J R Coll Physicians Edinb 2005; 35:25–27

Herbal medicines and the EU Directive

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ABSTRACT On 22 December, Lord Warner, the Health Minister, announced a number of new measures to regulate complimentary medicine in response to report of a House of Lords Select Committee and a DoH Consultation Document published in 2003. Although the final paper, describing the way in which the government proposes to regulate herbal medicines and complementary healthcare professionals, has yet to be published, the DoH has announced that it will make £900,000 available to The Prince of Wales's Foundation for Integrated Health over the next three years to develop robust systems for the regulation of the main complementary healthcare professionals. A new Herbal Medicines Advisory Committee will be set up to advise the Medicines and Healthcare Products Agency on the safety and quality of herbal medicines. The present Advisory Board on the Registration of Homeopathic Products will retain its status as a free-standing committee, able to advise the government directly. This paper reflects on current attitudes and legislation in the herbal arena.

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KEYWORDS Complementary and alternative medicine, EU Directive, herbal medicines, Medicines and Health Products Regulatory Agency.

LIST OF ABBREVIATIONS complementary and alternative medicine (CAM), Department of Health (DoH), European Medicines Evaluation Agency (EMEA), European Union (EU), Fourier-transform near infrared spectra (FT-NIR), Medical Research Council (MRC), Medicines and Health Products Regulatory Agency (MHRA), nuclear magnetic resonance (NMR), over the counter (OTC), quality of assurance (QA)

DECLARATION OF INTERESTS No conflict of interests declared.

The introduction of the Traditional Herbal Medicinal Products Directive by the EU on 31 March 2004[1] is a major step in the process of harmonisation of the regulation of medicines in Europe. It has broken new ground in the UK by, for the first time, providing a framework for the control of herbal medicines in one piece of legislation rather than the fragmented use of regulations mostly deriving from the Medicines Act 1968. In the UK, the emphasis has been to have a regulatory framework to control the safety and quality of herbal remedies which have been uncontrolled to date except for approved medicines under the Medicines Act or those which have had pharmacopoeia entries with appropriate standardisation. The House of Lords Select Committee on Complementary and Alternative Medicine[2] made strong recommendations in this area. It has been recognised that the evidence base for efficacy of herbals is variable and in most cases is not able to meet the requirements of a modern medicine submitted for approval to the national regulator, the MHRA[3] or to the EMEA.

In the UK, it may well be that the memories of patients and their families are clearer than those of physicians. It is less than 50 years ago that the majority of medicines used in the UK were directly herbal or derived from herbal extracts. The trend at the end of the twentieth century was towards evidence-based medicine and anecdotal and historical evidence of patient benefit was decried. Many healthcare professionals recognise that patients do derive benefit from herbal preparations even if the underpinning mechanisms are unknown and in truth, much of the benefit is symptomatic. However, if the patient feels benefit, this improvement may well have long-term advantage in terms of quality of life. On the other hand, mainland European culture has always had a greater acceptance of herbal medicine; pharmacopoeia entries are extensive and mainstream physicians readily accept the concomitant use of traditional and modern medicines.

In 2000, the House of Lords Select Committee on Complementary and Alternative Therapies reviewed the many and varied therapies and disciplines of the CAM world. They suggested three areas need regulation, the first of which included herbal medicine and was the most developed in terms of regulation. The second area included therapies which are most often used to complement conventional medicine and which do not proffer diagnosis. Examples would include aromatherapy

and the Alexander technique. The third area covered those disciplines which purport to offer diagnostic information as well as treatment but where the links to scientific principles of conventional medicine are less well founded. Ayurveda and traditional Chinese medicine were included in this group.

The House of Lords Committee was concerned that members of the public were unable to differentiate products that had met the stringent requirements of licensing from others which have not and encouraged the Medicines Control Agency (now the MHRA) to find an appropriate mechanism to achieve this. They strongly recommended that the government maintain its advocacy for regulation in this area. The Department of Health, in conjunction with the European Herbal Practitioners Association and the Foundation for Integrated Health set up a working group late in 2001 to report with recommendations on regulation of both herbal practitioners and also herbal preparations used in Section 12.1 (of the Medicines Act 1968). Their report was submitted to the government in July 2003 and published in September 2003.[4] The Department of Health undertook consultation in both areas during the latter months of 2003 and early 2004.[5] The results of these consultations are awaited.

The essence of both UK and EU legislation is the control of herbal products and in the case of the UK, of herbal practitioners too. The Royal Pharmaceutical Society, in common with others, recommended to the House of Lords Committee that it should be possible to control safety and quality of herbal remedies but that it would be difficult to control efficacy. The logic behind this position is twofold. First, modern analytical techniques should allow reproducible fingerprinting of herbal products such that QA is provided. Second, many herbs have been used traditionally in many countries for hundreds of years, especially in India and China and in these cases the safety question may be addressed by experience. Of course, a process assuring the quality of the growth, collection and transport of herbal medicine before final product preparation will be necessary. Good Agricultural Practice has been described and this along with Good Laboratory Practice, Good Manufacturing Practice and Good Clinical Practice needs to be established.

A second strand of interest in herbals is the widespread use of these remedies in the general population throughout the world; many of them obtained as OTC preparations. There are also an increasing number of herbal practitioners in various traditions including Western Herbalism, Traditional Chinese Medicine and Ayurveda. However, there is a perception among the general public, and among some scientists, that natural products are safe. This is not a secure generalisation. In July 2002, the Medicines Control Agency produced a report entitled *Safety of Herbal Medicinal Products*[6] that gives an excellent overview of this area with extensive references. The report clearly demonstrates that a wide range of herbs possess inherent toxicity and also raises the question of interactions between herbs and interactions with prescribed medications.

