

A Practical Guide to Licensing Herbal Medicinal Products

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Introduction

Elizabeth M Williamson

Background: why is the THMPD deemed necessary?

The Traditional Herbal Medicinal Products Directive (THMPD) 2004/24/EC is a regulatory process established to provide a mechanism whereby manufacturers of good-quality herbal medicines can register their products as medicines, rather than classifying them as food supplements, and thus allow them to make (restricted) medicinal claims on the packaging and the patient information leaflet (PIL). The Traditional Herbal Medicines Registration Scheme (THMRS) is designed for manufactured traditional herbal medicines that are suitable for use without medical supervision (EC Directive, 2004). It provides an assurance that the patient is receiving not only a good-quality product, but also more reliable advice on its use. Previous legislation provided very little in the way of safeguards and meant that the products could be sold with little regard to safety, quality or the provision of useful patient information. Although designed principally to protect the patient, the scheme also has advantages for the manufacturer. It means that, without needing to comply with the significantly more stringent requirements of a full marketing authorisation (MA), the product can still be considered to be a medicine with the greater freedom for sales promotion that registration confers, and, unlike unlicensed products, medicinal claims can also be made. Many of the conditions of the MA are almost impossible to meet for herbal products, and not registering at all does not protect the consumer. The THMPD is therefore now the main regulatory approval process for herbal medicines in the European Union (EU).

The EU was prompted to act because of the rising popularity and regular usage of herbal medicines, the mounting number of reports of adverse drug reactions (ADRs) and the increased understanding about the possibilities for side-effects and interactions between herbal and other medicines. There has also been growing concern about the safety and quality of some unlicensed products and about the lack of reliable information, as well as concerns about the professionalism of some practitioners. Recent reports have highlighted adverse, sometimes life-threatening, incidents which have resulted from use of poor-quality herbal medicinal products. In some cases, these have been tainted with other toxic plant species, microbial contaminants or heavy metals, and even adulterated with pharmaceutical drugs such as warfarin, dexamethasone and sildenafil.

Although many unlicensed herbal medicines on the market are already manufactured to reasonable and even good manufacturing practice (GMP) standards, without some form of approval by a regulatory body it is impossible for consumers to identify which unlicensed products are made to acceptable standards. This not only puts the public at risk but also penalises responsible companies whose products are indistinguishable in the public eye from poor-quality herbal medicinal products.

All of these concerns led to the EU directive on traditional herbal medicinal products (2004/24/EC), which requires each EU member state to set up its own traditional herbal registration scheme. In the case of the UK, the THMRS came into force on 30 October 2005, and, as a result of Directive 2004/24/EC, all new over-the-counter herbal medicines in the UK will require either a traditional herbal medicines registration (THR) or a full MA. However, products which were legally on the market before 30 April 2004 (i.e. those which complied fully with the requirements of Section 12(2) of the Medicines Act 1968) will benefit from transitional protection and can be sold as unlicensed herbal remedies until 30 April 2011. The scheme does not apply to products which are manufactured from isolated chemical constituents of plants, since these would not be regarded as a traditional herbal medicinal product and would not receive a registration.

Under the directive, the manufacturer first needs to demonstrate the safety of the herbal medicine by providing bibliographic evidence of a minimum of 30 years of traditional use for the product, of which at least 15 of the 30 years must have been within the EU. The product must be, quite literally, traditional in nature, in both its preparation and medical usage. Proof of this must also be provided since it is the 'traditional use' which is intended to replace the requirement to demonstrate efficacy (as needed for a full MA) and serves as the basis for permitting relevant, minor, therapeutic claims. If there are any further safety concerns which are not addressed by the traditional use, then regulators can also ask for more data.

Although there has been a relaxation of the requirement to prove efficacy, there has been no weakening of quality standards, and in fact these are now considerably tighter. Under THMPD, the herbal product must now comply with the normal rigorous quality standards required for all other medicines with an MA. It must therefore be manufactured under GMP, and pharmacovigilance (safety monitoring) requirements apply. As for any other over-the counter medicine, systematic patient information must be provided along with a statement on the label and in advertisements that the medicinal claim and indications are based on traditional usage.

