Herbal remedies

Joanna Wheeler and Geneviève Michaux of **Covington & Burling** analyse the new EU rules for traditional herbal medicinal products

On 30 April 2004, the European Commission published Directive 2004/24/EC on traditional herbal medicinal products (the Herbal Directive), which amends existing legislation on medicinal products, Directive 2001/83/EC, as amended by Directive 2004/27/EC. Member states must implement the Herbal Directive by 30 October 2005.

Scope of the Traditional Use Registration scheme

For the definitions of herbal medicinal products, see the box overleaf.

Availability of the Traditional Use Registration procedure

The Traditional Use Registration will only apply to a herbal medicinal product that:

(a) has an indication 'exclusively appropriate' to a traditional herbal medicinal product and is intended and designed for use without supervision of a medical practitioner;
(b) is exclusively for administration in accordance with a specified strength and posology;
(c) is an oral, external or inhalation preparation;
(d) satisfies the period of 'traditional use' (see below); and
(e) has adequate data to support the traditional use (ie it must not be harmful if used as directed, and its pharmacological effects or efficacy must be plausible based on long-standing use).

The Traditional Use Registration will not apply where national regulatory authorities judge that a herbal medicinal product satisfies the requirements for obtaining a marketing authorisation under amended Directive 2001/83/EC, for instance under the bibliographical authorisation procedure. The latter is available when the active ingredient has a 'well-established medicinal use' within the EU for at least ten years, with recognised efficacy and an acceptable level of safety under Annex I of amended Directive 2001/83/EC. Companies will need guidance from the Committee on Herbal Medicinal Products (HMPC) on the scope of the two review procedures and, in practice, there may be some overlap.

The Traditional Use Registration will also not apply to homeopathic products that fulfil the criteria for a standard medicinal product marketing authorisation or for homeopathic registration under amended Directive 2001/83/EC.

Combination products

The Herbal Directive permits registration of traditional herbal medicinal products that also contain vitamins and minerals, provided their action is ancillary to the active ingredient and only where proven safe. This potentially covers several products currently sold as dietary supplements.

Other active ingredients cannot be used.

Borderline products

The Herbal Directive relates to herbal products that are medicinal. Which products will be considered medicinal is unclear, because some products can be sold in other categories depending on their presentation. Categorisation criteria include: effects of the ingredients, the manner in which the product is presented and promoted, whether claims are made to treat or prevent disease, the product form, directions for use, and possible risks to consumers. Because the criteria are vague, they lead to different results in different member states. The Commission is organising a workshop to reach a more unified approach, but establishing a single practice will take time. For now, companies must rely on precedents and statements by national regulators.

The recitals to the Herbal Directive state that non-medicinal herbal products which fulfil EU food legislation criteria will

THE DIRECTIVE

The new Herbal Directive introduces:

- a new classification which recognises the specific nature of traditional herbal medicinal products;
- a new simplified registration system for these products (Traditional Use Registration);
- a new Committee on Herbal Medicinal Products (HMPC), set up within the European Medicines Agency, to approve traditional herbal medicinal products, and to develop EU herbal monographs and a positive list of herbal substances; and
- new labelling and advertising requirements to clarify that registered traditional herbal medicinal products have been approved on the basis of long-standing traditional use.

continue to be regulated under that legislation. Culinary herbs and certain other plants can therefore continue to be sold as food supplements. Examples include garlic, ginseng and Garcinia cambogia. However, companies wishing to make medicinal claims may be able to register such products under the Herbal Directive.

Traditional Use Registration

Traditional herbal medicines will need to meet specific standards of safety and quality, and to demonstrate 'traditional use'. These standards are lower than those that apply to innovative medicines, and are intended to be more flexible than those governing bibliographical applications. The Herbal Directive does not specify a dossier form but member state authorities will probably follow the Common Technical Document format used for other medicinal products.

Official list of herbal substances

The HMPC and the Commission will establish a positive list of herbal substances, preparations and combinations to be used in traditional herbal medicines (the List). The List will contain for each substance: the therapeutic indication; specified strength and posology; route of administration; and other relevant safety information. For products containing a substance on the List, applicants may refer to the List without having to demonstrate traditional use or safety, but administrative and quality data will still need to be submitted. It is unclear how the List will be used for combinations. Although drafts of the List may be circulated sooner, an official List is unlikely to be published until autumn 2005.

To promote harmonisation, member states will be required to recognise registrations of herbal medicinal products granted by other member states consisting of substances contained on the List (or covered by an HMPC monograph).

Products not covered by the List

For products not covered in all aspects by the List, the applicant will have to submit data supporting traditional use and safety.

Traditional use must be supported by bibliographic or expert evidence that the product, or corresponding product, has been in medicinal use for at least 30 years. At least 15 of the 30 years must have been in the EU. The Herbal Directive defines 'corresponding product' as one having the same active ingredients, the same or similar purpose, equivalent strength and posology, and the same or similar route of administration. The 30-year requirement is satisfied even if the product was marketed without specific authorisation or if the number or quantity of ingredients of the product has been reduced over the 30-year period. If the product (or corresponding product) meets all but the 15-years-in-the-EU requirement, it may be referred to the HMPC, which may reduce that requirement. If possible, the HMPC will establish an EU-wide herbal monograph.

