LEADING ARTICLE

Drug Safety 2003; 26 (12): 829-851
0114-5916/03/0012-0829/$30.00/0

Pharmacovigilance of Herbal Medicines

A UK Perspective

Joanne Barnes

Centre for Pharmacognosy and Phytotherapy, School of Pharmacy, University of London, London, United Kingdom

Abstract

There is an increasing awareness at several levels of the need to develop pharmacovigilance practices for herbal medicines. The current model of pharmacovigilance and its associated tools have been developed in relation to synthetic drugs, and applying these methods to monitoring the safety of herbal medicines presents unique challenges in addition to those described for conventional medicines. Several problems relate to the ways in which herbal medicines are named, perceived, sourced, and utilised. Other important challenges arise from the current regulatory framework for herbal medicines in the UK.

In the UK at present, the Committee on Safety of Medicines/Medicines and Healthcare products Regulatory Agency's (CSM/MHRA) 'yellow card' scheme for adverse drug reaction (ADR) reporting is the main method of monitoring the safety of herbal medicines. Despite recent initiatives to stimulate reporting of suspected ADRs associated with herbal medicines, such as extending the scheme to unlicensed herbal products, and including community pharmacists as recognised reporters, numbers of herbal ADR reports received by the CSM/MHRA remain relatively low. Under-reporting, an inevitable and important limitation of spontaneous reporting schemes, is likely to be significant for herbal medicines, since users typically do not seek professional advice about their use of such products, or report if they experience adverse effects. The herbal sector in the UK has initiated various spontaneous reporting schemes, based on the yellow card scheme, but targeted mainly at herbal-medicine practitioners. It is important that these schemes have a link with the CSM/MHRA so that potential signals are not missed. Several other tools used in pharmacovigilance of conventional medicines, such as prescription-event monitoring, and the use of computerised health-record databases, currently are of no use for evaluating the safety of herbal and other non-prescription medicines.

Proposed European Union legislation for traditional herbal medicinal products will require manufacturers of products registered under new national schemes to comply with regulatory provisions on pharmacovigilance. In the longer term, other improvements in safety monitoring of herbal medicines may include modifications to existing methodology, patient reporting and greater consideration of

pharmacogenetics and pharmacogenomics in optimising the safety of herbal medicines.

Pharmacovigilance has been defined as "*the study of the safety of marketed drugs under the practical conditions of clinical usage in large communities*".[1] It involves monitoring drug safety and identifying adverse drug reactions (ADRs) in humans, assessing risks and benefits, and responding to and communicating drug safety concerns; recently, it has been suggested that there could be more emphasis on extending knowledge of safety rather than focusing on demonstrating harm.[2]

The above definition makes no distinction between pharmacovigilance of conventional and herbal medicines.[1] Indeed, there is no need, nor is it desirable, to separate the two; pharmacovigilance should embrace all preparations used medicinally regardless of their regulatory status, pharmaceutical composition, cultural use and philosophical framework. Hence, the same aims and activities of pharmacovigilance apply to herbal medicines. However, pharmacovigilance activities largely have been focused on conventional medicines, and the current model of pharmacovigilance and its science and processes have developed in relation to synthetic drugs. Applying the existing model and its tools to monitoring the safety of herbal medicines presents unique challenges in addition to those described for conventional medicines, and it is important that these are understood by all stakeholders.

There is an increasing awareness at several levels of the need to develop pharmacovigilance practices for herbal medicines; the WHO, for example, has produced draft guidelines on this.[3] Awareness has arisen not only because of the extensive use of herbal medicines, but also because in recent years there have been several high-profile herbal safety concerns which have had an impact on the public health. Against this background, this paper aims to provide a critical overview of the current state of pharmacovigilance of herbal medicines in the UK, and to discuss the particular challenges that this area presents. The paper is written from a UK perspective, but also has wider international relevance, particularly to those countries with spontaneous reporting schemes and a healthcare system similar to those of the UK.

1. Herbal Medicines: Challenges for Pharmacovigilance

The unique characteristics of herbal medicines, and the ways in which herbal medicines are named, perceived, sourced, utilised and regulated raise important issues and challenges for pharmacovigilance.

Some issues arise because most herbal medicines can be obtained without a prescription from various outlets, not only pharmacies. Thus, the problems that apply to pharmacovigilance of conventional non-prescription medicines, for example, that generally their use does not involve a prescriber and is not recorded or monitored through the National Health Service (NHS), also apply to herbal medicines. Other problems are specific to herbal medicines and present difficulties over and above those described for conventional prescription and non-prescription medicines.

1.1 Characteristics of Herbal Medicines

Herbal medicinal products (also known as phytomedicines or phytotherapeutic preparations) are *"medicinal products containing as active substances exclusively herbal drugs or herbal drug preparations"*,[4] i.e. they contain as active ingredi-

1 For simplicity, the term conventional medicines is used here to describe licensed medicinal products typically comprising a single characterised chemical entity, but also includes more complex products such as vaccines. It is recognised there are licensed herbal medicinal products and that in the UK some of these are considered conventional medicines, for example, formulations of ispaghula husk licensed for use as bulk-forming laxatives and in hypercholesterolaemia, and standardised formulations of sennosides, licensed for use as stimulant laxatives.

Table I. Formal definitions and other terms used in relation to herbal medicines

Term	Definition
Herbal remedy	"a medicinal product consisting of a substance produced by subjecting a plant or plants to drying, crushing or any other process, or of a mixture whose sole ingredients are two or more substances so produced, or of a mixture whose sole ingredients are one or more substances so produced and water or some other inert substances."[5]
Herbal substance (herbal drug)	"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)."[6]
Herbal preparation (herbal drug preparation)	"preparations obtained by subjecting herbal substances to treatments such as extraction, distillation, expression, fractionation, purification, concentration and fermentation. These include comminuted or powdered herbal substances, tinctures, extracts, essential oils, expressed juices and processed exudates."[6]
Herbal medicinal product	"any medicinal product, 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; **in addition, the product may contain vitamins or minerals or other non-biological substances for which there is well-documented evidence for its safety; the action of the non-herbal substances must be ancillary to that of the herbal active ingredients.**"[7]a
Herbal constituent	a specific chemical compound found in a herbal ingredient, e.g. hyperforin found in the aerial parts (herb) of St John's wort.
Herbal ingredient	a specific individual medicinal plant and the plant part, present in a herbal medicine, e.g. St John's wort herb present in St John's wort tablets.

a The text in bold is a recent amendment, the wording of which is still to be confirmed at a European level.

ents only crude and/or processed plants and/or plant parts; an isolated chemical constituent which originates from plant material is not a herbal medicine. The term 'herbal medicines' is also used generally to describe both relatively crude preparations, such as herbal tinctures, usually supplied by herbal-medicine practitioners (medical herbalists), and manufactured or finished herbal medicinal products, usually formulated as tablets or capsules and available for purchase without a prescription. Legal definitions relating to herbal medicines and explanations of other terms used are given in table I.

In contrast with conventional medicines, herbal medicines are chemically rich complex mixtures comprising several hundreds of constituents, often more. For many herbal medicines, the chemical constituents are unknown, and even for those with well-documented phytochemistry, there are few for which the specific constituents responsible for pharmacological activity are fully understood. The profile of constituents is not uniform throughout a plant, and for many plants, only a specific plant part, or parts, such as roots or leaves, is (or should be) used medicinally. Moreover, the precise profile of constituents is likely to vary both qualitatively and quantitatively between different batches of herbal starting materials because of one or more of the following factors:

- inter- or intraspecies variation in constituents
- environmental factors, such as climate, and growing conditions
- time of harvesting – the profile of constituents can vary even over the course of a day
- post-harvesting factors, such as storage conditions and drying.[8]

The method of processing crude herbal material, for example, the type of extraction, can also influence the precise chemical composition of a herbal preparation or product. Many herbal medicinal products contain several herbal ingredients, and medical herbalists usually prescribe combinations of herbal tinctures often supplied as a mixture, in both cases, further adding to the chemical complexity of the herbal medicine taken by the patient. The chemical complexity of herbal medicines creates difficulties in determining their clinical pharmacokinetics, pharmacodynamics and toxicology and, equally, where a safety concern has been identified in association with a particular herbal medicine, establishing which constituent(s), even which herbal ingredi-

ent(s) with combination herbal medicines, are implicated is problematic.

For the reasons given above, it is likely that there will be variations in the chemical composition of herbal medicines containing the same herbal ingredient but produced by different manufacturers; this will apply to both licensed herbal medicinal products and unlicensed herbal medicines. Several studies have found important differences in the pharmaceutical quality of different products on the US market. For example, variations in the content of major constituents in St John's wort (*Hypericum perforatum*) products (which in several cases also differed markedly from concentrations stated on the label),[9] and variations in and unacceptably high concentrations (in several cases >25 000 parts per million) of ginkgolic acids, which potentially are allergenic, in ginkgo products.[10] Standardisation on content of certain constituents is an approach used by some manufacturers to achieve more consistent pharmaceutical composition, but its usefulness is limited at present since the specific active constituents are known only for a few herbal medicines.

Because of the variations that can exist between different manufacturers' products and preparations of the same herbal ingredient, evidence of safety (and efficacy) should be considered in this light; strictly speaking, evidence is product- or extract-specific, and should be extrapolated only to those products or extracts which have been shown to be pharmaceutically equivalent and bioequivalent.[11] This is largely impractical at present, given the limited data available for herbal medicines; nevertheless, the differences between different preparations of a herbal ingredient should not be ignored. In many cases, because of the nature of herbal medicines, a group of related constituents, rather than a single constituent, is likely to be responsible for an observed adverse effect. In this case, it may be appropriate to group together different preparations and products containing the same herbal ingredient or group of constituents in order to detect signals. In some ways, this is similar to investigating 'class effects' with conventional medicines.

The names that are used for herbal medicines present a further problem (see also section 2.1.1., ADR Reporting Form). Often, common or vernacular names are used to describe herbal medicines, but these vary widely, and may be used to describe more than one species, and cannot be precise.

