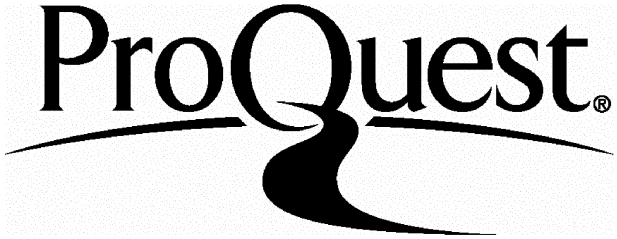
AN EXAMINATION OF THE ROLE OF THE COMMUNITY PHARMACIST IN THE PHARMACOVIGILANCE OF HERBAL MEDICINES

Thesis submitted in accordance
with the requirements of the University of London
for the degree of
Doctor of Philosophy
by

Anjana Mohini Aggarwal

Centre for Pharmacognosy and Phytotherapy
Department of Pharmaceutical and Biological Chemistry
The School of Pharmacy
University of London



Plagiarism Statement

This thesis describes research conducted in the School of Pharmacy, University of London between January 2003 and April 2007 under the supervision of Dr Joanne Barnes and Dr Catherine Duggan. I certify that the research described is original and that any parts of the work that have been conducted by collaboration are clearly indicated. I also certify that I have written all the text herein and have clearly indicated by suitable citation any part of this dissertation that has already appeared in publication.

A N Aggarwal 03/10/08

Signature Date

Experience is the name everyone gives to their mistakes.

- Oscar Wilde

Abstract

It is widely recognised that there is a need for further vigilance of herbal medicines and community pharmacists could play a key role in this area. Presently the spontaneous reporting system (yellow card scheme) is the main mechanism for the pharmacovigilance of herbal medicines (see section 1.5.7). However, such schemes have inherent limitations, particularly under-reporting of suspected ADRs, which are likely to be even more significant for herbal than for conventional medicines.

The thesis comprises several separate studies, utilising different research methods. The main aims of the thesis were to identify and describe current practices and problems in pharmacovigilance for herbal medicines and identify methods for improvement through utilisation of community pharmacists.

Current practices of national pharmacovigilance centres towards reporting ADRs associated with herbal medicines were shown to vary. Thus, it is advisable that further work is undertaken by these centres to harmonise their approach with each other to prevent any delays in signal detection. Through analysis of ADR reporting forms and accompanying guidelines for member states of the WHO-UMC programme, deficiencies in the UK's yellow card were identified for herbal medicines and specific modifications made to prompt for and capture more pertinent information required for herbal medicines.

Both qualitative and quantitative data showed pharmacists to have a lack of understanding regarding the definition, categorisation, licensing requirements, quality controls and pharmacovigilance of herbal medicines. However, pharmacists did perceive that herbal medicines are an integral part of their professional practice and that if they are to take a lead they needed further education/training and information on these products. Publication of relevant information sources for pharmacists such as a herbal BNF was deemed desirable. In a pharmacists' survey 94% of respondents agreed/strongly agreed that "community pharmacists have a professional responsibility to be able to provide reliable, objective information and advice to patients and the public on the safe, effective and appropriate use of herbal medicines". Also, more than 90% of respondents felt that topics covering the efficacy, safety, toxicity and pharmacovigilance of herbal medicines should be included in the MPharm core

curriculum. Thus, heads of schools of pharmacy, including new and proposed schools, need to consider whether or not their MPharm programme adequately prepares future pharmacists to advise on the safe, effective and appropriate use of herbal and complementary medicines.

From a survey of UK schools of pharmacy it was concluded that the extent of teaching and content for both core and elective programmes for pharmacognosy and its related areas varied between institutions and thus the knowledge of graduates would vary accordingly. More consistency could be achieved by providing direction in the accreditation guidelines for UK pharmacy degree courses set out by the Royal Pharmaceutical Society of Great Britain.

Due to the inherent problems associated with spontaneous reporting such as under-reporting, the final chapter explored an active surveillance method for herbal medicines. However, limitations such as missed consumer populations purchasing herbal medicines from non-pharmacy outlets and poor recruitment rates of community pharmacists resulted in the failure to fully implement the study protocol. This study showed that community pharmacy based active surveillance methods can be used to complement existing surveillance methods though, at this current time are not feasible for herbal medicines.

The results reported in this thesis further emphasise the importance of the role of the community pharmacist in the pharmacovigilance of herbal medicines. The overall findings indicated that there needs to be greater awareness for and importance attributed to herbal medicines amongst healthcare professionals and that this will only be achieved through greater education for healthcare professionals and collaborative working between organisations such as the Schools of Pharmacy, RPSGB, MHRA and the WHO.

Contents

List of figures

List of tables

Abbreviations

ADR	Adverse Drug Reaction
ADROIT	ADR On-line Information Tracking System
ANOVA	Analysis of Variance
BHMA	British Herbal Medicine Association
CAM	Complementary Alternative Medicine
CHM	Commission on Human Medicines
CPD	Continuing Professional Development
CPPE	Centre for Pharmacy Post-graduate Education
CSM	Committee on the Safety of Medicines
EMEA	European Medicines Agency
ESCOP	European Scientific Cooperation on Phytotherapy
EU	European Union
FDA	Food and Drugs Administration
GDP	Gross Domestic Product
GMP	Good Manufacturing Practice
GP	General Practitioner
GPRD	General Practice Research Database
GSL	General Sales List
ICH	International Conference on Harmonization
KMO	Kaiser-Meyer-Olkin
MEMO	Medicines Monitoring Unit
MEPG	Medicines Ethics and Practice Guidelines
MHRA	Medicines and Healthcare products Regulatory Agency
MPharm	Masters of Pharmacy
NIMH	National Institute of Medical Herbalists
OTC	Over-the-counter
P	Pharmacy medicines (licensed for sale only through a pharmacy)
PCA	Principal Component Analysis
PCT	Primary Care Trust
PEM	Prescription Event Monitoring

Abbreviations (continued)

PL	Product Licence (Reviewed to European standards)
PLR	Product Licence of Right
POM	Prescription Only Medicines
PPA	Prescription Pricing Authority
QL	Lower quartile
QU	Upper quartile
RCHM	Register of Chinese Herbal Medicines
RPSGB	Royal Pharmaceutical Society of Great Britain
SIQ	Semi-interquartile range
SPSS	Statistical Package for the Social Scientist
T1	Test 1 (pre-intervention)
T2	Test 2 (post-intervention)
THR	Traditional Herbal Registration
UMC	Uppsala Monitoring Centre (The WHO Collaborating Centre for International Drug Monitoring)
WHO	The World Health Organisation

Acknowledgements

First, I would like to acknowledge the School of Pharmacy for funding my PhD and Associate Professor Joanne Barnes (University of Auckland) and Dr Catherine Duggan (School of Pharmacy, University of London), my supervisors, for their advice, encouragement and support. I have learnt a great deal from having worked with the both of them and will take this with me forever.