Evidence can derive from many sources, such as herbal experts, current textbooks,

DEFINITIONS IN THE NEW RULES

The new rules only apply to 'herbal medicinal products' which are defined 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.'

A medicinal product is defined in amended Directive 2001/83/EC as:

> '… any substance or combination of substances presented as having properties for treating or preventing disease in human beings… [or] 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.'

Herbal substances are defined in the Herbal Directive as:

> '… all mainly whole, fragmented or cut plants, plant parts, algae, fungi, lichen in an unprocessed, usually dried, form but sometimes fresh.'

The Directive further states that:

> '… certain exudates that have not been subjected to a specific treatment are also considered to be herbal substances… [and that] herbal substances are precisely defined by the plant part used and the botanical name according to the binomial system (genus, species, variety and author).'

Herbal preparations are defined as:

> '… preparations obtained by subjecting herbal substances to treatments such as extraction, distillation, expression, fractionation, purification, concentration or fermentation… [and include] comminuted or powdered herbal substances, tinctures, extracts, essentials oils, expressed juices and processed exudates.'

Medicines manufactured from isolated chemical constituents of plants are not considered traditional herbal medicinal products.

pharmacopoeias, published information referring to specific product formulations (for example, the Martindale List of Preparations), and company archive material (eg brochures and invoices).

To demonstrate safety, a bibliographic review of relevant data and an expert report will be required. Regulatory authorities may request additional data when, for example, there are specific concerns regarding safety, an ingredient is relatively unfamiliar to science, or the medicine has been used predominantly in countries where there is no reporting system, a shorter life expectancy or a significantly different gene pool.

Timing

It is difficult to predict the length of a typical Traditional Use Registration procedure. One would expect it to take between 6 and 12 months – the time it takes for a 'well-established use' bibliographical application. Obviously, the process will be quicker for applications using the List.

Committee for Herbal Medicinal Products

The HMPC met for the first time in September 2004 and includes experts in herbal medicinal products. It has broad control over the Traditional Use Registration procedure, and is also responsible for authorising herbal medicinal products under the general bibliographical application rules of amended Directive 2001/83/EC.

The HMPC assumed this role from the CHMP Working Party on Herbal Medicinal Products. In order to ensure appropriate communication between the CHMP and the HMPC, the executive director of the agency will set up a formal co-ordination procedure.

Labelling and advertising rules

The labelling and leaflet information and advertising of products with a Traditional Use Registration will need to meet the requirements in amended Directive 2001/83/EC. Furthermore, the Herbal Directive requires labelling and leaflets to state clearly that the indications are based on information obtained from long-standing use – not scientific data – and users must be advised to consult a qualified practitioner if symptoms persist. The Herbal Directive also requires any advertisement to indicate:

> … traditional herbal medicinal product for use in specified indication(s) exclusively based upon long-standing use.

Manufacturing

The quality requirements applicable to licensed medicines will apply to Traditional Use Registration products. In particular, manufacturers will need to comply with the principles of good manufacturing practice (GMP) and to hold a manufacturer's licence or a wholesale dealer's licence, where appropriate. Manufacturers and importers must employ at least one qualified person who is able to certify that GMP standards have been met.

'Traditional use must be supported by bibliographic or expert evidence that the product has been in medicinal use for at least 30 years.'

Entry into effect

Member states must introduce a Traditional Use Registration scheme by 30 October 2005. Once they have implemented the new rules, industrially produced herbal medicines (including over-the-counter remedies sold in supermarkets, health food stores, etc) will require either standard medicinal product marketing authorisation or a Traditional Use Registration.

Herbal medicinal products that were on the EU market on 30 April 2004 will benefit from a seven-year transition period before they must comply with the new rules, subject to stricter national rules. During the transition period, companies may accumulate evidence of traditional use. Time is also allowed for stock depletion. Hence an unlicensed product marketed prior to implementation of the Herbal Directive may be sold after implementation.

Until national implementation (or until the expiration of transitional protection), products must continue to comply with national law.

Discussion

The new rules are the result of over five years of discussion at both European and member state level. Their goal is to provide greater health protection, increase consumer confidence in traditional herbal medicinal products and encourage a single market for these products.

Although beneficial for consumers, the new rules are likely to hinder small manufacturers. Not only will companies have to manufacture and market their herbal products to recognised standards, they will also incur costs of inspections, upgrades to machinery and premises, and licensing and registration fees.

Companies should consider whether their products fall under the scope of the new rules and, if so, the information they will need to submit. Also, companies wishing to reposition a product as medicine in order to make minor medicinal claims should identify reasonable evidence that their product (or corresponding product) has traditionally had medicinal use. Discussions are continuing about legal categorisation and the types of product claims available. Of particular interest are the herbal monographs that the HMPC is currently producing. For products not eligible for the Traditional Use Registration, it will be possible to submit an abridged application for a standard product marketing authorisation based on 'well-established medicinal use' and refer, at least in part, to a herbal monograph.

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