Contrary to popular belief, herbal medicines are not 'safe' because they originate from natural sources; some plants are highly poisonous, and many others have inherently toxic constituents. For example, metabolites of 'unsaturated' pyrrolizidine alkaloids, such as senecionine, are hepatotoxic in humans, and carcinogenic and mutagenic in animals.[8] Senecionine is found in liferoot (*Senecio aureus*) and in other *Senecio* species, such as *Senecio scandens*, which has been reported as an ingredient in a traditional Chinese medicine product Qianbai Biyan Pian found in the UK.[12,13] Other known intrinsically toxic groups of constituents, their effects and examples of plant sources include aristolochic acids (nephrotoxic and carcinogenic), found in *Aristolochia* species throughout the plant, sesquiterpene lactones (allergenic), found in feverfew (*Tanacetum parthenium*) and other species in the Asteraceae family, and furanocoumarins (phototoxic), found in angelica (*Angelica archangelica*) and other species belonging to the Apiaceae family.[8]

1.2 Utilisation of Herbal Medicines and Related Issues

The use of herbal medicines is a popular healthcare approach among patients and consumers in the UK, although there are few reliable estimates of the prevalence of use. Estimates of herbal-medicine use among adults in England come from a cross-sectional survey (n = 5010; response rate: 59%) carried out in 1998 which found that 19.8% (95% CI 18.3–21.3) had purchased an over-the-counter herbal medicinal product and that 0.9% (95% CI 0.6–1.3) had consulted a medical herbalist in the previous year.[14] There are no longitudinal data for prevalence of use of herbal medicines for the UK at present, although market research data indicate increasing sales – sales of licensed and unlicensed herbal medicinal

products were worth £75 million in 2002, an increase of 57% over the previous 5 years.[15] Studies carried out in other developed countries, such as Australia and the US, also suggest increasing prevalence of use of herbal medicines among the general adult population.[16,17] Extrapolating estimates of herbal medicine use from such studies suggests that large numbers of people are being exposed to herbal medicines; this in itself is of concern for the public health.

In the UK, herbal medicines are used by a wide range of individuals for both acute and chronic conditions. Many herbal medicinal products are purchased for maintenance of general health and well-being, and for use in the prevention and treatment of minor, common ailments. Use is not necessarily based on evidence, nor limited to symptoms and conditions suitable for self-treatment. Herbal medicinal products are also used by individuals with serious chronic diseases, including cancer, AIDS, multiple sclerosis, and asthma, and many other conditions, by older patients, and pregnant or breast-feeding women, and are administered by parents/guardians to children.[18] Similarly, medical herbalists use herbal medicines to treat a variety of conditions.[19] Some patient groups, such as children and older people, are at increased risk of adverse drug effects, and there is no reason why this should not also apply where they use herbal medicines. Other groups, for example, pregnant women, may use herbal medicines in preference to conventional medicines because they are perceived to be safer, without realising that little is known about the effects of herbal medicines taken during pregnancy.

Typically, users of herbal medicinal products do not seek professional advice in selecting herbal medicines, but rather rely on friends' or relatives' recommendations, and information in the popular media.[20,21] Herbal medicines are widely available for purchase over the internet and from retail outlets in which there is no trained healthcare professional available (see section 1.3.1).[22] Even where herbal medicinal products are purchased from pharmacies, a consumer or patient may not have any interaction with a pharmacist or trained pharmacy counter assistant, or if a consultation does occur, pharmacy staff may not have sufficient knowledge to feel confident about providing information and advice on herbal medicines.[23] A small proportion of users of herbal medicines seeks treatment from a herbal-medicine practitioner, but at present, there is no legal requirement for such practitioners to have undertaken training in herbal medicine or to belong to a professional organisation for herbal-medicine practitioners, and while many herbal-medicine practitioners will have taken these steps, some will not.

A related issue is that some users of herbal medicines may not disclose this use to a healthcare professional;[21] equally, healthcare professionals do not ask their patients routinely whether they are using herbal medicines, even when receiving reports from patients of suspected ADRs associated with conventional medicines, and rarely record information on herbal-medicine use on patient records.[24,25] It is possible, therefore, that undisclosed herbal-medicine use could be an alternative explanation for reports of suspected ADRs associated with conventional medicines.

Disclosure of herbal-medicine use to healthcare professionals is particularly important where patients start, stop, or are already receiving treatment with conventional medicines and, equally, individuals consulting medical herbalists should disclose their current use of conventional medicines, because there may be a potential for drug-herb interactions. Information on the extent to which concurrent use of herbal and conventional medicines occurs is limited, although preliminary data suggest that it may be extensive. In a cross-sectional survey of complementary-therapy use among adults in the US (n = 2055 respondents; 60% weighted overall response rate), 44% were regular users of prescription medicines and, of these, 18.4% were using concurrently a herbal or high-dose vitamin preparation.[16] In a small study conducted in the UK, 59% of herbal-medicine users identified in pharmacies and health-food stores claimed that they had used herbal medicines concurrently with conventional medicines, mostly prescription medicines, in the previous year.[21]

In summary, the ways in which herbal medicines are described (named), perceived and obtained, together with users' behaviour towards herbal medicines and issues relating to healthcare professionals' and herbal practitioners' practice present opportunities for herbal medicines to be used inappropriately, even unsafely, and for suspected ADRs to go undetected and unreported.

1.3 Regulation of Herbal Medicines

1.3.1 Current Regulatory Framework

As with all medicines, the origins of regulation and pharmacovigilance for herbal medicines lie in the thalidomide tragedy of the 1950s and 1960s. This was the milestone which led, of course, to the establishment of the Committee on Safety of Drugs (now the Committee on Safety of Medicines, CSM), an 'early-warning system' (the 'yellow card' scheme) for doctors to report their suspicions on adverse effects of drugs, and legislation in the form of the Medicines Act 1968 requiring pharmaceutical companies to satisfy the competent authority (now the Medicines and Healthcare products Regulatory Agency, MHRA) of the quality, safety and efficacy of their new medicines before marketing.

There are around 600 licensed herbal medicinal products on the UK market, although most of these are not 'new' marketing authorisations, but are products which initially were granted product licences of right (PLRs) as they were on the market when the medicines licensing system was set up in 1971. When PLRs for herbal medicinal products were reviewed by the competent authority, manufacturers of those intended for use in minor self-limiting conditions were permitted to rely on bibliographic evidence to support efficacy and safety, rather than being required to carry out new tests and controlled clinical trials.[8] So, although many herbal medicinal products have product licences, the products have not necessarily undergone the stringent testing required to obtain a full marketing authorisation today, but rather have relied on evidence from long-standing use.

Other herbal medicines available in the UK are sold either as herbal remedies exempt from licensing under section 12 of the Medicines Act 1968, or as unlicensed food supplements without making medical claims and regulated under food, not medicines, legislation.[8] Herbal medicines meeting the definition of a herbal remedy (see table I) and compounded and supplied by 'herbal practitioners' on their own recommendation currently are exempted from licensing requirements under section 12 (1).[5] This exemption was initially intended to give 'herbal practitioners' the flexibility to prepare remedies for their patients, although the term is not defined and, at present, there is no statutory regulation of herbalists in the UK. A Herbal Medicine Regulatory Working Group has been established to consider appropriate legislation and reform of section 12 (1) and is expected to report during 2003.[26]

Many herbal medicinal products are sold under the section 12 (2) exemption, which exempts from licensing requirements those herbal remedies consisting solely of dried, crushed or comminuted (fragmented) plants sold under the plant or botanical name and with no written recommendations as to their use.[5] In other words, such products must not contain any non-herbal 'active' ingredients, must not use proprietary names and must not make medical claims. Some manufacturers are unaware of, or ignore, these conditions and illegal unlicensed herbal products can be found for sale, as currently there is no requirement for manufacturers to consult the competent authority before placing an unlicensed herbal medicinal product on the market. MHRA does have the statutory power to decide whether a particular marketed unlicensed product satisfies the definition of a relevant 'medicinal product' and, therefore, is subject to the usual provisions of regulations relating to Medicines for Human Use, unless it meets criteria for exemption (i.e. as provided in section 12 of the Medicines Act). Herbal medicines available in the UK include some traditional Chinese medicines (TCM) and Ayurvedic medicines (both of which often also contain non-herbal substances), and these are subject to the same legislation as are 'Western' herbal medicines.[27] There are further restrictions on certain toxic herbal ingredients, such as *Aristolochia* species, found in

some TCM products, and on other herbal ingredients that may be confused with toxic herbal ingredients.[28] However, unlicensed herbal products containing these banned species continue to be found.[13]

In the UK, licensed medicinal products, including licensed herbal medicinal products, are classified as prescription-only medicines (POMs; generally may only be sold or supplied from a registered pharmacy in accordance with a prescription given by an appropriate practitioner), pharmacy medicines (P; may only be sold or supplied from a registered pharmacy and by or under the supervision of a pharmacist), and general sales list medicines (GSL; may be sold or supplied at registered pharmacies or other businesses which can be closed to exclude the public).[5] Most licensed herbal medicinal products are GSL medicines. Potentially hazardous herbal substances (e.g. *Digitalis* leaf) are controlled as POMs; certain other plants or plant parts (e.g. yohimbe bark; *Pausinystalia yohimbe*) are controlled as P medicines, but some of these (e.g. belladonna herb; *Atropa belladonna*) can be sold or supplied by 'herbal practitioners' (see earlier in this section) if certain conditions are met (e.g. limits on maximum dose, maximum daily dose and/or strength). In practice, these restricted herbal substances are rarely, if ever, sold or supplied by pharmacists, but some, such as *Ephedra* species, where permitted, are utilised by herbal practitioners in their practice.

The current regulatory framework presents several major problems for pharmacovigilance of herbal medicines. Whereas manufacturers of licensed herbal medicinal products are required to comply with regulatory provisions on pharmacovigilance as set out in Directive 2001/83/EC,[29] manufacturers of unlicensed herbal products and those sold under exemptions from licensing are not required to do so, i.e. for these products, which comprise the majority of herbal medicines on the UK market, manufacturers have no obligation to keep records of suspected ADRs associated with these products, nor to report these suspected ADRs to the competent authority. This is also the case where herbal medicines are supplied to patients by medical herbalists.