Though not officially one of my supervisors, I would like to also thank my husband Dr Brijesh Patel – they say that some are blessed with a guardian angel and I believe that I have been.

I would also like to thank all of those who have participated in my research as this thesis would not have been possible without them.

Finally I would like to thank my dear family and friends for their words of encouragement, support and for keeping me sane throughout this PhD. There are too many names to mention here and I am fearful that I may miss someone out, but I think you all know who you are.

Statement of conjoint work

Chapter 5 (Phase 1)

Dr Joanne Barnes:	Development and carrying out focus groups. Permission to use the focus group data.
Anjana Aggarwal:	Coding, analysis and write-up of qualitative data.

Chapter 6 (Phase 1)

1999/2000 survey:

Dr Joanne Barnes, Mr Mohammed Al-Shahib, Professor Felicity Smith:	Development and administration of the 1999/2000 survey.

2004/2005 survey:

Dr Joanne Barnes:	Permission to use the 1999/2000 survey data. Development of the 2004/2005 survey and preliminary analysis.
Miss Jaymini Morzaria	Development of the 2004/2005 survey.
Anjana Aggarwal:	Administration, data input, analysis and write-up of the 2004/2005 survey.

Chapter 6 (Phase 2)

Dr Joanne Barnes, Anjana Aggarwal:	Development and administration of test papers.
Anjana Aggarwal:	Data input, analysis and write up

Chapter 1
INTRODUCTION

1.1 Background

This chapter provides an overall introduction to the thesis and essential background material to each of the chapters. It is divided into four main sections. The first section defines and provides a historical context for pharmacovigilance. The second section presents the current methods used for pharmacovigilance and the problems associated with them. The third section outlines how the current methods of pharmacovigilance have been adopted for herbal medicines and the challenges that this presents. Lastly, the fourth section outlines the role that community pharmacists play in the pharmacovigilance of herbal medicines and how this can be improved.

1.2 Pharmacovigilance

1.2.1 Definition of pharmacovigilance

There are many different descriptions of pharmacovigilance, however the generally accepted definition is:

> "*the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other possible drug-related problems*"
>
> [World Health Organisation (WHO), 2002a].

The term has been derived from pharmacoepidemiology, which is the study of the use of and the effects of drugs in large groups of people (Strom, 1994). However, the term pharmacoepidemiology only encompasses the detection and evaluation of adverse drug reactions (ADRs), whereas the term pharmacovigilance also involves the processes of monitoring, evaluating (benefit-risk profile assessment) and responding to drug safety concerns, as well as the communication of this information to stakeholders (Waller *et al.*, 1996).

1.2.2 History and evolution of pharmacovigilance

It has been suggested that the concept of pharmacovigilance goes back as far as 150 years, where The Lancet invited doctors to keep a record of anaesthesia-related deaths (Routledge, 1998). However, it was not until the 1960s that the concept of pharmacovigilance was developed and the first international efforts to address drug safety issues were initiated. The incident that instigated this cascade was associated with the drug thalidomide.

In the 1950s and 60s a number of women took the drug thalidomide for morning sickness on the basis that the manufacturers thought it was safe. Even at the time of its withdrawal, Martindale stated:

> *"It is said to be relatively free from side effects but occasionally causes dizziness and nausea"*
>
> (Martindale, 1961)

In the relatively short time that thalidomide was on the market (1956-1961), it is estimated that above 10 000 children were either born with congenital abnormalities or died at birth (Porche, 1999). Reports of these congenital abnormalities were received as early as 1958 to the marketing company but it took another 3 years for the drug to be withdrawn from the market (Chetley, 1990; McBride, 1961). If proper post-marketing systems had been in place, it is possible that total number of children affected would have been much lower.

1.2.3 Regulatory activities

Previous to the "thalidomide incident", there was no requirement for the independent testing of a marketed drug (for its safety, efficacy and quality) by a pharmaceutical manufacturer. Thus, as a direct effect of this tragedy, legislation to control medicines for human use and agencies concerned with the pre- and post-marketing surveillance of medicines were set up. Within the UK this led to the formation of the Committee on Safety of Drugs, a precursor to the Committee on Safety of Medicines (CSM). The committee introduced several standards and in particular introduced the 'Yellow Card' scheme for ADR reporting. The CSM in October 2005 was replaced by the formation of a new Commission on Human Medicines (CHM) which combined the functions of the Medicines Commission (committee that advises

the Ministers) and the CSM. The CHM is an expert committee within the Medicines and Healthcare products Regulatory Agency, advising the government on the licensing of medicines, and on their safety once marketed (MHRA, 2007). The MHRA was formed in 2003 through the merger of the Medicines Control Agency (MCA) and the Medical Devices Agency (MDA). The MHRA itself acts as the overall drug regulatory body in the UK - ensuring that all medicines on the UK market meet acceptable standards of safety, efficacy and quality (MHRA, 2007).

The thalidomide incident also prompted further legislation on the regulation of medicines. In the UK, legislation to regulate medicines was set in 1968 (Medicines Act, 1968) following the enactment of the first European Economic Community Directive on medicines in 1965 (Directive 65/65/EEC). The Medicines Act introduced a legal framework for the manufacture, sale, supply and importation of medicinal products in the UK (MHRA, 2007).

Despite a considerable increase in the number of laws, regulations and guidelines for reporting and evaluating the safety, efficacy and quality of medicines in the 1960s and 70s, there was little harmonisation between countries, which resulted in increased costs to pharmaceutical companies and replication of work for the licensing of new products (Harman, 2004). The formation of the European Union (EU) showed that harmonisation between countries could be achieved. Thus, the regulatory authorities of Europe, Japan, US and experts from the pharmaceutical industry were brought together to form the International Conference on Harmonisation (ICH) of technical requirements for registration of pharmaceuticals for human use with the objective to overcome problems with multiple registrations. It was decided that the topics selected for harmonisation would be divided into four major categories; safety, efficacy, quality and multidisciplinary to reflect the basic approval criteria (ICH, 2006). Within the EU the ICH guidelines are submitted to the Committee for Proprietary Medicinal Products (CPMP) for endorsement. The guidelines are subsequently distributed for comments by the European Medicines Agency (EMEA) and then published by the European Commission (ICH, 2006).