Which products can be considered for registration under the scheme?

The scheme only covers products that are classified as medicines. While many herbal products are medicines, others are not, and so do not require registration under the THMRS. Certain 'borderline' products contain similar ingredients which can be regarded as medicines, foods or cosmetics, depending on presentation, and there are many herbal ingredients that have accepted usage in a range of different regulatory categories such as these. If a product is currently sold legally as a food, cosmetic or general consumer product, companies can continue to sell their products under these regimes. However, there may be cases where a company might find it advantageous to reposition a product formerly sold as a food by modifying its presentation to that of a medicine, and that company will then be able to make medicinal claims based on traditional use. Indeed there is no reason to prevent a company applying for a THR for any product that can meet the requirements of the THMRS, regardless of its previous incarnation. The Medicines and Healthcare products Regulatory Agency (MHRA) has produced a comprehensive document, *Guidance for Retailers, Wholesalers, Importers and Manufacturers on the Requirements of the THMR Scheme* (MHRA, 2007) which covers most of the key elements of the current regulations. It must be noted that registration is only suitable for herbal products that are taken orally, applied externally or inhaled – injectables will not be considered under the scheme. However, the scheme allows traditional herbal remedies to be combined with vitamins and minerals where there is evidence of safety, and where the action of the nutrient is ancillary to the herb rather than the nutrient

being considered to be the major active ingredient. Products containing other non-herbal ingredients (other than excipients), are not covered by the THMRS.

When may a product be refused registration?

If the data on traditional use are deemed to be insufficient, and if pharmacological effects or efficacy of the herbal medicinal product do not appear to be not plausible on the basis of long-standing use and experience, registration may be refused. Substantial evidence that a herbal remedy has been used over a significant period is considered to demonstrate that some degree of efficacy is at least plausible. However, if the proposed indication is in direct contradiction to the known activity of some of the ingredients, or if the ingredient most associated with the proposed indication is omitted from the medicine, this would reduce the plausibility and registration would probably be refused.

On the other hand, sometimes a herbal medicine has a great deal of modern scientific and clinical supporting evidence, and such a medicine is not suitable for THR either. The directive states that, where a medicine fulfils the criteria for a full MA (and in this context the efficacy requirements will be particularly relevant), a traditional use registration should not be granted. For some herbal medicines there is sufficient evidence in the public domain for an applicant to be able to obtain an MA, 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 THR but will instead ask the applicant to apply for an MA. This likely to apply in only a minority of cases, and it will need consideration of all the relevant details of the proposed product. The MHRA has indicated that it will not take the view that a product ought automatically to follow the ‘well-established’ route to an MA simply because the medicine contains a particular herbal ingredient – it may be that some herbal medicines have several accepted indications, of which one might be appropriate for an MA 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 efficacy is plausible based on long use and experience.

Potential applicants need to be aware that, historically, in relation to herbal medicines, 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.

What does safety mean in the context of the THMPD?

The concept of safety, whether applied to a conventional drug or herbal medicine, covers many facets, but these may be roughly divided into two main categories which can be described as medical and pharmaceutical. Problems may result because the medicine is not right for a particular disorder or patient, the dose is too high or the medicine interacts with other medicines taken concurrently by the patient. These are medical errors of diagnosis and prescribing, but more worrying is the possibility of intrinsic toxicity, especially when the active principles themselves are toxic, and for herbs containing poisonous compounds such as aristolochic acid. Genotoxicity would also fall into his category and this is very difficult to assess, since the *in vitro* methods for mutagenicity which are often employed

for this purpose are not always relevant to *in vivo* effects. Pharmaceutical issues associated with the quality of the product are particularly important because these are often avoidable and can be controlled through legislation more easily than the other categories. Unfortunately herbal medicines are by their nature highly susceptible to problems of consistency and quality, and this is exacerbated by the lack of regulation in the area, so this is one of the main aspects which the new THMPD was designed to address.