In addition, the range of possible regulatory actions that the competent authority can take in response to a herbal safety concern is limited for unlicensed herbal medicinal products and, for some responses, requires the voluntary co-operation of herbal-medicines manufacturers. For example, after important interactions between St John's wort and certain prescription medicines emerged around 1999/2000, MHRA took the decision that provision of warnings on St John's wort products was an appropriate part of the regulatory response, but this required the co-operation of manufacturers of unlicensed St John's wort products. At the same time, marketing authorisation holders of conventional medicines believed to interact with St John's wort products were obliged to make variations to product information for their relevant products. Similarly, when an association between use of kava-kava (*Piper methysticum*) preparations and liver toxicity was being investigated by the CSM, the herbal sector agreed to withdraw kava-kava products from sale. Voluntary withdrawal worked reasonably well initially, but as the period of evaluation drew on, some retail outlets began selling kava-kava products again. Community pharmacists, however, had a professional and ethical responsibility not to do so.[30,31]

Other issues relevant to pharmacovigilance arise because manufacturers of unlicensed herbal medicinal products are not required to demonstrate to MHRA the quality, safety and efficacy of their products before marketing. The importance of pharmaceutical quality for the safety (and efficacy) of herbal medicinal products is well-recognised,[8,32,33] but manufacturers are required only to demonstrate pharmaceutical quality standards for their licensed herbal medicinal products. Some manufacturers of unlicensed herbal medicinal products may have appropriate quality control and quality assurance procedures for their products, but others do not, and the pharmaceutical quality of many unlicensed herbal medicinal products is of real concern. In addition to difficulties with assuring pharmaceutical quality due to the variation in chemical composition, quality problems with unlicensed herbal products include intentional or accidental substitution of species, con-

tamination with restricted or toxic substances, including prescription medicines, and differences between labelled and actual contents.[8,13] It is essential, therefore, when assessing reports of suspected ADRs associated with a particular unlicensed herbal medicine to establish whether the herbal ingredient(s) implicated are what the product actually contains, and whether the product could be adulterated or contaminated. Ideally, a sample of the suspected herbal medicine should be retained for pharmaceutical analysis if necessary.

There is a general lack of objective information on the safety of many herbal medicines. This has arisen in part because under the current regulatory framework there is little incentive for manufacturers to carry out pre-clinical tests and clinical trials. Postmarketing surveillance studies involving certain herbal medicinal products have been conducted by some manufacturers (usually those based in Germany), but this is the exception. Generally speaking, there is a lack of information on the types and frequency of adverse effects, including interactions with other medicines, foods, alcohol, disease and so forth, and other aspects relevant to safety for herbal medicines, such as their active constituents, pharmacokinetics, pharmacology, use in special patient groups (e.g. children, older people, individuals with renal or hepatic disease, pregnant or breast-feeding women), effects of long-term use, and so on. It is often argued that herbal medicines have a long history of traditional use and that this provides evidence for their safety (and efficacy). However, while the 'test of time' may have identified inherently toxic plants, it cannot, for example, identify delayed adverse effects, effects that may arise from use in patients with 'modern' illnesses, such as HIV/AIDS, and safety issues arising from how herbal medicines are utilised today, for example, concurrently with conventional medicines.[34] Certainly, there are examples of type A reactions (those that typically are dose dependent and related to the pharmacological effects of the medicine) and type B reactions (typically unrelated to dose, idiosyncratic) and other types of ADRs (e.g. delayed effects in the user or offspring remote from medicine use in the user) associated with the use of certain herbal medicines.[35]

In addition, the efficacy of many herbal medicines has not been evaluated in randomised clinical trials. Even for well-tested herbal medicines, such as certain extracts of St John's wort herb which have been assessed in around 30 randomised clinical trials in depression, only a small number of clinical-trial participants has been exposed to a specific manufacturer's product. Furthermore, there are few long-term clinical trials of herbal medicines intended for long-term use. For comparison, conventional medicines have been tested in around 1500 patients before they reach the market. The lack of information on the safety and efficacy of herbal medicines makes it difficult to carry out benefit-risk assessments.

In summary, in the UK, the current regulatory framework allows unlicensed herbal medicines, which may be of inadequate pharmaceutical quality and for which there is a lack of information on safety aspects, to be placed on the market and obtained by consumers and patients from a range of retail outlets without a prescription or other involvement of a healthcare professional. Manufacturers are under no obligation to carry out pharmacovigilance of such products. By contrast, conventional P or GSL medicines are permitted to be sold or supplied without a prescription because they have a history of relative safety.

1.3.2 Proposed New Regulatory Framework

The need for a new regulatory framework for herbal medicinal products was first discussed in the late 1980s and, for several reasons, today it is recognised widely that the existing regulatory framework does not adequately protect the public health. In particular, the current system does not give consumers and patients adequate protection against poor-quality and unsafe unlicensed herbal medicinal products. It also discriminates against manufacturers of licensed herbal medicinal products as their costs are likely to be higher because of the need to comply with the principles of good manufacturing practice and other regulatory provisions.

Table II. Key features of proposed European Union (EU) Directive 2002/0008 (amends 2001/83/EC) on traditional herbal medicinal products[6,7]

Establishes a Committee on Herbal Medicinal Products which will be part of the EMEA and will take over the tasks of the CPMP with regard to authorisations or registrations of herbal medicinal products by member states. Other tasks will include producing EC herbal monographs, and establishing a 'positive list' of herbal substances (to include indication, route of administration, strength and so on) allowed under the directive.
Requires EU member states to set up a specified simplified national registration procedure for traditional herbal medicinal products that could not fulfil medicines licensing criteria.
Main features of requirements for registration include:
• products for oral, external or inhalation use only
• minor indications only (suitable for self-diagnosis and self-treatment)
• evidence that the herb has been used traditionally for at least 30 years, including at least 15 years within the EC; period of traditional use can include the transition period
• reliable identification of raw materials and use of appropriate quality herbal ingredients, i.e. compliance with Ph Eur standards where they exist and with manufacturer's own specification otherwise
• systematic quality assurance and quality control throughout the manufacturing process: compliance with principles of GMP and other relevant European guidelines; qualified person responsible for release of batches onto the market; manufacturer's licence or wholesale dealer's licence where appropriate; inspection of premises
• provision of bibliographic data on safety with an expert report
• labelling, information and advertising requirements in accordance with 2001/83/EC and relevant national regulations
• compliance with pharmacovigilance requirements in accordance with 2001/83/EC
• transition period of at least 5 years, probably 7 years, once the directive comes into force

CPMP = Committee on Proprietary Medicinal Products; **EC** = European Community; **EMEA** = European Agency for the Evaluation of Medicinal Products; **GMP** = good manufacturing practice; **Ph Eur** = European Pharmacopoeia.

Against this background, a draft European Union (EU) directive (2002/0008, which amends 2001/83/EC) has been produced which aims to establish a harmonised legislative framework for authorising the marketing of traditional herbal medicinal products.[6] The directive will require EU member states to set up a simplified national registration scheme for traditional herbal medicinal products meeting defined criteria. The key features of the directive at the time of writing are summarised in table II, although the directive is still under discussion and amendments may yet be made. In essence, the proposed directive will require manufacturers wishing to obtain registrations for their traditional herbal medicinal products under a national scheme to demonstrate the quality and, to some extent, the safety of their products, whereas the usual efficacy and, to some extent, safety requirements will be replaced by evidence of traditional use. Another major change is that manufacturers of products registered under the directive will be required to comply with information and labelling requirements. Currently there is no requirement for manufacturers of unlicensed herbal medicinal products to provide systematic information with their products.

The proposed directive will have an important impact on pharmacovigilance of herbal medicines, once it comes into force. Manufacturers of traditional herbal medicinal products registered under the UK national scheme established under the directive will be required to comply with relevant existing pharmaceutical legislation, including the provisions on pharmacovigilance.[29] Several of these may pose problems for manufacturers with little or no experience in this area. For example, the requirement to have constant access to an appropriately qualified and experienced person responsible for pharmacovigilance, implementation of the use of Medical Dictionary for Regulatory Activities (MedDRA) and connection to and compliance with EudraVigilance. There has been some discussion about the possibility of making some allowances for manufacturers with regard to the qualified person responsible for product quality; it is not clear whether any similar allowances will be made with respect to the qualified person responsible for pharmacovigilance. According to the current time-scale, the directive is

expected to come into force around the end of 2004; following this, there will be a transition period of at least 5 years (the precise duration is currently under discussion but probably will be 7 years).[36]

Other developments at the European level are concerned, at least in part, with pharmacovigilance of herbal medicines. The European Agency for the Evaluation of Medicinal Products' Herbal Medicinal Products Working Party (previously the *ad hoc* Herbal Medicinal Products Working Group, set up in 1997) has several pharmacovigilance issues on its agenda.[37]

2. Methods for Pharmacovigilance of Herbal Medicines

Some standard methods used in pharmacovigilance, particularly spontaneous reporting schemes, are used to monitor the safety of herbal medicines, although these methods are less well-established than for conventional medicines. Other methods, such as prescription-event monitoring, have not yet been applied to exploring the safety of herbal medicines. All available pharmacovigilance tools have important limitations with regard to their use in investigating the safety of herbal medicines, in addition to those already recognised, and it is likely that modified, even novel, methods are required. This section discusses the available methods, with a focus on spontaneous reporting schemes, and the particular challenges that herbal medicines present for each.

2.1 Spontaneous Reporting Schemes

The future of spontaneous reporting schemes in pharmacovigilance has been questioned,[2] although it is likely that this point was raised in relation to conventional medicines for which other well-established tools, such as computerised health-record databases, can be used for pharmacovigilance purposes. By contrast, spontaneous reporting for herbal medicines is in the early stages of its development and, at present, in the absence of other tools and/or resources, is the main method of generating and detecting signals of potential safety concerns associated with herbal medicines. Spontaneous reporting schemes appear to function reasonably effectively as a pharmacovigilance tool for herbal medicines in countries such as Germany where herbal medicinal products are regulated as medicines, frequently prescribed by physicians and well known to other healthcare professionals, particularly pharmacists.[38] However, spontaneous reporting is likely to be far less effective in countries such as the UK where herbal medicines are marketed mainly as unlicensed products with no obligation for manufacturers to report suspected ADRs to the competent authority, and where herbal medicines are used mostly in self-treatment without any supervision from a healthcare professional.