1.2.4 Marketing authorisation

The European Community Directive (2001/83/EC) defines a "medicinal product" as:

"Any substance or combination of substances presented as having properties for treating or preventing disease in human beings; any substance or combination of substances which may be used in or administered to human beings either with a view to restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action, or to making a medical diagnosis"

In the UK, all products meeting this criteria are termed as medicinal products and require a marketing authorisation (formerly known as a product licence) before they can be marketed (MHRA, 2007). However, there are a number of borderline products, for example, vitamins, amino acids, minerals and in particular herbal medicines. The majority of these products fall outside of the Medicines Act definition and are therefore subject to the Food Safety and Food Labelling Legislation 1990. However, as herbal ingredients can have multiple indications, they often fall between the two regulatory categories – the implications of this are outlined under section 1.5.5.

In order for a marketing authorisation to be granted, information about the product is assessed to ensure that it is safe and effective and also that the quality of the product is sufficient. For a new active substance, this will require full toxicological, pharmacological and clinical data (MHRA, 2007). The number of humans exposed to a new drug before marketing (phase I – III) remains relatively low (table 1.1). This increases the importance of post-marketing surveillance (phase IV).

Table 1.1 Numbers of volunteers used in pre-marketing studies (Clinical Trials, 2007)		
Phase	**Description**	**Median number of healthy volunteers**
Pre-clinical	Study of the drug's animal toxicology	N/A
I (Human pharmacology)	First use in humans	20-80
II (Therapeutic exploratory)	Administration of the drug to selected populations	100-300
III (Therapeutic confirmatory)	Principal information source	1 000 -3 000
IV (Post-marketing surveillance)	Post-marketing surveillance - looks at the drug's use in licensed indications. Monitors a drug throughout it's life cycle	N/A

1.2.5 The need for pharmacovigilance

Each year, around 40 new drug entities are licensed for human use (Duerden, 2002). Despite extensive requirements for evidence of safety, efficacy and quality in order to gain a marketing authorisation, data regarding adverse effects are often limited (Rawlins and Jeffreys, 1993; Montastruc *et al.*, 2006). Therefore, at the time of marketing, the knowledge of a drug's tolerability may be incomplete; largely due to the design of the pre-marketing trials. First, clinical trials are usually conducted in highly selected samples (*i.e.* excluding the elderly, children, pregnant women *etc*) which poorly represent the target population. Secondly, between 1500 and 3000 patients will have been given the drug prior to it receiving a marketing authorisation, therefore to observe rare ADRs these numbers may not be sufficient. Furthermore, side effects associated with long term and or chronic use may not be identified.

It has been argued that all new drugs should be marketed on a probationary period and should only be prescribed by designated specialists until a more complete profile of the drug is developed (Duerden, 2002). However, this would deprive many potential users of a potentially much needed drug. It has also been suggested that by increasing the number of subjects used in clinical trials the need for effective pharmacovigilance would decrease. Due to the increased

costs to the pharmaceutical industry associated with such a proposal, this approach is unfavourable. Furthermore, it would be impossible to trial the medicine on all possible population subgroups and the need for epidemiological techniques to cover the whole life-cycle of the drug would still be required.

Randomised clinical trials are popularly termed the 'gold standard' for assessing the effects of medicines, as they are capable of assigning causality and can calculate the frequency of an adverse effect. Nevertheless, for reasons outlined above, other methods are required for the detection of adverse events - these are presented in the hierarchy system of available designs in pharmacoepidemiology (figure 1.1).

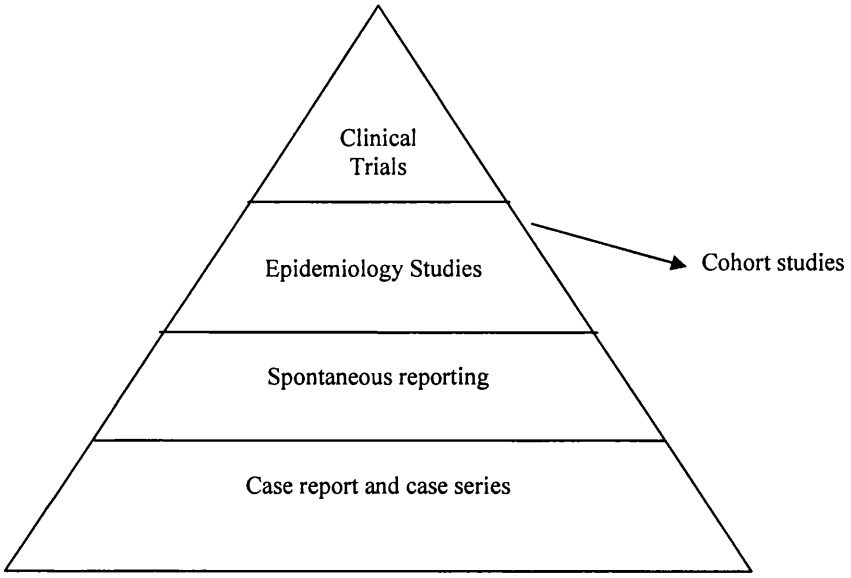


Figure 1.1 Hierarchy of available study designs in pharmacoepidemiology (Hallas, 2001)

1.3 Current practices of pharmacovigilance

Major centres in developed countries have established active surveillance systems to collect epidemiological data. Initially pharmacovigilance was based purely on spontaneous reporting. However, due to the limitations of this method a number of countries have developed surveillance systems to complement this conventional method of drug monitoring. These methods involve two key study designs; cohort and case control.

1.3.1 Cohort studies

Cohort studies are prospective in design and follow up both exposed and non-exposed populations for a defined period. This method can be either experimental or observational. Experimental cohort studies are not feasible for post-marketing surveillance and are usually conducted in the pre-marketing phase of drug development. Observational cohort studies involve the identification of a patient on a particular medicine, through their prescribing doctor, dispensing pharmacist or *via* prescription monitoring methods. Advantages of this method include that it is non-interventional, it allows for the identification of new risks and predisposing risk factors and estimation of their absolute incidence (Rawlins, 1995). However, a disadvantage of this method is that the sample needs to be large enough to show a statistical difference and must include a control group. An example of this method in post-marketing surveillance is Prescription Event Monitoring (section 1.3.3).

1.3.2 Case control studies

Case control studies are retrospective. This method highlights an association between a particular condition and exposure to a drug (Rawlins 1995). The advantage of this method is that it avoids the need for exposure of large numbers of patients to the drug. However, the disadvantages of this method include that it is necessary to have a prior hypothesis to test and it does not measure absolute risk, just relative risk. A variant of this method is a case cohort study where instead of comparing drug exposure rates with individual controls, exposure amongst an appropriate population is used instead.

