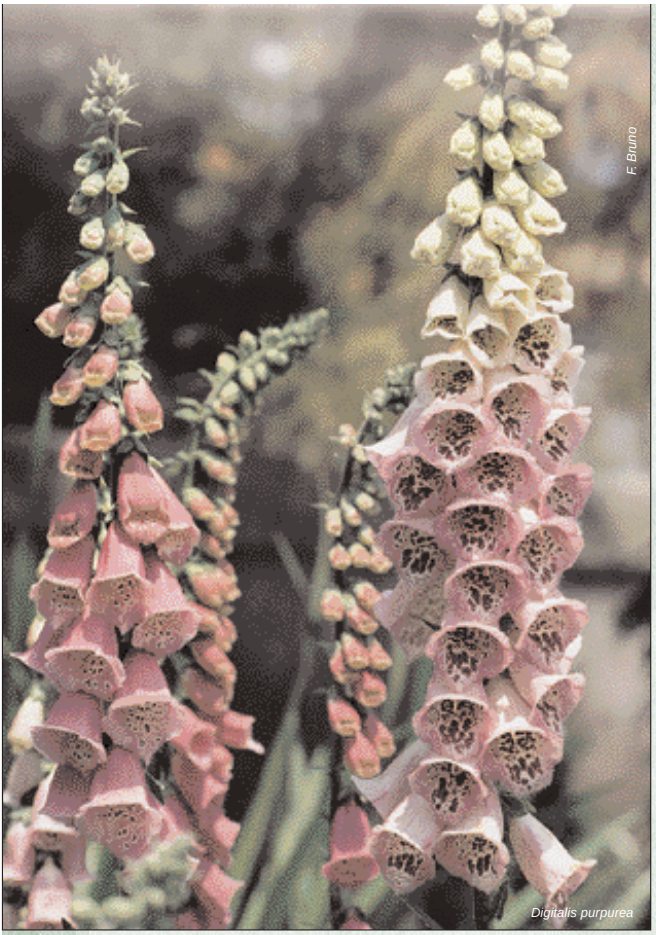

Digitalis purpurea

IMPLEMENTATION OF THE TRADITIONAL HERBAL PRODUCTS DIRECTIVE IN THE UNITED KINGDOM

*** Sue Harris**

Licensing of medicines in the EU is carried out according to the requirements of Directive 2001/83/EC, the Community code on medicinal products for human use. Directive 2004/24/EC (the Traditional Herbal Medicinal Products Directive - THMPD) amends this code to introduce the Traditional Herbal Medicines Registration Scheme and to apply many of the existing requirements in Directive 2001/83/EC to traditional herbal medicinal products.

This article looks at the existing controls in the UK; considers the weaknesses of the current systems and the problems that have arisen because of these weaknesses; consider what the new regulations will provide and outlines how the UK has been preparing for THMPD.

Currently, herbal medicines are marketed in the UK in one of three ways. They may be sold as licensed herbal products, or as herbal products exempt from licensing (under Section 12 of the UK Medicines Act 1968) or as food supplements.

Currently, the MHRA receives less than 10 new licence applications per year for herbal medicinal products and there are a number of reasons for this small number. Firstly, many familiar herbals, such as Ginkgo would be considered as new active substances in the UK and would be assessed as such. Secondly, indications may be for “major” conditions such as depression and would need to be supported by a full clinical data package. Thirdly, there are strict criteria for quality, safety and efficacy and applicants would find it difficult to satisfy the legal requirements for safety and efficacy of herbal medicines.

Section 12 of the Medicines Act 1968, which is subdivided into Section 12 (1) and Section 12(2), allows certain herbal remedies to be exempt from normal licensing requirements. These exemptions only apply where the product consists of herbal active ingredients i.e. there are no ancillary substances such as vitamins or minerals present. Section 12(1) exempts from licensing any herbal remedy supplied following a face to face consultation with a herbal practitioner, provided that the remedy is made or assembled on premises occupied by the practitioner. There is no restriction on the process to which the herbal ingredients have been subjected. In other words, the practitioner can use extracts and tinctures as well as dried plant material and so on. Section 12(2) on the other hand, exempts from licensing only remedies made by simple processes (i.e. dried, crushed or comminuted products). The product is not permitted to have a brand name; only the plant name and process used may be referred to. In addition, there are no written recommendations for using the product and there is no requirement for a consultation with a practitioner. Section 12.(2) products can be sold in shops, Section 12 (2) is not enforced.