2.1.1 UK National Spontaneous Reporting Scheme

The CSM/MHRA's national spontaneous reporting scheme for suspected ADR reporting by healthcare professionals (also known as the 'yellow card' scheme because of the form used to report suspected ADRs to the CSM/MHRA) has applied to licensed medicines, including licensed herbal medicines, since its inception in 1964. However, the inclusion of licensed herbal medicines in the scheme was not well-publicised until October 1996, over 30 years later, when the scheme was extended to include reporting for unlicensed herbal medicines.[39] This move followed a 5-year study of traditional remedies and food supplements, carried out by a UK Medical Toxicology Unit,[40] which identified suspected ADRs associated with these types of products. The extension allowed those with official reporter status – at the time, doctors, dentists and coroners only – to submit reports for unlicensed herbal medicines, but did not (and could not) place any statutory obligation on manufacturers to report suspected ADRs associated with their unlicensed herbal products.

In April 1997 and November 1999, the scheme underwent further extensions to allow reporting of suspected ADRs by all hospital and community pharmacists, respectively.[41] Community pharmacists were encouraged by the CSM and MHRA to concentrate on areas of limited reporting by doctors, namely licensed and unlicensed herbal products, and other non-prescription medicines.[41] This extension

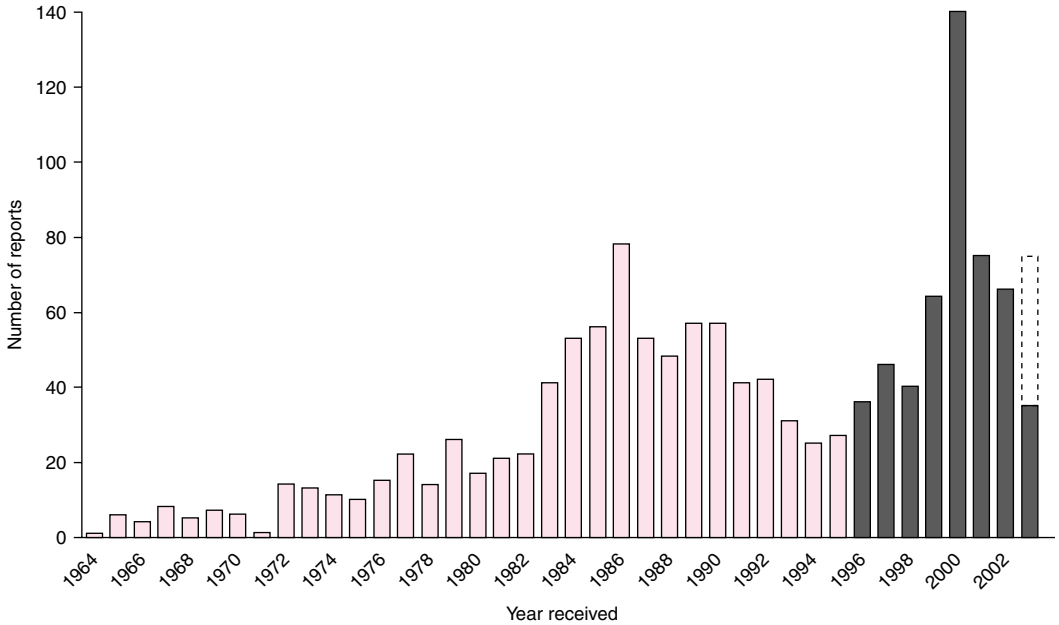

Fig. 1. Numbers of reports of suspected adverse drug reactions associated with herbal medicines received by the UK Committee on Safety of Medicines/Medicines and Healthcare products Regulatory Agency's yellow card scheme for the period 1964 to July 25th, 2003. Blue bars (i.e. pre-1996) represent licensed herbal medicines; black bars (1996 onwards) represent reports for both licensed and unlicensed herbal medicines following extension of the scheme to unlicensed herbal medicines in October 1996; the dotted line above the 2003 bar represents an estimate of the total number of reports for the full year. Source: Adverse Drug Reactions On-line Information Tracking.[43]

followed a 1-year pilot scheme for community pharmacist ADR reporting, carried out in the four CSM regions during 1997–98 and involving around 3200 pharmacies, which showed that community pharmacists, compared with general practitioners (GPs), submitted a greater proportion of reports of suspected ADRs associated with herbal medicines (the numbers of herbal ADR reports as a proportion of the total number of reports submitted by pharmacists and GPs were 4/96 (4.2%) and 8/1975 (0.4%), respectively; $p < 0.001$).[42] However, numbers of herbal ADR reports submitted by both groups of reporters were very low and represented an average of only one and two reports per CSM region for pharmacists and GPs, respectively.

Despite these initiatives to stimulate reporting of suspected ADRs associated with both licensed and unlicensed herbal medicines, numbers of herbal ADR reports submitted to the CSM/MHRA remain very low. From 1964 until the end of 1995, 832 reports were received.[43] For the period 1996 (when the yellow card scheme was extended to unlicensed herbal medicines and when its inclusion of herbal medicines was first well publicised) to 2002 inclusive, 467 reports of suspected ADRs associated with herbal medicines were received (see figure 1). Most frequently, these reports related to products containing the herbal ingredients St John's wort (*Hypericum perforatum*), ginkgo (*Ginkgo biloba*), peppermint (*Mentha piperita*), *Echinacea* species, senna and valerian (*Valeriana officinalis*). It is not known whether the low numbers of reports of suspected ADRs associated with herbal medicines simply reflect a low frequency of adverse effects with herbal medicines, or whether there are other explanations, for example, substantial under-reporting.

The number of herbal ADR reports received increased over the period 1999–2002, with a peak in the year 2000 around the time that reports emerged of suspected interactions between St John's wort and certain prescription medicines. In part, this simply reflected an increase in numbers of reports of

suspected ADRs associated with St John's wort – 60% (82/140) of herbal reports for the year 2000 (42% for 1999 and 13% for 1998), and 40% (138/345) of all herbal reports received during this period related to St John's wort, with around 40 reports in total describing drug interactions with St John's wort – but there was also a (small) general increase in numbers of herbal ADR reports submitted during this period.[43]

It is not yet clear whether this just reflects year-to-year variation, or whether it has been sustained. Typically, a year-on-year increase in the number of herbal suspected ADR reports submitted could be expected, with further increases with the addition of new recognised reporters and initiatives aimed at stimulating herbal ADR reporting. However, the inclusion of pharmacists does not yet appear to have had a marked impact in this regard, since the additional reports of suspected ADRs associated with herbal medicines submitted during 1999–2002 were not submitted solely by pharmacists but also by other recognised reporters.[43,44] For comparison, in 1964 when the yellow card scheme began, there were 1414 submitted reports of suspected ADRs associated with conventional medicines. This increased steadily until 1977 when there was a surge in reporting (10 921 reports for the year) around the time practolol was associated with oculomucocutaneous syndrome and withdrawn from the market, and when initiatives to encourage reporting of suspected ADRs were introduced, for example, the introduction of the newsletter *Current Problems in Pharmacovigilance*.[45] Annual reporting rates have since increased, with some fluctuations, currently to around 20 000 reports per year (which includes the small number of herbal ADR reports), giving a total of over 450 000 reports to the end of 2002.

Further extensions to the reporter base for the yellow card scheme occurred in October 2002 when all nurses, midwives and health visitors became recognised reporters.[46] At the same time, electronic reporting of suspected ADRs over the internet was launched in an attempt to facilitate reporting,[47] and in April 2003, a pilot scheme was introduced to allow patient reporting of suspected ADRs via one of the NHS's 22 NHS Direct telephone call centres.[48] The impact that these new reporter groups and initiatives will have on the reporting of suspected ADRs associated with herbal medicines is not yet known. The results of the pilot scheme for patient ADR reporting via NHS Direct will be relevant for herbal medicines, given that many users of herbal medicines select and self-treat with such preparations without the advice or supervision of a healthcare professional, and that some users may not report suspected ADRs associated with herbal medicines to their doctor or a pharmacist.[20] Evaluations of pilot schemes have indicated that the completeness of all reports submitted by community pharmacists and GPs was similar,[42] although in the pilot scheme for ADR reporting by nurses there was some evidence that completeness of doctors' reports was slightly better than that of nurses.[49]

ADR Reporting Form

The minimum information required for a report of a suspected ADR is the same for both conventional and herbal medicines, and a standard yellow card is used to collect data, regardless of the type of preparation implicated. In the year 2000, a modified yellow card was introduced which included in the section for "*Other drugs*" the prompt "*(including self-medication and herbal remedies)*".[50] Apart from this, the yellow card does not mention herbal medicines specifically, and its current design has several deficiencies with regard to prompting for and collecting information on herbal medicines.

The section '*Suspected drug'* presents several problems. First, the reporter is asked to provide the brand (proprietary) name of the suspected drug(s). While licensed herbal medicinal products are likely to have brand names, unlicensed herbal products legally are not permitted to use them – only the vernacular and/or botanical name, such as St John's wort or *Hypericum perforatum* should be used, although this is ignored by some manufacturers. For unlicensed herbal medicines it would be more appropriate to request the name of the herbal ingredient(s) and the name of the manufacturer/supplier. Identifying the manufacturer is particularly important for reasons mentioned earlier, namely because

the composition of products containing the same herbal ingredient can vary both qualitatively and quantitatively between manufacturers. Also, there may be other problems with the pharmaceutical quality (e.g. contamination) of unlicensed herbal products which should be considered when assessing ADR reports. Ideally, the form should also include space to indicate whether a sample of the suspected product(s) is available.