1.3.3 Prescription Event Monitoring (PEM)

This method was set up in the UK during the 1980's by Dr Inman (WHO-UMC, 2004). Most ADRs occur during the early period of treatment, especially within the first month (Wong, 1999). Based on this information, large cohorts of users of various drugs (mainly newly marketed drugs) are identified *via* the Prescription Pricing Authority (PPA) and information is collected from the first 50, 000 prescriptions of the drug under investigation (Breckenridge *et al.*, 2005). The patient's general practitioner (GP) is then sent a questionnaire after a set interval (usually 6 months) and requested to provide information on any events that have

occurred (Wong, 1999). The average rate of each event is then calculated and compared to the average rate for the general population – an increased average rate indicates a possible ADR (Shakir, 2002). Variants of this method have also been set up in New Zealand and Japan.

Unlike spontaneous ADR reporting, PEM does provide a denominator of exposed patients and a high ascertainment of suspected ADRs. It is also non-interventional as there is no interference with the doctor's decision to prescribe the medicine. However, the drug must be prescribed by a GP and in adequate numbers within a reasonable time period. Another disadvantage of this method is that it can not be used for a rapid response to an urgent safety concern, as it takes time to retrieve data from the PPA. GP participation is voluntary and without incentives some GPs do not complete the questionnaires and the effect of these non-responders is unknown. Also, the sample needs to be large enough to show a statistical difference (data is required from more than 10000 questionnaires for each drug) and must include a control group, which makes this method highly labour intensive. Furthermore, there is no accurate estimate of patient compliance to the drug.

1.3.4 General Practice Research Database (GPRD)

This system was established in 1987 in the UK (Breckenridge *et al.*, 2005), with management transferring to the MHRA in 1999. The database holds patient records for approximately 5% of the total population, covering patients from different age groups in more than 450 registered national health practices. Data recorded includes patient demographics, details of illnesses and treatment received, referrals to hospital, laboratory tests and lifestyle factors *e.g.* smoking. Both the richness of data and diversity of the population allow for cohort and case control studies to be conducted and for the study to be either disease or drug orientated. Furthermore, drug safety studies can be carried out rapidly in response to a safety concern and the absolute risk can be calculated (Wong, 1999). The database has the potential to cover the lifespan of patient, as long as the patient remains with the same practice. Disadvantages of the GPRD database include that it does not contain all hospitalisation data, it only records items prescribed by the GP as opposed to the dispensing of the product, the patients in a particular general practice may not be representative of the general population and additional data such as lifestyle factors are not recorded in a standardised format. Also, as most studies are conducted retrospectively, all data required may not be available.

1.3.5 Record linkage systems

In the USA and Canada, large comprehensive population databases have been developed by health insurance systems and have been used to retrieve adverse event data (WHO, 2002a). In the UK, the University of Dundee has set up a Medicines Monitoring Unit (MEMO), which undertakes hypothesis-testing pharmacovigilance studies using record linkage (Breckenridge *et al.*, 2005). It consists of three datasets and has access to records of 400 000 patients registered with GPs in Tayside (Wong, 1999). MEMO is similar to GPRD except that it has additional links to hospital records, thereby allowing the collection of data from different sources *e.g.* dispensed prescriptions, hospital morbidity, laboratory tests *etc.* A further advantage of MEMO is that it uses data from dispensed prescriptions, unlike GPRD which uses data from prescribed medicines, thus to a certain degree it eliminates non-compliance. The main disadvantage of this database is that it is relatively small and therefore it can only be used to assess commonly used drugs. Also with the Canadian and American system, one major disadvantage is that when patients change healthcare suppliers, completeness of the database might be compromised.

1.3.6 Intensive monitoring schemes

Countries such as Australia and the UK have set up intensive monitoring scheme for specific classes of medicines. The UK have targeted both HIV and paediatric medicines. Each scheme has a specific ADR reporting form to collect the required details, for example with the HIV scheme (set up in November 1997) the viral load and CD4 count are requested. These systems have increased the level of reporting for these classes of medicines. In the first 7 months of the HIV medicines intensive monitoring scheme, the number of reports increased from 112 to 207, of which 129 were received *via* the intensive monitoring scheme (MHRA, 1998). Of the reactions recorded, 50% were previously unknown and 73% of them were classified as serious.

The paediatric intensive monitoring scheme was set up on the basis that the metabolism and elimination of drugs differs in children compared to adults and that some reactions might occur only in children. Also, prescribers often have to use medicines in children outside of their licensed indication, as suitable formulations may not be available or the appropriate

dosage is not known. Therefore, to address these issues, a paediatric regional monitoring centre based at Derbyshire Children's hospital was set up in 1996. To stimulate reporting, proactive interventions were made, for example, by sending monthly reminder letters and giving presentations to staff in the identified hospitals. Within the first year of setting up the scheme, 95 reports were received compared to 40 from the previous year (MHRA/CSM, 1999). However, due to the considerable financial cost associated with such a scheme, the paediatric monitoring centre subsequently had to close.

1.3.7 Case registers

Case registers are registers of all individuals prescribed a particular drug, or can be individuals with a particular disease or condition *e.g.* pregnant. Case registers are similar to the intensive monitoring scheme except that it is used to calculate the incidence of a specific adverse reaction to a particular drug. The British Paediatric Surveillance Unit's survey of Reye's syndrome initiated in 1981 (Rawlin, 1995), was one such example.

1.3.8 Spontaneous reporting

Despite the development of different pharmacovigilance methods, spontaneous reporting of suspected ADRs remains the main method used for pharmacovigilance globally. The method was developed in the wake of the "thalidomide incident". The system was first initiated in Australia, Canada, Czechoslovakia, Ireland, the Netherlands, New Zealand, Sweden, the UK, the US, and West Germany between 1961 and 1965 (Wiholm *et al.*, 2000).

The system involves the systematic collection and evaluation of individual case histories of ADRs from recognised reporter groups. For most national systems, the reporting of ADRs is voluntary and reports are mainly received directly from healthcare professionals. Depending on the volume of reports received, the seriousness of the reaction, assignment of causality of the reaction to the suspected drug and the risk/benefit profile, a safety concern (signal) might be generated. A signal is an alert from any source that a medicine may be associated with a previously unrecognised hazard, or that a known hazard may be more frequent or different from existing expectations (Meyboom *et al.*, 1997). Subsequent action that might be taken includes amendment of a product licence, voluntary suspension or withdrawal of the product

by the marketing authorisation holder and withdrawal of a products licence by the regulatory authority (Wong, 1999). In the EU, urgent safety concerns are brought to the healthcare professionals' attention by producing circulars under the cover of Dear Doctor/Pharmacist letters (MHRA, 2007).

