competent authorities judge that a medicine fulfils the criteria for a Marketing Authorisation, they should not grant a Traditional Herbal Registration (Article 16a(3) Directive 2001/83).

"…in cases where the competent authorities judge that a traditional herbal medicinal product fulfills the criteria for authorisation in accordance with Article 6 …the provisions of this chapter shall not apply."

Use for 15 years within the Community

Evidence must be produced to the Medicines and Healthcare Products Regulatory Agency ("MHRA") to show that a **traditional herbal medicinal product**, or a corresponding product, has been in medicinal use throughout a **30 year period preceding the date of application**, including at least **15 years within the Community** (Article 16c(1)(c) of Directive 2001/83/EC (as amended)).

*"(c) **bibliographical or expert evidence to the effect that the medicinal product in question, or a corresponding product has been in medicinal use throughout a period of at least 30 years preceding the date of the application, including at least 15 years within the Community**. At the request of the Member State where the application for traditional-use registration has been submitted, the Committee for Herbal Medicinal Products shall draw up an opinion on the adequacy of the evidence of the long-standing use of the product, or of the corresponding product. The Member State shall submit relevant documentation supporting the referral;"*

Article 16c(2) Directive 2001/83/EC (as amended) describes a '**corresponding product**' as

"*A corresponding product, as referred to in paragraph 1(c), 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**.*"

Qualified Person

Any manufacturer holding a traditional herbal registration and manufacturing a traditional herbal medicinal product or a medicinal herbal product under a marketing authorisation must hold a **manufacturer's/importer's authorisation** ("MIA").

Under European legislation, the services of at least one **qualified person** must be permanently and continuously at the disposal of the holder of a MIA, who would take responsibility for the quality of the products manufactured at the site where manufactured.

The **qualified person** must be named on the MIA.

The **qualified person** does not have to be a full time employee; he or she could be a contractor. The main point is to have a technical agreement between the manufacturer and the **qualified person** setting out the contractual responsibilities of the **qualified person**.

The duties of a **qualified person** include:

- **Good Manufacturing Practice** ("GMP") are followed;
- Adhering to the terms of the **traditional herbal registration** or the **marketing authorisation**;
- Ensuring **validation of manufacturing and testing processes**;
- All necessary quality control checks and tests have been conducted;
- Ensuring all imported products meet the legal requirements;
- Ensuring the testing of all products imported from outside the European Economic Area ("EEA") are tested within the EEA to meet the requirements of **traditional herbal registration** or the **marketing authorisation**;
- Each batch is certified/recorded that the requirements of **traditional herbal registration** or the **marketing authorisation** are met;
- Maintaining record and ensuring entries are recorded as soon as practicable after each batch has been manufactured and before the batch is released for sale.

A **qualified person** must be resident within the UK.

Responsible Person

The holder of a **wholesale dealer's licence** must have a **responsible person** in accordance with Article 79(b) of Directive 2001/83/EC (as amended). The

Responsible person is responsible for safeguarding products against potential hazards arising from poor distribution practice.

The **responsible person** is responsible for the following:

- To safeguard product users against potential hazards arising from poor distribution practices;
- To ensure that the conditions of the **wholesale dealer's licence** are met;
- Compliance with the guidelines of **Good Distribution Practice**.

A **responsible person** must be resident within the UK.

MHRA Guidelines

According to the MHRA Guidelines, for some herbal medicines there is sufficient evidence in the public domain for an applicant to be able to obtain a Marketing Authorisation under the provisions for products containing active substances with **'well established'** use by referring to appropriate scientific literature. Where this is the case the MHRA will not grant a traditional use application but will instead ask the applicant to apply for a Marketing Authorisation. Based on the MHRA's experience it is likely that this would apply in only a minority of cases. The MHRA will not take the view that a product ought to follow the **'well established'** route to a Marketing Authorisation simply because the medicine contains a particular herbal ingredient. It may well be that there are some herbal medicines that have several accepted indications, of which one might be appropriate for a Marketing Authorisation under the **'well established use'** provisions while another is suitable for traditional use registration.

Likewise, it may be that the **'well established use'** provisions are applicable to a range of products that use a particular **herbal ingredient**. However, traditional use might be applicable where that ingredient is used in combination with other active herbal ingredients, particularly for other therapeutic indications. Such combinations would need to satisfy the requirements for traditional use registration including that the efficacy is plausible - based on long use and experience. There have been some differences of interpretation of the **'well established'** provisions between regulatory authorities in different EU Member States. Advice given in other EU Member States will not necessarily be applicable in the UK and vice versa.

Potential Grounds for Revocation of a Traditional Herbal Registration

The following are **potential grounds** upon which Company A may challenge the traditional herbal registration for certain products of Company B. Supporting evidence would be required to substantiate the assertions by Company A.

- The products that have been granted a traditional herbal registration, are **not traditional herbal medicinal products** and the traditional herbal registration of Company B ought to be revoked on the following grounds:-

    - The products upon which Company B has based its application for the traditional herbal registration, were **developed as part of a pharmaceutical process** using herbal ingredients;

    - Only Company A owns the **rights to the process** (know-how);

    - The product owned by Company A with identical/similar composition to the products owned by Company B has been **on sale in Europe for less than 15 years**;

    - There is a question mark over the safety of the products owned by Company B;

    - The products owned by Company B require a Marketing Authorisation in order for Company B to sell these products in the UK and the rest of the European Union;

    - Marketing Authorisations **already exist** for an identical (if not, similar) product owned by Company A.

What is a borderline product?

Article 1 of Directive 2001/83/EC (as amended) as amended defines a medicinal product as:

"Any substance or combination of substances presented as having properties for treating or preventing disease in human beings;
Any substance or combination of substances which may be used in or administered to human beings either with a view to restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action, or to making a medical diagnosis."

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 product which is for use only as a toiletry, disinfectant, food or beverage is not normally regarded as a medicinal product, and would not require a marketing authorisation to be sold in the UK.

Dietary supplements containing vitamins, amino acids or minerals, are generally subject to food safety and food labelling legislation rather than medicines control.

In the event that a food and/or cosmetic contain a **pharmacologically active substance or make medicinal claims** (*claims to treat or prevent disease, or to interfere with the normal operation of a physiological function of the human body are regarded as medicinal*).

Conclusion

Companies manufacturing and/or distributing herbal medicines must ensure compliance with the law.

The author is Dr Rosanna Cooper of RT Coopers Solicitors. She is an expert in regulatory law, in particular, herbal medicines. Dr Cooper is a chartered chemist and a fellow of the Royal Society of Chemistry. She may be contacted on +44 (0) 207 488 9947 or by email: enquiries@rtcooperssolicitors.com. For more information on the services provided by RT Coopers on cosmetic law, visit http://www.rtcoopers.com/practice_regulatory.php.