To identify specifically the herbal ingredient(s) implicated, the binomial botanical name (genus and species) should be given. For example, 'echinacea' is insufficient, since three different *Echinacea* species (*E. purpurea*, *E. pallida* and *E. angustifolia*) are used medicinally and these differ in their phytochemical composition. In addition, the specific plant part used should also be stated, since one or more plant parts may be used medicinally and, again, the phytochemical composition can vary. For example, both the root and the herb (aerial parts) of *E. purpurea* and nettle (*Urtica dioica*) are used medicinally. However, there is no specific request for these details on the yellow card.

Other relevant information not specifically requested includes the method of processing the crude herbal material (e.g. type of extract), since this can also influence the precise chemical composition and, therefore, the potential toxicity of a herbal preparation,[38] the strength of the preparation (e.g. drug : extract ratio), and the formulation of the product (e.g. tablets, tincture). Also, many herbal medicinal products contain several herbal ingredients, some include non-herbal ingredients, such as vitamins and minerals, and herbal practitioners often prescribe several herbal tinctures together supplied as a mixture. With respect to these preparations, one or more herbal ingredient(s) may be the suspected agent(s), yet there is limited space on the current yellow card to provide this level of detail.

Although it is not desirable to introduce different reporting forms for different types of preparations, it could be argued that herbal medicines present a special case and that a more specialised reporting form is required. Alternatively, modifications to the existing reporting card could be made so that important details on herbal medicines can be requested.

Signal Detection and Assessment

At present, because of the relatively small number of reports of suspected ADRs associated with herbal medicines held on the MHRA's ADROIT (Adverse Drug Reaction On-line Information Tracking) database reports, signals are detected simply by numbers of reports. It may be possible to obtain proportional reporting ratios for some suspected ADRs associated with certain herbal medicines, such as St John's wort for which around 150 reports in total have been received since 1996. In this case, the comparison is made against the rest of the database, rather than only against the subset of herbal ADR reports. The assumptions made in proportional analysis, and the importance of considering the effect of selected backgrounds, has been discussed in the context of conventional medicines.[51] Since there are additional biases and other issues in pharmacovigilance of herbal medicines, what is an appropriate comparator requires consideration. This subject is, however, beyond the scope of this article.

Following confirmation of a signal relating to a herbal safety concern, the next stages in its evaluation are also difficult with respect to herbal medicines. In the UK, quantifying the risk is probably impossible as there is no reliable way of determining the number of individuals exposed to the herbal medicine of interest. Benefit-risk analysis is problematic because of the limited clinical data on safety and efficacy of herbal medicines, and identifying at-risk groups is also difficult because the user profile for herbal medicines is poorly defined. A particular problem is that a specific herbal medicine can have numerous uses and may be taken by healthy individuals for 'general well-being', as well as by patients with chronic disease. These problems are further compounded if the variation in different preparations of the same herbal ingredient is considered.

The concerns regarding kava-kava (*Piper methysticum*) and hepatotoxicity illustrate the process of assessing and responding to safety issues relating to unlicensed herbal medicinal products. A signal concerning kava-kava and liver toxicity was

first raised in 2000 following a cluster of cases reported in Switzerland, and was strengthened a year or so later following further spontaneous reports from Switzerland and Germany.[52] The UK CSM undertook an initial evaluation, including causality assessment, and found that the risks of kava-kava appeared to outweigh its benefits. No regulatory action was taken at that time, although the herbal sector instigated a voluntary withdrawal of products containing kava-kava while the safety concerns were investigated further.

The next stage involved further data collection and evaluation. The CSM set up a working group to assess the issue and requested additional data on benefits and risks of kava-kava from the herbal sector and regulatory authorities. When the CSM next considered the issue in July 2002, a total of 68 reports originating from several countries had been received, although only three originated in the UK.[52] The severity of the liver damage described in the reports varied from abnormal liver function test results to liver failure and death; six patients received liver transplants. Different preparations of kava-kava were available (e.g. different types of extracts) and consideration was given as to whether only certain types of kava-kava preparation might be associated with liver toxicity. However, there appeared to be no relationship between the method of processing/type of extract, strength or dose, and the adverse reactions. Thus, on the basis of the data available, the CSM advised that the possible benefits of preparations containing kava-kava do not outweigh the risks, that kava-kava had the potential to cause hepatotoxicity which could be serious in nature, and that kava-kava should be prohibited in unlicensed medicines. On January 13, 2003, a statutory order came into effect in the UK prohibiting the sale, supply and import of unlicensed medicines containing kava-kava. Product licences for licensed kava-kava products were revoked.[53]

Some of the difficulties in assessing safety concerns with unlicensed herbal medicines were evident here. For example, the number of unlicensed herbal products containing kava-kava available in the UK, their extent of use, and the extent of use of kava-kava preparations by patients consulting medical herbalists, were not known; reports involved different types of kava-kava preparations; only a very low number of reports was received in the UK; the quality and completeness of the reports was poor, and some reports were duplicated; there are few clinical trials of kava-kava products and a lack of clear evidence of efficacy; regulatory options in responding to the signal were limited, and alternatives, such as including warning information with products, would have required the voluntary cooperation of manufacturers of unlicensed kava-kava products and MHRA would have had no means of enforcement.

Strengths and Weaknesses

Spontaneous reporting schemes have recognised advantages and limitations, and several of these may be even more important with regard to herbal medicines (see table III). In particular, under-reporting is a well-recognised, important and inevitable limitation of any spontaneous reporting scheme, but for several reasons it may be an even greater problem for herbal medicines.

Under-reporting of suspected ADRs associated with herbal medicines could occur at several levels.

Table III. Summary of advantages and limitations of spontaneous adverse drug reaction (ADR) reporting schemes with respect to herbal medicines

Advantages
Monitor all drugs, including all herbal medicines, all the time and for all consumers and patients
Provide early warnings of undocumented drug safety concerns; important for herbal medicines as information on safety is limited
Relatively cheap to run; important as the herbal sector may not have the resources to conduct large-scale postmarketing surveillance studies
Limitations
Under-reporting; likely to be greater for herbal medicines
Poor quality of data available to or provided by reporter; yellow card does not cater specifically for recording information on herbal medicines as suspected drugs
Biases in reporting
Cannot estimate frequency of an ADR as do not provide accurate information on number of individuals exposed to the drug of interest; probably not possible to obtain denominators for unlicensed herbal medicinal products
Suspected ADRs may be identified/reported outside the formal system (e.g. to herbalists, health-food stores)

First, because of the perception that herbal medicines are 'safe', users of these preparations may not associate an adverse event with their use of a herbal medicine, particularly if they are taking other (conventional) medicines. If the user does make an association between use of a herbal medicine and an adverse event, they may take steps to resolve the problem themselves (for example, stop taking the preparation) and/or may not inform a healthcare professional.[20] Under-reporting can also occur at the level of the healthcare professional, since doctors, pharmacists and other recognised reporters could filter out reports of suspected ADRs described by patients.[54] Reasons for under-reporting among healthcare professionals are well-documented, although studies exploring this area have been carried out in the context of conventional medicines, and it is not known if these same reasons apply to under-reporting for herbal medicines.

Several studies involving community pharmacists indicate that many pharmacists are unaware that they should report suspected ADRs associated with herbal medicines. A cross-sectional survey carried out in 1998 of over 1300 community pharmacists (response rate: 67%) not involved in the CSM/MHRA pilot scheme for community pharmacist ADR reporting found that 47% of respondents were not aware that the yellow card scheme applied to herbal medicines at all, 37% were aware it applied to licensed herbal medicines, and only 16% knew it applied to both licensed and unlicensed herbal medicines.[25] This finding is not so surprising since these pharmacists were not recognised reporters at the time of the study and would not have received training materials on ADR reporting. Of more concern is that studies conducted since all community pharmacists became recognised reporters and were encouraged to focus on reporting suspected ADRs associated with herbal and other non-prescription medicines have continued to find that many community pharmacists are unaware of the need to report suspected ADRs associated with herbal medicines,[55,56] particularly unlicensed herbal medicines.[55] There may also be biases favouring ADR reporting for herbal medicines. An audit of medicines information pharmacists working in a Medicines Information Centre in Wales found that although they encouraged only 41% of enquirers about ADRs to complete yellow cards, they were more likely to give encouragement where an 'alternative' medicine was involved rather than a conventional medicine.[57] In addition, all these studies revealed deficiencies in community pharmacists' knowledge on other aspects of ADR reporting, such as the level of certainty required regarding a causal relationship.

To date, there are very few studies that provide any information on the extent of under-reporting of suspected ADRs associated with herbal medicines. In one cross-sectional survey of community pharmacists who were not involved in the CSM/MHRA pilot scheme for community pharmacist ADR reporting (see earlier in this section), respondents were asked to describe any reports of suspected ADRs associated with complementary medicines that they had received or identified over the previous 12 months.[24,25] In total, among 818 respondents, 44 reports of suspected ADRs associated with herbal medicines were described, an average of one report per 19 pharmacists. By contrast, the CSM/MHRA pilot scheme, which ran over approximately the same period covered by the survey, and involved around 3200 pharmacies, received only four reports.[42,58] Conclusions cannot be drawn from these crude comparisons, since these studies used different methodologies, involved pharmacists/pharmacies in different regions of the UK, and so on. They do, however, raise the hypothesis that there is significant under-reporting by pharmacists of suspected ADRs associated with herbal medicines.

It is recognised that pharmacists can make an important contribution to ADR reporting for herbal medicinal products, but it is likely that greater vigilance on the part of the pharmacist and initiatives to encourage herbal ADR reporting by pharmacists are required. Against this background, there have been several recent papers in a journal received by all UK pharmacists,[18,44,59] and a fact-sheet on ADR reporting by pharmacists has been produced by the Science Committee of the Royal Pharmaceutical

Society of Great Britain (the professional and regulatory body for all pharmacists in the UK) which provides guidance and reminds pharmacists of their professional and ethical responsibilities in this regard.[60]

A further limitation of spontaneous reporting schemes is that herbal medicines are widely available from a range of outlets without the need for interaction with a healthcare professional and, therefore, suspected ADRs associated with herbal medicines may be identified by or reported to an individual (e.g. herbalist) who is outside the formal system for ADR reporting. Health-food stores are a major outlet for herbal medicinal products, but it is not known if staff in these outlets receive reports of suspected ADRs associated with such products, and if they do, what action, if any, they take.