It is estimated that only some 10-15% of all ADRs are captured by spontaneous reporting, thus under-reporting is a major drawback of this method (Breckenridge *et al.*, 2005). Due to under-reporting the spontaneous reporting scheme is susceptible to significant bias, which can result in false positive signals. Lack of time, lack of knowledge about spontaneous reporting systems, fear of litigation and the need to attribute causality before submitting a report have been identified as contributors to under-reporting (Crombie, 1984; Belton *et al.*, 1997). Respondent bias, recall bias, information bias, incomplete information on reports, attributing causality and the inability to calculate the frequency of a reaction are further disadvantages to the spontaneous reporting system (Sacristan *et al.*, 2001; Clarkson and Choonara, 2002). Furthermore, if the ADR experienced is common in the untreated population *e.g.* myocardial infarction, it is difficult to ascertain whether or not the ADR is a natural occurrence/progression of an underlying disease or due to the drug. More recently, the spontaneous reporting system has been shown to be vulnerable to manipulation. A case in Poland was brought to attention where numerous complaints against a generic medicine were received by the national pharmacovigilance unit (Gibson, 2005). However, when further investigations were conducted, it was believed that the reports may be part of a marketing strategy set up by the manufacturer of the branded drug.

Methods used to tackle under-reporting have mainly centered on expanding the reporter groups and types of products covered. There have been individual initiatives such as the regular posting of bulletins and the inclusion of reporting cards on prescription pads; such methods have been found to elicit a temporary increase of the ADR reporting rate (Castel *et al.*, 2003). Bracchi *et al.* (2005) studied the impact of a pharmacovigilance distance-learning package (linked to educational credits) on the rate and quality of ADR reporting. The results of this controlled study showed that spontaneous ADR reports from those that passed the course assessment increased in number and improved in quality compared to those who had not taken the course. This indicates that distance learning packages could have a crucial role to play in improving the collection of yellow card data. However, in both studies (Castel *et al.*,

2003; Bracchi *et al.*, 2005) the longevity of the impact of this method was not investigated. It is widely reported that lack of knowledge is a contributor of under-reporting and that greater teaching of healthcare professionals in this area could increase levels of reporting (Pharm J, 1999; Bateman *et al.*, 1992; Wingfield *et al.*, 2002). Despite these claims, no studies to date have fully investigated this area or identified a direct relationship between knowledge and reporting rates. For example although Rosebraugh, (2003) showed that a 15 minute teaching intervention to medical students does have the potential increase the quality and number of reports and Granas *et al.* (2007) showed that pharmacists receiving 1 day educational intervention have a more positive attitude to ADR reporting compared to the control group, both studies failed to evaluate if the number of reports received by the national pharmacovigilance centre increased, the longevity of the intervention or if participant's knowledge of ADR reporting had subsequently increased.

The main advantages of spontaneous reporting include that it is relatively inexpensive, it has the potential to cover the total patient population including special care groups *e.g.* the elderly, it monitors the drug throughout its life-cycle, therefore making it ideal for detection of long-term and rare side effects and it is non-interventional. Furthermore, from the data generated, comparisons between products within the same therapeutic classes and information on predisposing factors to adverse reactions can be obtained (Wong, 1999).

1.3.8.1 Th e UK's yellow card scheme

The yellow card scheme was pioneered in 1964 by the University of Southampton (WHO-UMC, 2004). Yellow was chosen because during the war the colour had been used for warnings that could be picked out by hooded car lights driving in the blackout. The scheme is a decentralised system where it consists of a national pharmacovigilance unit along with yellow card centres. In total there are five selected regional yellow card centres; Mersey, Wales, Scotland, Northern and Yorkshire and West Midlands. Yellow cards can be sent to these regional monitoring centres, but their main function is to follow-up reports in their particular region.

Suspected ADRs to medicinal products are submitted to the MHRA on a voluntary basis by recognised reporter groups and by pharmaceutical companies holding a marketing

authorisation. The data are then stored on the Adverse Drug Reactions On-line Information Tracking system (ADROIT) and scrutinised in order to identify "signals" that require further investigation *i.e.* hypothesis generation (Evans *et al.*, 2001).

The scheme initially accepted reports from doctors, dentists and coroners only. Since 1997, pharmacists, nurses, midwives, health visitors and patients have been gradually added to the scheme (see figure 1.2). Initially, patient reporting was restricted to reports through the telephone helpline NHS Direct, before forms were made available from GP surgeries, community pharmacies and other outlets. In the first year of operation, approximately 700 reports had been submitted (compared with over 20,000 from health professionals), which were generally of high quality (MHRA, 2007). Since the launch of the scheme yellow card reporting forms have been made simpler and easier to use and an updated online system has been implemented (MHRA/CHM, 2008a).

The empirical literature suggests that patient reporting has both advantages and disadvantages. In a methodological study in Grampian, it was found that only 54% of patients reported some or all of their symptoms to their doctor, a case-note review of a sample of these patients found that only 22% were recorded by the doctor and just 0.4% of all symptoms were reported to the regulators (Jarernsiripornkul *et al.*, 2002) thus, patient reporting potentially could have allowed for the reporting of these ADRs. However, as the number of reporter groups increases it is possible that there will be an increase in duplicate reports and general background noise, which might drain resources. So far, there is little evidence to prove the worth of extending ADR reporting to patients. Egberts *et al.*, (1996) showed that patient reports compared with those obtained from pharmacists were often crude and incomplete however, it must be noted that this study was conducted over ten years ago.

1961 thalidomide incident

↓

1963 Committee on Safety of Drugs (CSD)

↓

1964 CSD sets up 'yellow card' scheme

(for doctors, dentists and coroners)

↓

Oct 1996 scheme extended to unlicensed herbal remedies

↓

April 1997 scheme extended to hospital pharmacists

&

Pilot study for community pharmacist ADR reporting

↓

Nov 1999 scheme extended to all community pharmacists

&

Reminder for ADR reports for unlicensed herbal remedies

published in Current Problems in Pharmacovigilance bulletin

↓

Nov 2002 scheme extended to nurses, health visitors & midwives

&

Launch of the electronic yellow card

↓

Oct 2005 pilot study for patient reporting *via* NHS direct

↓

Nov 2005 scheme extended to patients

Figure 1.2 A schematic diagram for the history of the UK's yellow card scheme

Since the introduction of the yellow card scheme licensed medicines, including licensed herbal medicines have been monitored. In October 1996, the scheme was extended to unlicensed herbal remedies, following a report by Guy's Hospital Toxicology Unit on potentially serious adverse reactions associated with herbal medicines. This report included 9 confirmed cases of heavy metal toxicity, 21 cases of liver toxicity, including two deaths associated with the use of traditional Chinese remedies (Shaw *et al.*, 1997). The yellow card was also subsequently revised to include herbal medicines under the concomitant section and guidelines requested for further details to facilitate assessment, for example the ingredients, source, the name and address of the practitioner and retention of a sample of the product in serious cases.