The need for continual evaluation of the safety of herbal medicines remains of crucial importance if these products are to take their rightful place as mainstream therapeutic agents, but even so pharmacovigilance for herbal medicines is a topic still in its infancy. Herbal products have unarguably been used for longer than any other medicines, so there is a tendency to think that they have been 'tried and tested', but the increasing number of reports which concern adverse events and interactions with drugs shows that this is not necessarily the case. Herbal medicine, like mainstream medicine, changes and evolves and the problems faced now are not necessarily the same as those previously encountered, so it is no longer sufficient to rely on historical use to demonstrate safety, as the new THMPD shows. Even herbs with a long previous record of safety are at risk of causing adverse events if they are prepared or prescribed in ways not used before, or if their quality has been compromised in some way.

In 1996 the UK yellow card scheme, whereby doctors, other healthcare professionals and now patients can report ADRs, was widened to encourage reporting of suspected ADRs associated with herbal medicines (EC Directive, 2004). This led directly to the ban on the use of *Aristolochia* species in 1999 and the sale of Kava Kava in 2003. On a global level, the World Health Organization (WHO) Drug Monitoring Centre at Uppsala, Sweden, collates reports on all types of ADRs. In 2006 the total number of reports in the WHO ADR database had exceeded 3.6 million and, of those, 41 439 had listed a herbal drug as suspected, interacting or concomitant. In 17 112 of these reports, the herbal drug was listed as a suspected or interacting drug. The USA was the top reporting country, followed by France and Germany. The UK was fourth with 1456 reports. The most frequently reported medicinal herbs were *Ginkgo biloba* (595) and *Hypericum perforatum* (493), although *Nicotiana tabacum* was also cited (1426), and the most frequent ADRs were pruritus, urticaria and skin rash (MHRA, 2004a). The proportion of ADRs for herbal drugs is thus a very small percentage, but this may of course be an indication of underreporting.

Many of the more serious ADRs, for example those involving aristolochic acid and some imported traditional Chinese medicines are due to poor quality – and even downright fraudulent – products. Reports of ADRs often do not specify the type of product or method of preparation, and the name and the origin or name of the manufacturer may not be noted. The new THMPD, with its focus on quality and safety, should help to reduce the frequency of these incidents but that will also depend on the consumer understanding the scheme and what it means and then deciding to use only registered products.

The issue of quality is probably the most important single consideration for ensuring safety for herbals. If the source of the raw plant material changes, or there is doubt as to its identity, purity or authenticity, then safety cannot be guaranteed. There may also be some ambiguity over nomenclature or errors in translation from other languages. The first step in assuring safety is therefore to ensure that the plant has been correctly identified, grown and collected in accordance with good agricultural practice, processed according to GMP and that storage has been carefully monitored. If this is done, then ADR reports will be valid and useful, but if not, or there is a lack of knowledge about the nature of the product involved, the report is meaningless and may even lead to the herbal medicine in question being given an undeserved reputation for causing adverse events. Both the original condition of the herb and manufacturing processes to which it has been subjected affect the quality of the final product, and although herbals are also used in the food and cosmetic industries, the approach to standards applied in each sector differs widely. In the EU, the quality and safety requirements governing

the registration of herbal medicinal products (see Kayne, 2006, for full details) offer some protection to the consumer and industry alike, but if the product is sold as a food supplement then these safeguards are lacking.