2.1.2 WHO/Uppsala Monitoring Centre Traditional Medicines Project

ADR reports, including herbal ADR reports, from the CSM/MHRA yellow card scheme and (in 2003) those from 70 other countries with national ADR monitoring schemes are fed into the WHO/Uppsala Monitoring Centre (UMC). The UMC recognises the problems inherent in ADR reporting for herbal medicines and has established a Traditional Medicines project to stimulate reporting in this area and to standardise information on herbal medicines, particularly with regard to nomenclature.[61] For example, a special set of herbal anatomical-therapeutic-chemical (ATC) codes has been developed which is fully compatible with the regular ATC classification system for conventional medicines.[62]

The UMC database, established in 1968, held over 2 million reports of suspected ADRs by 1999, of which around 0.5% involve herbal medicines.[62] For the period 1968–1997, almost 9000 reports involving herbal medicines were received by the UMC. The UK is among the top five countries in terms of absolute numbers of herbal suspected ADR reports submitted.

2.1.3 Herbal-Sector-Initiated Spontaneous Reporting Schemes

At present, herbal medicine practitioners are not recognised as reporters by the CSM/MHRA yellow card scheme. Several herbal-medicine practitioner and other herbal-sector organisations have initiated their own ADR reporting schemes for herbal medicines based on the CSM/MHRA scheme. While this is a responsible and potentially useful step forward where these schemes have developed a link with the CSM/MHRA or WHO/UMC, *ad hoc* schemes are not encouraged because there is a risk that reports will be dispersed and signals may be not be detected as early as possible, or may be missed. As with any spontaneous reporting scheme, herbal-sector-initiated schemes are also likely to be prone to limitations such as under reporting. It is not known whether reasons for under-reporting of suspected herbal ADRs by the herbal sector are different to those for herbal ADR reporting by conventional healthcare professionals. It is possible that there may be concerns among the herbal sector that the availability of herbal medicines and their freedom to practise herbal medicine may be threatened if significant numbers of herbal ADR reports are submitted.

The National Institute of Medical Herbalists (NIMH), the major organisation for medical herbalists in the UK, requests from its members reports of suspected ADRs associated with herbal treatments. Reports are submitted on a modified 'yellow card' form, which has some additional data fields relevant to herbalists' prescriptions. The NIMH sends an annual summary of reports received to MHRA. For the period January 1994–November 2001, 23 reports were received by the NIMH.[63] Most reports described reactions experienced by patients who had received a combination of several herbs, which is typical of medical herbalists' treatment approach. A similar scheme has been set up by the Register of Chinese Herbal Medicine (RCHM) which also uses a modified yellow card form to collect data from its practitioners of Chinese herbal medicine. The RCHM scheme also has a link with MHRA. At the time of writing, nine reports (three in 2000) had been received by the RCHM from its members.[64]

Other schemes have been established which are not restricted to herbal-medicine practitioners. Phytonet is a password-protected, internet-based system for gathering reports of suspected ADRs associated with herbal medicines that was set up by a UK university on behalf of the European Scientific Co-Operative on Phytotherapy in 1996.[65] Phytonet uses an electronic form based on the CSM/MHRA yellow card, but differs from the schemes described above in that it accepts reports from healthcare professionals, herbal practitioners, patients and the public. Submitted reports are assessed by an expert panel and, where appropriate, fed into the WHO/UMC. Few reports have been received, however, and support is needed to revive the system. As there is no obligation for manufacturers to report suspected ADRs associated with their unlicensed herbal products, the British Herbal Medicine Association (BHMA), whose members include many herbal-medicines manufacturers, has addressed this in its voluntary code of practice for its members.[66] The code includes the requirement that manufacturers send reports of suspected ADRs associated with their unlicensed herbal products to the BHMA, which may, at its discretion, forward such reports to MHRA. At the time of writing, the BHMA had not received from its members any reports of suspected ADRs associated with unlicensed herbal medicinal products. The University of Westminster, London, UK, in conjunction with a supermarket retailer, is developing an ADR reporting scheme for consumers, nutritional advisers and other health practitioners to report suspected ADRs associated with herbal and 'complementary' medicines.[67] There is at least one other scheme in the UK, set-up by a herbal supplier in Leicester, UK, which is inviting purchasers of its products to submit reports of suspected ADRs. It is not clear what are the aims of this scheme, given that it is stated that the information will be used only by the herbal supplier. This is of concern if, for example, a herbalist submits a report of a suspected ADR associated with a herbal medicine to this scheme alone.

2.1.4 Intensive Monitoring Schemes

Extensions to the CSM/MHRA yellow card scheme were launched in 1997 and 1998 to stimulate reporting of suspected ADRs associated with medicines used in the treatment of HIV infection, and of ADRs occurring in children.[45] The HIV reporting scheme, launched in 1997, targets specialist healthcare professionals working with HIV-infected individuals and encourages reports of suspected ADRs on a modified yellow card form which does not request the patient's name. The paediatric reporting scheme also targeted healthcare professionals but did not involve a modified yellow card. Numbers of reports increased following the introduction of these schemes, although the underlying reporting rate increased only with the HIV scheme; ongoing promotion of the scheme, for example, through a regular newsletter is stated to be important.[45] To date, CSM/MHRA have not introduced an intensive monitoring scheme for herbal medicines and, given that the impact of initiatives to stimulate reporting of herbal ADRs has so far been limited, it may be an appropriate time to set up such a scheme together with a programme of ongoing promotion aimed at maintaining its effectiveness.

The herbal sector has not yet set up any such schemes for pharmacovigilance purposes, although a pilot study run by the Medicinal Plant Research Group collected detailed data, including outcomes, from around 30 herbalists on all their patients treated for irritable bowel syndrome.[68]

2.2 Prescription Event Monitoring

The methodology of prescription event monitoring (PEM) in monitoring the safety of newly marketed prescription drugs is well-established.[69][2] The

2 PEM is a hypothesis-generating, non-interventional, observational form of monitoring for newly marketed medicines carried out by the Drug Safety Research Unit, Southampton, UK. Current PEM methodology involves sending a 'green form' to GPs who have prescribed the medicine being studied; these data are obtained from the UK Prescription Pricing Authority. The green form comprises a simple questionnaire, which requests data on all health events the patient who was prescribed the drug experienced during treatment. These forms are usually sent to the GPs around 6 months after the patient was first prescribed the medicine under study.

valuable contribution that PEM has made to pharmacovigilance of conventional medicines is clear, but the existing method is of no use at present for pharmacovigilance of herbal medicines because they are rarely prescribed.

A protocol for modified PEM methodology has been developed by the Drug Safety Research Unit, Southampton, UK, in collaboration with the NIMH, the University of Southampton, the Medical Toxicology Unit at Guy's and St Thomas' Hospital Trust, London, and the School of Pharmacy, University of London. This approach involves using herbalists to provide adverse event data on green forms for patients treated with a specific herbal medicine. Where patients give permission, a green form requesting adverse event data would also be sent to their GP. There are limitations to this method, such as whether sufficient patient numbers could be achieved and, particularly, that the herb of interest is not 'newly marketed' so there may be preconceptions about its safety profile. Nevertheless, the protocol represents a step forward in attempting to develop methods for pharmacovigilance of herbal medicines. Funding is being sought to carry out a pilot study of the modified PEM methodology.

Another potential approach, based on PEM concepts, is to use community pharmacists to recruit a cohort of purchasers (where consent is given) of a specific herbal medicinal product who would then be followed up over time and adverse event data collected. The feasibility of this approach has been demonstrated in a pilot study using a conventional non-prescription medicine,[70,71] but needs to be evaluated as a method for pharmacovigilance of herbal medicinal products.

2.3 Other Pharmacoepidemiological Study Designs

The methodology for case-control and cohort studies is well established and these study designs can be used to investigate safety concerns with herbal medicines, although few studies have been carried out to date. One study explored the relationship between colorectal cancer and use of preparations containing anthranoid laxatives.[38] The strengths and limitations of case-control and cohort studies are well documented,[72] but as with other study designs, some of the problems are compounded when these study designs are applied to herbal medicines. For example, to establish and verify both cases' and controls' exposure to the herbal medicine(s) of interest is particularly problematic since herbal medicines are rarely prescribed; even where herbal medicinal products are purchased from pharmacies, pharmacists do not routinely record use of herbal and other non-prescription medicines on computerised patient medication records.[24,25] In addition, for reasons explained earlier, there are likely to be variations in different manufacturers' products and, therefore, defining exposure precisely will be difficult at best.

Case-control and cohort studies involving conventional prescribed medicines can be carried out using UK computerised health-record databases such as the General Practice Research Database and the Medicines Monitoring Unit database, but such tools currently are of no use for studies involving herbal medicines since herbal medicines are rarely prescribed and information on non-prescription medicines, including herbal medicines, is not recorded on GPs' patient records.

As with case-control and cohort studies, experimental studies can be applied to investigating the safety of herbal medicines. At present, notwithstanding recognised limitations, such as sample size and ethical considerations, well-designed and well-conducted randomised clinical trials (RCTs) overcome some of the difficulties that herbal medicines present for other pharmacoepidemiological studies. For example, precisely establishing exposure is simpler since compliance checks can be carried out, and RCTs are unlikely to use herbal medicinal products (containing the same herbal ingredient) from different manufacturers, so product variation and, usually, batch-to-batch variation in products, is eliminated. There is always the possibility of course that clinical-trial participants could take purchased herbal medicines in addition to the study medication.

Systematic reviews and meta-analyses of adverse event data from RCTs of specific herbal medicines

have been carried out, but this introduces other problems. Many existing RCTs of herbal medicinal products are of poor or limited methodological quality, and/or published reports of studies do not follow Consolidated Standards of Reporting Trials (CONSORT) guidelines. In addition, clinical trials of a particular herbal ingredient usually will have been carried out using several different manufacturers' products, but systematic reviews and meta-analyses often ignore variations between products.