The MHRA receives one of the highest numbers of reports in Europe (Rawlins, 1995). Since 1964, there have been around 500 000 suspected ADRs reported *via* the yellow card scheme. Over the years, reporting has increased from 2 000 to 3 000 reports *per* annum to the current rates of approximately 20,000 (MHRA/CHM, 2008b). Figure 1.3 shows the number of reports from 1998-2004. A significant increase in ADR reporting occurred in 2000, during a nationwide vaccination campaign to the meningococcal C conjugate vaccine for all children under 18 years of age due to nurses administering the vaccine being asked by the MHRA to submit ADR reports (MHRA, 2007).

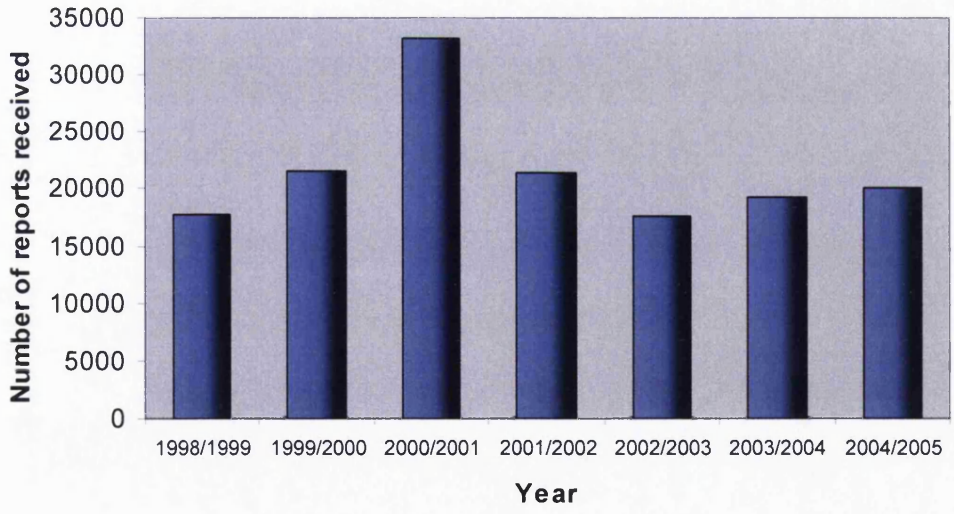


Figure 1.3 Total number of reports submitted to the MHRA (1998 – 2004)

1.3.9 WHO-Uppsala Monitoring Centre (UMC) programme

After the "thalidomide incident", the WHO set up a pilot research project for international drug monitoring, which has been developed into the WHO programme for International drug monitoring and is now co-ordinated by the UMC. The core function of the WHO-UMC programme is to maintain a database for the centralised collection of ADR reports for the rapid detection of signals of safety concern and also to facilitate communication between member countries (WHO, 2007).

The WHO-UMC programme started off with 10 member countries in 1968 and has expanded to include more than 80 countries (WHO, 2007). The national pharmacovigilance centre of each member country varies considerably in terms of the resources available and activities carried out, but spontaneous reporting remains the core activity. Each national pharmacovigilance centre is required to submit all received reports of suspected ADRs to the UMC in a standardised reporting manner. At present the WHO-UMC database contains more than 3.7 million case reports (WHO, 2007). The database is scanned every three months and information components are generated from which the signals are then derived. Signals detected are relayed back to the member countries for further analysis and possible regulatory action.

1.3.10 European Medicines Agency

As well as the WHO-UMC programme, there is also an EU pharmacovigilance system, which pools together data from all of the member states of the EMEA. The principal function of the EMEA is the protection and promotion of human and animal health in the EU *via* the co-ordination of pre- and post-authorisation systems

The EMEA has established a pharmacovigilance working party that takes a lead in the development of pharmacovigilance guidelines. Each member country exchanges pharmacovigilance information and all spontaneous ADR reports are entered into a centralised database called Eudra Vigilance.

1.3.11 Future of pharmacovigilance

The role that spontaneous reporting schemes might play in the future has been questioned, in part because there may be more efficient ways of detecting signals of safety concerns (Waller and Evans, 2003). However, it is not likely that there will be fundamental changes to the above system, as at present the focus is to develop methods to enhance levels of reporting and secondly to develop novel methods to complement the current system. Important challenges will result from the expansion of the systems to other countries, in particular developing countries and no doubt there will be advances in science and technology to aid the current systems.

1.4 Role of the community pharmacist in ADR reporting

Pharmacists have long been used as sources of ADR reporting in many countries such as Australia, Germany and the USA (D'arcy, 1991; Roberts *et al.*, 1993). In the Netherlands, which has an established ADR reporting system, the contribution of pharmacists is substantial, both in quantity and quality of the reports submitted. It has been reported that, pharmacist reporting has been estimated to contribute up to 40% of the total reports submitted (Van Grootheest *et al.*, 2002a; Van Grootheest *et al.*, 2002b). Early studies in the UK showed that clinical pharmacists were already involved with ADR queries and had the potential to increase ADR reporting (Roberts *et al.*, 1993; *Pharm J*, 1987; Wolfson *et al.*, 1993). However, it was in April 1997, after 15 years of campaigning, that hospital pharmacists were officially recognised as yellow card reporters. At the same time, a pilot scheme for community pharmacists was set up in four regional areas linked to a regional monitoring centre. Pharmacists were asked to focus on those areas where there was limited reporting by doctors *e.g.* over-the-counter (OTC) and unlicensed herbal medicines. A distance learning pack on ADR reporting from the Centre for Pharmacy Post-graduate Education (CPPE) was also made available.

The first year report of the pilot scheme showed that community pharmacists submitted only 96 reports, which were comparable to those from GPs in terms of the proportion of serious reports and reactions associated with "black triangle" drugs (Davis and Coulson, 1999). Pharmacists did however submit a higher number of reports in connection with suspected generic inequivalence and reactions associated with herbal remedies compared with GPs

(Davis and Coulson, 1999). The contents of the pharmacist reports were considered to be of an appropriate nature and of a good quality (*Pharm J*, 1997; *Pharm J*, 1998). As a result of this pilot scheme, all community pharmacists became eligible to send in ADR reports in November 1999. Community pharmacists were initially asked to discuss the case with the patients' GP or consultant before submitting a suspected ADR report and were again specifically encouraged to report for OTC medicines and herbal medicines.

Generally the number of reports submitted by pharmacists is considerably low compared with that for GPs and hospital doctors. Overall in 2006, community pharmacists submitted 3% of the yellow card ADR reports and hospital pharmacists 9% (see figure 1.4). Hospital doctors submitted the highest (17%) number of reports followed by general practitioners (MHRA, 2007). This trend has been similar for the preceding years.