Drug interactions with herbal medicines are an increasing focus for research, although they are difficult to characterise and predict. The main problems may occur because the practitioner is not informed that the patient is taking a herbal medicine alongside a prescribed drug (patients fear disapproval); herbs may not be considered to be 'drugs' at all; an interaction may not be recognised as such, or only reported if it is considered serious; and, most significantly, it is almost impossible to assess the reliability of reports which involve only one patient, or those concerning only animal or *in vitro* experiments. Many herb–drug interactions are mediated via cytochrome P450 isoenzymes which are present in the liver, and may be induced or inhibited as a result of drug or herb ingestion. If another medicine, whether herb or drug, is taken at the same time, its metabolism will be affected and thus its therapeutic blood levels will also be affected. Complications arise because there are important variations in the expression and regulation of these enzymes not only between species, but there are also genetic variations between human populations and individuals, so assessing their relevance to a human clinical situation can be difficult. If *in vitro* or *in vivo* experimental results can be used to support clinical reports, and provide a rationale for the mechanism by which the interaction may be mediated, it considerably strengthens the case.

It must now be apparent than conclusively demonstrating the safety of herbal products is not easy! The quality of the product is paramount and this is one aspect at least which the manufacturer can control. Therefore, in the documentation required for registration under THMPD, quality assurance must be given a priority (MHRA, 2004b). Compliance with a monograph published in either the *British Pharmacopoeia* or the *European Pharmacopoeia* (PhEur) for the starting material and, if appropriate, the extract is a good starting point. There are many of these monographs and all of the more common European herbs are now covered. The development programme for herbal monographs in the PhEur also includes many Chinese herbal materials and the *British Pharmacopoeia* intends to deal with the more important Ayurvedic herbs. This programme has been given priority status and a new expert group of the PhEur has recently been convened to deal with Asian and oriental traditional medicines. Another major requirement for documentation under the THMPD is demonstrating that the manufacturer has been monitoring the literature for reports of ADRs for not only the product involved, but related products and the herb itself. If data have been published in this area, the manufacturer has a duty to find and record it – ignorance is no excuse.

In certain groups of people, such as pregnant women, breast-feeding mothers, children and the elderly, the safe use of herbal medicines has not been established. Care should always be taken in these vulnerable patient groups, and it is unlikely that even herbal products registered under the THMPD will ever be considered entirely safe for them. The same applies to patients with liver or kidney conditions or any other long-standing or serious disease. However, it must be remembered that this cautious approach does not mean that the products are dangerous to these patients, only that their safety cannot be guaranteed.

Finally, the safety of a particular product is only one aspect of the pharmacovigilance of herbals, and the problem of unqualified or unregistered practitioners of herbal medicine must also be addressed. At present, any individual can put a sign on the door and set up in practice as a 'herbalist' – it is possible to advertise, see patients and prescribe and dispense potent herbs without needing to meet specific standards of training or competence. Approximately 300 herbalists are currently registered with voluntary regulatory bodies, but statutory regulation of herbal practitioners is under review (Kayne, 2006). There is no evidence that such herbal practitioners are responsible for many ADRs but they are as liable to have the same issues regarding the quality of the products they make or buy as anyone else.

Latest developments in the UK and the future of the THMPD

The MHRA granted the first UK product registration under the European directive on traditional herbal medicinal products in October 2006. By October 2007, five products had been registered. Although there will be a delay until these products appear on the market following their registration, a steady stream of such products is expected to appear from now until the end of the transitional period, which is 30 April 2011. This therefore gives the industry a few years in which to upgrade manufacturing facilities and procedures and prepare the documentation and dossiers which are necessary to apply for registration using the THMRS. Guidance for all those concerned in this process is provided by the MHRA in the document *Guidance for Retailers, Wholesalers, Importers and Manufacturers on Registering Herbal Medicine under the THMR Scheme* (MHRA, 2007).

In summary, although there is concern about the safety of herbal remedies, and despite the fact that ‘natural’ does not ever equate with ‘safe’, the fact remains that these products – even if not strictly tried and tested – have a long history of use and, in general, if produced to high-quality standards and used properly, probably do have a good safety profile. This is the reasoning behind the THMPD, and for a reputable manufacturer there seems to be little point in trying to avoid registration, and much to be gained from complying with these standards and being rewarded with the certificate of registration and the authority which it provides. Consumers can also gain confidence in the product they are buying from the letters THR and the registration number which follows on the packaging. This book aims to make achieving that vital registration number more straightforward and easier.

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