3. Communication of Herbal Safety Concerns

The importance of the timing, content and method of delivery of messages regarding safety concerns has been discussed extensively, and the requirements for successful communication of safety concerns should apply equally to herbal medicines. However, communicating information on herbal safety concerns presents additional difficulties for several reasons. 'Dear Doctor/Pharmacist' letters can be sent, but healthcare professionals are unlikely to know which of their patients are using herbal medicines and, therefore, will be unable to pass on safety messages to specific individuals. Medical herbalists may keep some records of their patients' treatment, but as there is no statutory regulation for herbal-medicine practitioners, lists of all individuals practising herbal medicine are not available.

Moreover, most users of herbal medicines obtain these medicines from outlets where there is no healthcare professional present and without seeking professional advice. Methods aimed at reaching the public directly (e.g. the internet) and the popular media are often the only ways of communicating herbal safety information to such individuals. There is a lack of research on how herbal-medicine users interpret information on risks associated with herbal medicines. It should not be assumed that users' understanding of risk associated with herbal medicines is the same as that for prescription medicines or conventional non-prescription medicines. It has been shown that individuals may overestimate the risks of adverse effects associated with prescription medicines and conventional non-prescription medicines,[73,74] but given that herbal medicines are widely perceived to be safe, the hypothesis that users of herbal medicines may underestimate risks needs to be tested. Furthermore, once the proposed directive on traditional herbal medicinal products comes into force, manufacturers of products registered under the new national scheme will be required to provide systematic information with their products, including information on adverse events and special warnings. The impact of this on users' perceptions of the risks associated with herbal medicines will also require evaluation.

The action taken by MHRA to communicate information on interactions between St John's wort and certain prescription medicines after this issue emerged in the year 2000 provides an example of the process of communicating information on herbal safety concerns. Following its decision that manufacturers should include warning information on product packaging, MHRA used various ways of communicating the message. 'Dear Doctor/Pharmacist' letters were sent, and pharmacists in particular were asked to provide advice to consumers and patients on interactions between St John's wort and conventional medicines. A telephone help-line was set up, and information for patients was posted on the MHRA website. However, it is difficult to assess the effectiveness of these measures. Since February 2000 when the information was made public, the CSM/MHRA yellow card scheme has continued to receive reports of suspected interactions between St John's wort and conventional medicines (>30 from February 2000–April 2003), for example, reports of breakthrough bleeding and unintended pregnancy in women taking St John's wort products concurrently with oral contraceptives.[43]

It is likely that there is scope for improving communication with the public on herbal safety issues. Recognising this, an area on the MHRA website has been set up which is dedicated to providing early information on herbal safety concerns.[13]

4. The Future for Pharmacovigilance of Herbal Medicines

The potential for herbal medicines to have a significant negative impact on the public health needs to be kept in perspective. Nevertheless, a parallel can be drawn between the lack of a formal medicines regulatory system before the thalidomide disaster and the current situation in the UK as regards herbal medicinal products in that the sector largely is unregulated. Most herbal medicinal products, including herbs from China, South America and many other countries, which are new to the UK, are sold without any requirement to demonstrate to the licensing authority evidence of quality, safety and efficacy. Post-thalidomide, new initiatives in drug safety monitoring initially followed further high-profile drug safety problems.[75] Likewise, several recent high-profile herbal safety concerns, such as renal failure and urothelial cancer associated with exposure to *Aristolochia* species,[76] drug interactions with St John's wort,[77] and hepatotoxicity associated with kava-kava,[78] have contributed to the increasing awareness of the need to monitor the safety of herbal medicines. Against a background of increasing use of herbal medicines, particularly by patients using conventional drugs concurrently and those with serious chronic illness, it is likely that new safety concerns will continue to emerge.

However, improvements in the safety and pharmacovigilance of herbal medicines can be expected, if the proposed EU directive for traditional herbal medicinal products is implemented as planned.[6] Manufacturers of traditional herbal medicinal products registered under national schemes established under the directive will be required to adhere to quality standards, to provide bibliographic evidence of the safety of their products, and to comply with regulatory provisions on pharmacovigilance. These improvements may not happen immediately across all manufacturers, since some may take advantage of the transition period (which will be at least 5 years, probably 7 years, from the date the legislation comes into force) before submitting their dossiers to MHRA in order to apply for product registrations.

Another effect of the directive may be to shift the emphasis of research involving herbal medicines. At present, most research in the herbal medicines area is aimed at discovering the pharmacological activities of medicinal plants and providing evidence of clinical efficacy; rather less effort is focussed on investigating safety. However, since the proposed traditional herbal medicinal products directive does not require manufacturers to demonstrate efficacy (other than by way of traditional use), there may be more interest among manufacturers and researchers in extending knowledge of the safety of herbal medicines. While research into the safety of herbal medicines is to be welcomed, research into efficacy is also needed in order to develop herbal medicinal products with favourable benefit-risk profiles.

Statutory regulation of herbal-medicine practitioners, as recommended by The House of Lords' Select Committee on Science and Technology's report on complementary/alternative medicine[79] is also expected to be implemented over the next few years. Once this has been achieved, it seems reasonable to expect that the yellow card scheme would be extended to include state-registered herbal-medicine practitioners as recognised reporters who would be encouraged to report suspected ADRs associated with herbal medicines.

In the longer term, modified, even novel tools for monitoring the safety of herbal medicines may be developed. Pharmacy-record linkage is used in The Netherlands for pharmacovigilance purposes, but no such tool exists currently in the UK. A new Department of Health report,[80] however, discusses the possibility of community pharmacists being able to access a common electronic health record which will be created for all patients and, presumably, to add community pharmacy data to it. While such a system probably would apply only to prescription medicines initially, with technological advances it might also be developed into a computerised record-linkage database that could be used to monitor the safety of herbal and other non-prescription medicines. Consideration should also be given as to whether consumers and patients could have a greater role in pharmacovigilance of herbal medicines,

possibly by their inclusion as recognised reporters in spontaneous reporting schemes and by collecting data directly from patients in studies based on modified PEM methodology.

The future for ensuring the safety of herbal medicines may lie, at least in part, with pharmacogenetics and pharmacogenomics. The importance of genetic factors in determining an individual's susceptibility to ADRs is well documented,[81] and this applies to herbal medicines as well as to conventional drugs. However, optimising treatment, including reducing the potential for ADRs, on the basis of a patient's genotype has barely been discussed in the context of herbal medicines.

Acknowledgements

The author thanks Mrs Leigh Henderson, Medicines and Healthcare products Regulatory Agency (MHRA) for providing data from the ADROIT system, and Dr Linda Anderson, MHRA, and the referees for their comments.

No sources of funding were used to assist in the preparation of this manuscript. The author has no conflicts of interest directly relevant to the contents of this review. The views expressed are those of the author alone and do not necessarily represent the views of the MHRA or the individuals mentioned above.

References

1. Mann RD, Andrews EB, editors. Pharmacovigilance. Chicester: Wiley, 2002
2. Waller PC, Evans SJW. A model for the future conduct of pharmacovigilance. Pharmacoepidemiol Drug Saf 2003; 12: 17-29
3. World Health Organization. Draft WHO guidelines on safety monitoring and pharmacovigilance of herbal medicines. Geneva: World Health Organization, 2003
4. European Agency for the Evaluation of Medicinal Products (EMEA) Committee for Proprietary Medicinal Products (CPMP). Note for guidance on quality of herbal medicinal products. CPMP/QWP/2819/00 (EMEA/CVMP/814/00). London: EMEA, July 26, 2001 [online]. Available from URL: http://www.emea.eu.int/pdfs/human/qwp/281900en.pdf [Accessed 2003 Aug 13]
5. The Medicines Act. London: The Stationery Office, 1968
6. Commission of the European Communities. Proposal for amending the directive 2001/83/EC as regards traditional herbal medicinal products. 2002/0008 (COD). Brussels: European Commission, 2002
7. Commission of the European Communities. Amended proposal for a Directive of the European Parliament and of the Council amending the directive 2001/83/EC as regards traditional herbal medicinal products. 2002/0008 (COD). Brussels: European Commission, 2003
8. Barnes J, Anderson LA, Phillipson JD. Herbal medicines: a guide for healthcare professionals. London: Pharmaceutical Press, 2002
9. De Los Reyes GC, Koda RT. Determining hyperforin and hypericin content in eight brands of St John's wort. Am J Health Syst Pharm 2002; 59: 545-7
10. Kressman S, Muller WE, Blume HH. Pharmaceutical quality of different *Ginkgo biloba* brands. J Pharm Pharmacol 2002; 54: 661-9
11. Loew D, Kaszkin M. Approaching the problem of bioequivalence of herbal medicinal products. Phytother Res 2002; 16: 705-11
12. Woodfield R. Senecio species in unlicensed herbal remedies [letter]. London: Medicines Control Agency, 2002
13. Medicines and healthcare products Regulatory Agency. Herbal safety news [online]. Available from URL: http://medicines.mhra.gov.uk [Accessed 2003 Jul 29]
14. Thomas KJ, Nicholl JP, Coleman P. Use and expenditure on complementary medicine in England: a population based survey. Complement Ther Med 2001; 9: 2-11
15. Mintel International Group Ltd. Complementary medicines, UK. April 2003. London: Mintel International Group Limited, 2003
16. Eisenberg DM, Davis RB, Ettner SL, et al. Trends in alternative medicine use in the United States, 1990-1997: results of a national follow-up survey. JAMA 1998; 280 (18): 1569-75
17. MacLennan AH, Wilson DH, Taylor AW. The escalating cost and prevalence of alternative medicine. Prev Med 2002; 35: 166-73
18. Barnes J. Herbal therapeutics (1): an introduction to herbal medicinal products. Pharm J 2002; 268: 804-6
19. Barnes J, Ernst E. Traditional herbalists' prescriptions for common clinical conditions: a survey of members of the UK National Institute of Medical Herbalists. Phytother Res 1999; 12: 369-71
20. Barnes J, Mills SY, Abbot NC, et al. Different standards for reporting ADRs to herbal remedies and conventional OTC medicines: face-to-face interviews with 515 users of herbal remedies. Br J Clin Pharmacol 1998; 45: 496-500
21. Gulian C, Barnes J, Francis S-A. Types and preferred sources of information concerning herbal medicinal products: face-to-face interviews with users of herbal medicinal products [abstract]. Int J Pharm Prac 2002; 10 Suppl.: R33
22. Vickers AJ, Rees RW, Robin A. Advice given by health food stores: is it clinically safe? J R Coll Phys Lond 1998; 32 (5): 426-8
23. Quinn CG, Waterman P. A comparison of the teaching of herbal medicine in the United Kingdom and Europe. University of Strathclyde, 1997
24. Barnes J, Abbot NC. Experiences with complementary medicines: a survey of community pharmacists [abstract]. Pharm J 1999; 263: R37-43
25. Barnes J. An examination of the role of the pharmacist in the safe, effective and appropriate use of complementary medicines [PhD thesis]. University of London, 2001
26. Department of Health. Herbal Medicine Regulatory Working Group [online]. Available from URL: http://www.doh.gov.uk/herbalmedicinerwg [Accessed 2003 Jul 29]
27. Medicines Control Agency. Traditional ethnic medicines: public health and compliance with medicines law. November 2001. London: Medicines Control Agency, 2001
28. The Medicines (Aristolochia and Mu Tong) (Prohibition) Order 2001 (SI 2001/1841). London: The Stationery Office, 2001