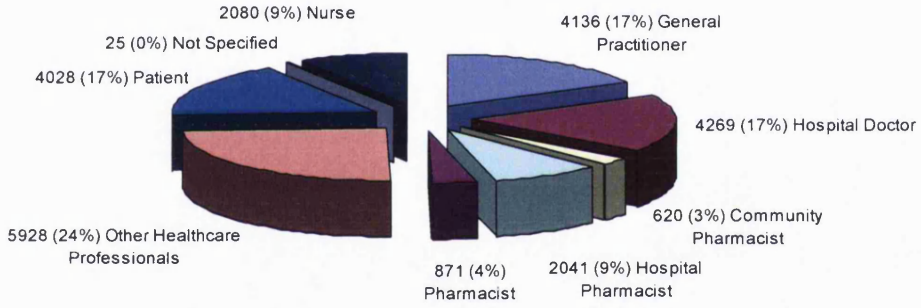


Figure 1.4 Number of ADR reports submitted in 2006 by each healthcare professional

The number of reports submitted by community and hospital pharmacists has gradually increased since 1997 (see figure 1.5). Since their inclusion, pharmacists are estimated to represent on average 15-16% of total reports' submitted (MHRA/CHM, 2008a), of which hospital pharmacists submit a notably higher number. This might be due to the fact that the hospital scheme has been running for approximately two years longer than the community pharmacist scheme or that hospital pharmacists are more likely to interact with patients who have experienced ADRs or are more confident in reporting them.

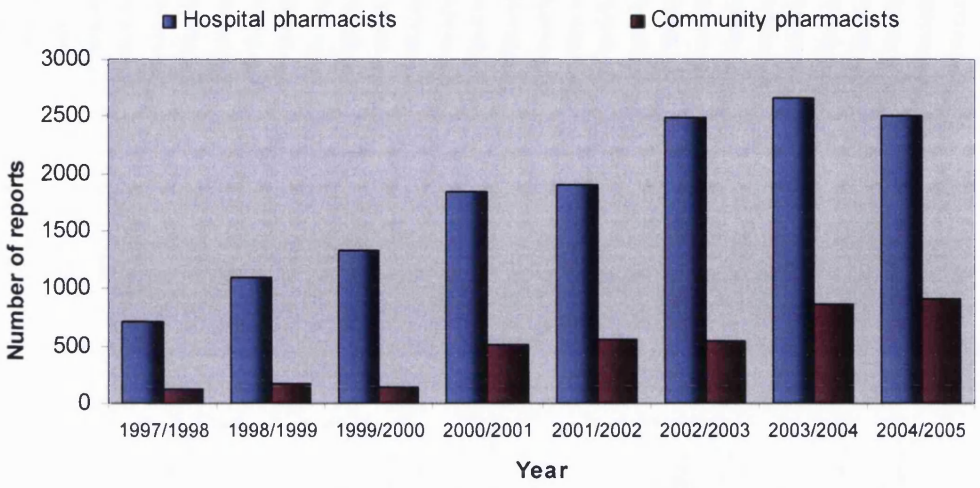


Figure 1.5 Number of reports submitted to the MHRA by pharmacists

Community pharmacists have been criticised for their low levels of ADR reporting (Major, 2002), but to date no studies have specifically looked into the reasons for the low uptake of the yellow card scheme or in particular the low level of reporting of ADRs associated with herbal medicines by community pharmacists. Investigation into the attitudes of community pharmacists towards ADR reporting, suggest a lack of understanding of the system. Few recognised the need to report reactions to herbal remedies or knew the reporting criteria for "black triangle" drugs (Green *et al.*, 1999a; Barnes, 2001; Wingfield *et al.*, 2002). Causality was revealed to be the major deterrent which reflects a lack of understanding of the system, as the scheme applies to suspected ADRs. Greater education/training was identified to increase the level of reporting (Houghton *et al.*, 1999; Green *et al.*, 1999a). The majority of pharmacists have been shown to be reluctant in reporting ADRs associated with OTC products that they had recommended (Green *et al.*, 1999a). This is likely to be due to the fear of litigation, which raises concerns on the future levels of ADR reporting from community pharmacist's once full prescribing rights are introduced.

Targeting pharmacy undergraduates and pre-registration trainees could encourage ADR reporting from an early start. In a study by Sweis and Wong (2000) it was identified that those pharmacists who had received training on ADR reporting were more likely to report and also that certain individuals repeatedly submit ADR reports *e.g.* 2.5% of all hospital reports in 1997 were from just five reporters (Cox, 2002). Often pharmacists have highlighted the need for

the RPSGB to take a further lead to encourage ADR reporting and have criticised the RPSGB for not doing so (Sweis and Wong, 2000; *Pharm J*, 2000). However, the RPSGB Code of Ethics (2006) does mention that pharmacists providing professional practice should ensure that:

> *"They take action to report to the prescriber and relevant authorities, suspected adverse drug reactions where this is likely to assist in the future treatment of the patient, or the future use of the medicine."*

ADR reporting is already seen as a professional obligation by many pharmacists (Houghton *et al.*, 1999; Green *et al.*, 1999a; Green *et al.*, 1999b). Countries such as America, where the system is mandatory for certain healthcare professionals, have a much higher level of reporting compared to the UK. However, no studies to date have investigated the impact of making ADR reporting compulsory.

ADR reporting by pharmacists in the UK is in its infancy and there is much progress to be made before it reaches the levels of reporting as in America and The Netherlands. However, there is potential for pharmacists to enhance their role in this area as the part they play in both supplementary and independent prescribing grows (*Pharm J*, 2006).

1.5 Herbal medicines

Certain herbs have been long used as food products and for their healing properties. Many current medicines have been derived from herbs, *e.g.* digoxin which was developed after reports of dropsy after the intake of *digitalis* by William Withering. Natural sources, particularly plants, continue to yield new medicines of importance in pharmacy (Jones *et al.*, 2006). In more recent years pharmacognosy has led to the development of the anticancer drug paclitaxel and galantamine for Alzheimer's disease (Balunas and Kinghorn, 2005).

1.5.1 Definition of herbal medicines

Much confusion surrounds the definition of herbal medicines. It is often assumed that herbal medicines are unconventional/alternative medicines though there are a number of conventional medicines that are herbal medicines, *e.g.* senna. Herbal medicines are a broad class of medicines and cover a number of different therapies such as ayurvedic medicine, traditional Chinese medicine, homeopathy and aromatherapy. Thus, herbal medicines should not be included in the general term for complementary alternative medicines (CAM), as they span across both "conventional" and "unconventional" medicines. This argument has also been raised in a recent letter in The Pharmaceutical Journal (Houghton, 2006).