Potent plants, such as Digitalis and Rauwolfia are controlled by the POM (Prescription Only Medicine) Order. The Medicines (Retail Sale and Supply of Herbal Remedies) Order

1977 (SI 2130) restricts certain plants but allows herbalists to use some relatively potent plants at specific dosages. For example, Gelsemium sempervivans (yellow jasmine) which is restricted to a maximum dose of 25mg and a maximum daily dose of 75mg. The UK has also put into place specific Banning Orders e.g. for Aristolochia, and Kava.

It is abundantly clear that there are serious weaknesses with these existing controls. The majority of UK herbal medicinal products are unlicensed and the Medicines Act exemptions did not envisage today's market, which includes traditional Chinese and Ayurvedic medicines. Although therapeutic claims are not permitted, some products make unauthorised claims or 'health claims'. There are safety issues because patients have little or no information on what the product is for or how to use it, on safe use in, for example, pregnancy, lactation, in children and the elderly, on safe use preoperatively or on potential interactions with existing medicines.
In summary, the MHRA has no knowledge of the products or ingredients. Unlicensed herbal medicines are currently not required to meet any specific safety or quality standards and many products are of poor quality with some containing undeclared illegal ingredients. Many products contain non-herbal ingredients
Lack of adequate controls means a number of things can go wrong. For example, the herbal medicine may contain the wrong plant. It might contain the right plant but that plant is toxic. The plant might have been unavoidably or accidentally contaminated with pesticide or fumigant residues, or with mycotoxins, heavy metals or other toxic elements, or it might have been exposed to microbial contamination. There have also been cases of deliberate adulteration.

Aristolochia species causes kidney failure and cancer. Patients with kidney failure require dialysis for the rest of their lives or a transplant. The prognosis is poor for cancer patients. There have been a number of instances of Aristolochia being used instead of Stephania, and Clematis. In Belgium 110 cases renal failure and 18 cancers caused by such substitution have been reported. Cases occurring in the UK led to the Aristolochia Banning Order in 2001. In spite of the ban, the MHRA continues to find products such as Xie Gan Wan Tablets and Jingzhi Kesou Tanchuan. This type of substitution is a special problem with ethnic medicines and UK legislation does not


Aristolochia grandiflora

cover species used in ethnic products.

Products may also be deliberately adulterated with poor quality materials, other plant parts, stem instead of root for example, conventional drugs, such as steroids, fenfluramine etc., with heavy metals / toxic elements and with non-herbal ingredients
With regard to quality issues, MCA issued advice about the poor quality of traditional Chinese medicines in September 2001. The situation did not improve and the advice was re-issued in September 2004. Finally, MHRA issued a statement that they cannot give assurances about the quality of unlicensed herbal remedies. Some TCM and Ayurvedic products have been found to contain heavy metals and/or toxic elements. For example, Muhayogaraj Guggulu, an Ayurvedic product, was found to contain mercury, lead and arsenic and Fufang luhuijiaonang, a TCM product, 11.7% mercury. Other products have been found to contain undeclared pharmaceutical substances including, for example, fenfluramine, nitrosofenfluramine, glibenclamide, corticosteroids, sidenafil, and ephedrine. Shubao Slimming Capsules were found to contain nitrosofenfluramine and have been associated with a UK case of irreversible liver failure. Slim 10/ ShubaoJianfeijiaolang /Qian Er/ Ma zin dol/ Chaso/Onshido were also found to be contaminated with nitrosofenfluramine. Traditional Chinese Medicine slimming aids such as Qing zhisan tain shou have been found to contain sibutramine and there have been recent reports from the Netherlands that Li Da Dai Dai Hua and Meizitang also contain sibutramine

Potential interactions between the herbal remedy and and conventionl drugs presents a very real risk to patient safety. St. John's wort (Hypericum perforatun) induces cytochrome P450. It affects P-glycoprotein and is known to interact with indinavir, ciclosporin, warfarin, digoxin, theophylline, oral contraceptives, and SSRIs. MHRA has granted thousands of variations to existing licensed products to include warnings in their patient information leaflets of such interactions and all unlicensed Hypericum products have warning labels. However, products sold on internet are a problem.