29. Commission of the European Communities. Directive 2001/83/EC. Brussels: European Commission, 2001
30. Adcock H. Medicines Control Agency proposes ban for kava-containing products. Pharm J 2002; 269: 128
31. Royal Pharmaceutical Society of Great Britain. Medicines, ethics and practice: a guide for pharmacists. London: Royal Pharmaceutical Society of Great Britain, 2003 Jul: 92
32. De Smet PAGM, Hänsel R, Keller K, et al., editors. Toxicological outlook on quality assurance of herbal remedies. In: Adverse effects of herbal drugs. Vol 1. Berlin: Springer Verlag, 1992
33. Busse W. The significance of quality for efficacy and safety of herbal medicinal products. Drug Inf J 2000; 34: 15-23
34. Ernst E, De Smet PA, Shaw D, et al. Traditional remedies and the "test of time". Eur J Clin Pharmacol 1998; 54 (2): 99-100
35. De Smet PAGM. Health risks of herbal remedies. Drug Saf 1995; 13 (2): 81-93
36. Woodfield R. Proposed directive on traditional herbal medicinal products: progress in European negotiations [letter]. London: Medicines and Healthcare products Regulatory Agency, 2003
37. Press release (revised). Meeting of the Working Party on Herbal Medicinal Products. February 24-25, 2003, European Agency for the Evaluation of Medicinal Products, London. Document reference: EMEA/CPMP/HMPWP/1090/03Rev.1
38. De Smet PAGM. An introduction to herbal pharmacovigilance. In: De Smet PAGM, Keller K, Hänsel R, et al., editors. Adverse effects of herbal drugs. Vol. 3. Berlin: Springer-Verlag, 1997
39. Extension of the yellow card scheme to unlicensed herbal remedies. Curr Prob Pharmacovigilance 1996; 22: 10
40. Shaw D, Leon C, Kolev S, et al. Traditional remedies and food supplements: a 5-year toxicological study (1991-1995). Drug Saf 1997; 17 (5): 342-56
41. Extension of the yellow card scheme to pharmacists. Curr Prob Pharmacovigilance 1997; 23: 3
42. Davis S, Coulson R. Community pharmacist reporting of suspected ADRs: (1) the first year of the yellow card demonstration scheme. Pharm J 1999; 263: 786-8
43. Medicines and Healthcare Products Regulatory Agency. Adverse drug reaction on-line information tracking (ADROIT) system, Jul 25, 2003
44. Major E. The yellow card scheme and the role of pharmacists as reporters. Pharm J 2002; 269: 25-6
45. Davis S, Raine JM. Spontaneous reporting: UK. In: Mann RD, Andrews E, editors. Pharmacovigilance. Chicester: Wiley, 2002: 195-207
46. Committee on Safety of Medicines and Medicines and Healthcare Products Regulatory Agency. The yellow card scheme: extension of the yellow card scheme to nurse reporters [online]. Available from URL: http://medicines.mhra.gov.uk/aboutagency/regframework/csm/csmhome.htm [Accessed 2003 Jul 25]
47. MCA launches web version of yellow card scheme. Pharm J 2002; 269: 631
48. Patients able to report ADRs via NHS Direct. Pharm J 2003; 270: 608
49. Morrison-Griffiths S, Walley TJ, Park BK, et al. Reporting of adverse drug reactions by nurses. Lancet 2003; 361: 1347-8
50. Updated "yellow card" launched. Pharm J 2000; 265: 387
51. Gogolak VV. The effect of backgrounds in safety analysis: the impact of comparison cases on what you see. Pharmacoepidemiol Drug Saf 2003; 12: 249-52
52. Medicines Control Agency. Consultation MLX 286: proposals to prohibit the herbal ingredient kava-kava (Piper methysticum) in unlicensed medicines. London: Medicines Control Agency, 2002 Jul 19
53. The Medicines for Human Use (Kava-Kava) (Prohibition) Order 2002 (SI2002/3170). London: The Stationery Office, 2003
54. Van Grootheest K, de Graaf L, de Jong-van den Gerg LTW. Consumer adverse drug reaction reporting: a new step in pharmacovigilance? Drug Saf 2003; 26 (4): 211-7
55. Wingfield J, Walmsley J, Norman C. What do Boots pharmacists know about yellow card reporting of adverse drug reactions? Pharm J 2002; 269: 109-10
56. Green CF, Mottram DR, Raval D, et al. Community pharmacists' attitudes to adverse drug reaction reporting. Int J Pharm Prac 1999; 7: 92-9
57. Biscoe R, Houghton JE, Woods FJ. An audit of the level of encouragement given by medicines information pharmacists to enquirers of suspected adverse drug reactions to complete a yellow card report: perspectives in patient safety [abstract]. 28th UK Medicines Information Conference Proceedings; 2002 Sep 19-21; Chester, UK
58. Pharmacists' adverse drug reaction reporting to start on April 1. Pharm J 1997; 258: 330-1
59. Cox A. Embracing ADR reporting could improve pharmacists' standing [letter]. Pharm J 2002; 269: 14
60. Moffat T. Adverse drug reaction (ADR) reporting by pharmacists. London: Royal Pharmaceutical Society of Great Britain, 2003. In press
61. Farah MH, Edwards R, Lindquist M, et al. International monitoring of adverse health effects associated with herbal medicines. Pharmacoepidemiol Drug Saf 2000; 9: 105-12
62. World Health Organisation Collaborating Centre for International Drug Monitoring. Draft guidelines for herbal ATC classification. Uppsala: The Uppsala Monitoring Centre, 2002
63. Broughton A. Yellow card reporting scheme. Eur J Herb Med 2001; Dec: 3-6
64. Ward T. Register for Chinese Medical Herbalists. 2002 Sep 18
65. European Scientific Co-operative on Phytotherapy (ESCOP). PhytoNET [online]. Available from URL: http://www.escop.com [Accessed 2003 Jul 29]
66. British Herbal Medicine Association. Code of good practice: unlicensed herbal remedies. Bournemouth: British Herbal Medicine Association, 1997 Mar
67. Nutraceuticals adverse events database. Executive summary [online]. Available from URL: http://www.wmin.ac.uk/sih/research/proj_nutraceuticals.html [Accessed 2003 Jul 25]
68. Logue M, Pendry B, Waters E, et al. Irritable bowel syndrome: herbal research update [abstract]. Phytotherapy Research Conference; 2002 Apr, Glasgow
69. Shakir SAW. PEM in the UK. In: Mann RD, Andrews EB, editors. Pharmacovigilance. Chicester: Wiley, 2002: 333-44
70. Layton D, Sinclair HK, Bond CM, et al. Pharmacovigilance of over-the-counter products based in community pharmacy: methodological issues from pilot work conducted in Hampshire and Grampian, UK. Pharmacoepidemiol Drug Saf 2002; 11: 503-13
71. Sinclair HK, Bond CM, Hannaford PC. Pharmacovigilance of over-the-counter products based in community pharmacy: a feasible option? Pharmacoepidemiol Drug Saf 1999; 8: 479-91
72. Strom BL. How should one perform pharmacoepidemiology studies? Choosing among the available alternatives. In: Strom BL, editor. Pharmacoepidemiology. 3rd ed. Chicester: Wiley, 2000: 401-13

73. Berry DC, Knapp PR, Raynor DK. Is 15% very common: informing people about the risks of medication side effects. Int J Pharm Prac 2002; 10: 145-51
74. Berry DC, Raynor DK, Knapp P, et al. Patients' understanding of risk associated with medication use: impact of European Commission guidelines and other risk scales. Drug Saf 2003; 26 (1): 1-11
75. Edwards IR, Olsson S. WHO programme: global monitoring. In: Mann RD, Andrews EB, editors. Pharmacovigilance. Chicester: Wiley, 2002: 169-82
76. Cosyns J-P. Aristolochic acid and 'Chinese herbs nephropathy': a review of the evidence to date. Drug Saf 2003; 26 (1): 33-48
77. Henderson L, Yue QY, Bergquist C, et al. St John's wort (*Hypericum perforatum*): drug interactions and clinical outcomes. Br J Clin Pharmacol 2002; 54: 349-56
78. Kava-kava and hepatotoxicity [news item]. Curr Prob Pharmacovigilance 2002; 28: 6
79. House of Lords Select Committee on Science and Technology, Session 1999-2000, 6th report. Complementary and alternative medicine. London: The Stationery Office, 2000
80. Department of Health. A vision for pharmacy in the new NHS. London: Department of Health, 2003 Jul
81. Pirmohamed M, Park BK. Genetic susceptibility to ADRs. Trends Pharmacol Sci 2001; 22 (6): 298-305

Correspondence and offprints: Dr *Joanne Barnes*, Centre for Pharmacognosy and Phytotherapy, School of Pharmacy, University of London, 29-39 Brunswick Square, London, WC1N 1AX, UK.
E-mail: joanne.barnes@ulsop.ac.uk