Analytical control for herbals has also been an active area of debate. Classical analytical dossiers for medicines are less easy to achieve for herbal medicines. The costs of generating such regulatory dossiers is high and would place an undue burden on companies wishing to come within the regulations with products where the commercial potential is low but where there is strong customer demand. Modern technologies such as FT-NIR or high-field NMR may provide a more cost-effective answer and have given early indications that fingerprinting herbals may give adequate QA. This is crucially important in this arena as the adulteration of products by similar plant species – the 'Aristolochia problem' or by chemicals such as heavy metals or steroids is a constant problem. The MHRA has clear evidence of contamination by such materials and are supportive of the new legislation.

In contrast, efficacy poses a more difficult question. In very few cases has it been possible to show clinical efficacy in classical controlled studies. Where this has been demonstrated, such products have achieved Product Licenses. The EU Traditional Use Directive recognises the same issues and suggests that evidence of 30 years' use, of which 15 years must be in the Community, would be sufficient to comment on the safety element and would also allow recognition of areas of utility on suitable product labels. This is meant to accommodate the increasing use of herbal remedies in the EU, many of which have derived from outside the UK, particularly from India and China.

From a pharmacological viewpoint, efficacy is at least as important as safety and quality. Given the costs of clinical trials it is unlikely that classical clinical trials will be conducted with many of the existing remedies but it is expected that most will be covered by the Traditional Use Directive mentioned above. However, whilst many pharmacologists believe the efficacy goal may never be achieved with many herbals, all of us who have dealt with patients recognise that improvements in symptomology are common using herbal preparations and in some cases can be maintained for extended periods of time, even years. This is clearly more than a 'placebo effect' but is difficult to quantify using classical trial techniques.

Better descriptors of patient benefit in controlled studies need to be defined in the herbal arena and research is necessary to achieve this. The MRC and the Wellcome Trust have discussed this and fund some work in the area. The MRC and the Health Care Research Collaboration, in

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Brighton, in February 2003, supported an excellent workshop in this area, chaired by Professors Robert Horne and Paul Dieppe and a report was issued.[7] It reflected on the tensions between allopathic and CAM practitioners and the problems created for patients in the current well-informed patient world. Evidence was provided that clinical benefit was achieved with some CAM therapies but the measures and tools were less than optimal to properly describe patient benefits. Clearly, more research is needed.

In tandem with this methodology research, current studies with cannabis and other plant-derived materials in classical studies will continue to close the circle in this very interesting arena.[8, 9] There are hints from many of these studies that there may be synergy between the various constituents of plant materials and protocol design will become increasingly important. Although the cost-effective drive with allopathic medicines is to get to Phase 3 pivotal studies as quickly as possible, it is possible that in the herbal arena, wide ranging and good Phase 2 data alongside traditional safety data could allow more rapid clinical or commercial exploitation.

Following the post genomic revolution it may seem hard for many to realise that it is only in the last 30–40 years that the balance of medicines has shifted from plant or bacterial-derived to chemically derived molecules. Digitalis (Digoxin), rauwolfia (reserpine), senna (sennosides) and penicillin (*Penicillium notatum*) at the start of this period and then Pacific yew (paclitaxel, *Taxus brevifolia*), tacrolimus (*Streptomyces tsukubaensis*), galantamine(*Caucasian snowdrop*), ivermectin (*Streptomyces avermitilis*), and artemisinin (*Artemisia annua*) at the end gave direction to medicinal chemistry and major synthetic programmes to discover medicines have flourished. The shortage of leads for new medicines has led to the creation of many start-up companies in Europe and the US using phytochemistry in combination with high throughput screening and combinatorial chemistry to look for new novel medicines.

Many patients take prescription medicine alongside OTC medicine and herbal remedies. The pharmacist already provides effective counselling in this area and this is increasing. The proposed regulatory changes should allow more effective consultations between patients and primary care practitioners and also should ensure access to quality preparations prescribed and supplied by registered practitioners.

REFERENCES

1 Directive 2004/24/EC of the European Parliament and of the Council, OJ 30.4.2004, L136/85-90 (http://medicines.mhra.gov.uk/ourwork/licensingmeds/types/thmpd/introduction.htm).

2 House of Lords Select Committee Report on Complementary and Alternative Medicine, ordered to be printed 21 November 2000, HL Paper 123. London: The Stationery Office; 2000 (http://www.publications.parliament.uk/pa/ld199900/ldselect/ldsctech/123/12301.htm).

3 http://medicines.mhra.gov.uk/ourwork/licensingmeds/herbalmeds/herbalmeds.htm

4 http://www.users.globalnet.co.uk/~ehpa/

5 http://www.dh.gov.uk/Consultations/ClosedConsultations/ClosedConsultationsArticle/fs/en?CONTENT_ID=4083508&chk=9dE%2B/o

6 *Safety of Herbal Medicinal Products*. A report produced by the Medicines Control Agency in July 2002 (http://medicines.mhra.gov.uk/ourwork/licensingmeds/herbalmeds/herbalmeds.htm#safety).

7 MRC/HSRC CAM Workshop Report, February 2003. *Complementary and Alternative Medicine (CAM): 'Why do people use CAM and what benefits do they derive from it?'*

8 Goodwin D. Marijuana and multiple sclerosis. *Lancet Neurology* 2004; **3:**79–80.

9 Zajicek J, Fox P, Sanders H *et al.* Cannabinoids for treatment of spasticity and other symptoms related to multiple sclerosis (CAMS study): multicentre randomised placebo-controlled trial. *Lancet* 2003; **362:**1517–26