Reports of problems with warfarin interacting with cranberry, ginseng and garlic led, in August 2004, to the Patient Information Leaflets for all warfarin products being varied to include the warning:
"Always tell your doctor if you are taking other medicines including herbal remedies and non-prescription medicines".
The UK Government's position on herbal remedies is that the public


A natural shop

should have access to safe/high quality herbal remedies, with appropriate information for safe use.
However, it is recognised that the present regulatory arrangements have limitations as there are no specific safety or quality standards for herbal medicinal products. The Government also recognises that there is a need to achieve a balance between consumer safety and consumer choice.
The European Directive on Traditional Herbal Medicinal Products, 2004/24/EC was adopted in March 2004 and Member States must have their registration schemes in place by the end of October 2005. The Directive gives a transition period of 7 years for products on the market before 30 April 2005.
The new regulations provide a simplified registration scheme, and here it has to be remembered that the scheme is simplified, it is NOT simple! Claims may be made for the treatment of minor conditions only, there must be not a need for medical intervention for diagnosis or treatment. The products must be for administered via oral, external, or inhalation routes only, i.e. injectables are not permitted. They must have been available for 30 years in the EU or 15 years in EU plus 15 years in other specified territories. The products may also contain vitamins and or minerals as ancillary substances.
The MHRA welcomes THMPD in terms of its implications for quality, safety and efficacy. We view it as an important step to protect public health whilst ensuring consumer choice and believe that its advantages outweigh its disadvantages. Although not all products will fit, many safe products suitable for self-medication will be eligible under the scheme. Registration offers considerable advantages to patients and will provide a major benefit to pharmacists in advising patients on choice.
To help get ready for the new registration scheme, the UK is actively involved in negotiations on THMPD. There is considerable liaison with the Herbal Forum, an organisation that has represented UK manufacturers since being started in 1999 and represents health food manufacturers, herbal medicine manufacturers TCM/Ayurvedic companies and aromatherapy companies. MHRA has regular meetings with the Herbal Forum; there is an open exchange of information which is beneficial to all concerned.
In May 2004, the MHRA launched a voluntary Pre-application Notification Scheme, the purpose of which was to enable the MHRA to offer scientific and regulatory advice to companies and to get some idea of the number of potential applications so that we can plan our resources. So far, the MHRA has met with more than 40 companies and discussed in the region of 700 products. We have discussed Western herbal medicinal products, TCM and Ayurvedic products, Tibetan herbal products and herbal products sourced from South American. Many of the products discussed have been combinations, the maximum number of active ingredients to date being 34!
The meetings have enabled us to identify potential problems facing applicants. Some are unable to demonstrate 30/15 years usage of their products. There may be major problems with combination products, particularly those with large numbers of actives.
Some products we have seen contained no herbal ingredients, some contained conventional drug substances and some contained non-herbal active ingredients such as menthol, camphor and glucosamine. One product contained an Aristolochia species! Many products had indications unsuitable for self-medication such as epilepsy, diabetes and hypertension
MHRA has published comprehensive guidance on our website at:
http://medicines.mhra.gov.uk/ourwork/licensingmeds/types/thmpd/introduction.htm#introduction

The site is set out as follows:
Traditional Herbal Medicines Registration Scheme:
Guidance and information
- **Introduction**
- **Scope**
- **Who needs to comply**
- **Key requirements**
- **Requirements for manufacturers/**
- **wholesale dealers/ importers**
- **Guidance notes**
- **Forms and procedures**

MHRA is currently consulting on product registration fees and once these have been agreed, the application form will be finalised and added to the website.
The Traditional Herbal Medicinal Products Registration Scheme goes live on 1st November 2005, which is now only some 3 months away. We have left the foothills of the mountain we have to climb and the MHRA is looking forward to the challenges ahead.

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Kazuo Yamasaki
Ginseng yellow