There are a number of definitions for herbal medicines (see table 1.2) and each vary in terms of the products covered, for example, the WHO definition allows for certain countries that by tradition include non-plant materials such as minerals and animal products to be included as herbal medicines.

Table 1.2 Examples of definitions of herbal medicines

Medicines Act 1968

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."

European Pharmacopoeia's Definition 2007

Herbal medicinal product

"any medicinal product, exclusively containing as active ingredients one or more herbal substances or one or more herbal preparations, or one or more such herbal substances in combination with one or more such herbal preparations"

Herbal substances

"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)."

Herbal preparations:

"preparations obtained by subjecting herbal substances to treatments such as extraction, distillation, expression, fractionation, purification, concentration or fermentation. These include comminuted or powdered herbal substances, tinctures, extracts, essential oils, expressed juices and processed exudates."

World Health Organisation 2004

Herbal medicines

"include herbs, herbal materials, herbal preparations and finished herbal products, that contain as active ingredients parts of plants, or other plant materials, or combinations. In some countries, herbal medicines may contain, by tradition, natural organic or inorganic active ingredients that are not of plant origin (*e.g.* animal and mineral materials)"

European Scientific Co-operative on Phytotherapy (ESCOP) 2007

Herbal medicines

"are medicinal products containing as active ingredients only plants, parts of plants or plant materials, or combinations thereof, whether in the crude or processed state."

As a result of these different definitions, confusion often arises over what products/preparations are to be termed as herbal, which raises concerns in the misclassification of products and the potential to miss signals.

However, all of the above definitions are consistent in terms of that they include plants (whole or in part) in a relatively unprocessed state *i.e.* they are not semi-synthesised products or contain chemically isolated constituents. Thus according to the above definitions, aspirin and digoxin are categorised as non-herbal even though they have botanical origins and the homeopathic preparation arnica is categorised as a herbal medicine.

1.5.2 Prevalence of use and expenditure on herbal medicines

In 1998, a representative study of over 5000 adults in England found that 20% had purchased OTC herbal medicines in the previous year (Thomas *et al.*, 2001). UK market research data for 2002 valued the sales of herbal medicines at £75 million, which is likely to be a gross underestimate as a number of additional products are marketed as food supplements (Mintel, 2003). The majority of sales of such products were found to be made in pharmacies (Mintel, 2003). Since then, the sales of herbal medicines in the UK have continued to expand, increasing by 16% from 2002 to 2004 (Mintel, 2005).

Previous work has shown that most pharmacies sell herbal medicines (Barnes and Abbot, 1999) to patients/consumers and that pharmacists are asked for information and advice on these products. Herbal medicines are also available in the UK from various other retail outlets such as health food shops, supermarkets, mail order companies and over the internet, which can result in them being purchased with little or even no support from a doctor or pharmacist. Health food stores have also come under scrutiny for misinforming consumers on the potential side effects and interactions of herbal medicines (Vickers *et al.*, 1998; Mills *et al.*, 2003). Studies comparing advice given by pharmacy staff and health food shop assistants provide conflicting information on whether or not community pharmacists are any better than health food stores on the quality of information provided to consumers (Glisson *et al.*, 2002; Healy *et al.*, 2002).

1.5.3 Reasons for using herbal medicines

Herbal medicines are used by many different patient groups and for a variety of indications *e.g.* including for general well being and for chronic conditions such as cancer and HIV/AIDS (Barnes, 2002; Liu *et al.*, 2005; Humpel and Jones 2006). Disappointment to conventional treatments in their inability to cure chronic diseases and due to side effects experienced, patients are increasingly turning to alternative therapies such as herbal medicines (Wirth *et al.*, 2005; Liu *et al.*, 2005). Furthermore, herbal medicines continue to be promoted, described and perceived as being 'natural' and 'safe', or at least safer than conventional medicines, which all contribute to their popularity. However, it must be considered that a number of conventional medicines such as warfarin and theophylline, which are known for their side effects, have botanical origins. Alongside this, a number of plants are known to be poisonous, for example the deadly *Atropa belladonna* has a long history for its poisonous effects and the intrinsic toxic constituent aristolochic acids contained in *Aristolochia* species are known for their nephrotoxic and carcinogenic effects (Medicines Control Agency, 2002). Hence, it can not be assumed that plants from a natural source will be free from potential adverse effects.

Under the Medicines Act, all new licensed products are marketed initially as prescription only medicines (POMs). As evidence on their safety becomes available, these medicines are gradually deregulated to pharmacy sale only medicines (P) and then general sale list medicines (GSL). Thus, it can be presumed that medicines without a prescription or without restricted sales are relatively safe. However, as unlicensed herbal medicines are not regulated in the same manner this is not necessarily true. Furthermore, as herbal medicines are widely/freely available from pharmacies, this adds to the perception that they are safe and are of the same quality as a conventional medicine.

Under the RPSGB Code of Ethics (2006) pharmacists providing homeopathic or herbal medicines or other complementary therapies do have a professional responsibility:

i. to ensure that stocks of homeopathic or herbal medicines or other complementary therapies are obtained from a reputable source of supply;
ii. not to recommend any remedy where they have any reason to doubt its safety or quality;

iii. only to offer advice on homeopathic or herbal medicines or other complementary therapies or medicines if they have undertaken suitable training or have specialised knowledge".

It is debatable how strictly these guidelines are adhered to, in particular, whether or not the pharmacist has the ability to control what products are stocked, especially within large multiples and within a consumer driven market.

The perception that herbals are safe is further enhanced by the fact that a number of the herbs marketed are consumed regularly within the diet (*e.g.* garlic) and have been used traditionally as a medicine for years. This is supported by a survey of 515 users of herbal medicines, where it was revealed that fewer consumers would consult their GP for a suspected ADR associated with a herbal medicine compared to a similar ADR associated with a conventional OTC medicine (Barnes *et al.*, 1998).

Further to this, herbal medicine use is often not considered by healthcare professionals or rarely recorded on patient medication records (Barnes, 2001; Brown *et al.*, 2005). A survey by Barnes and Abbott (1999) investigating pharmacists' experiences with complementary medicines revealed that the majority of pharmacists do not routinely ask patients specifically about their use of complementary medicines when receiving reports of suspected ADRs to conventional medicines, so that complementary medicine use could not be considered or excluded as a possible cause. The implications of herb-drug interactions and their management are further discussed by De Smet, (2007). However, pharmacists who had undertaken relevant training were more likely to consider and record complementary medicine use and overall were found to submit a greater proportion of ADR reports associated with complementary medicines (Barnes, 2001).

1.5.4 Herbal safety concerns

Alongside the widespread use of herbal medicines, in recent years, herbal medicines have been associated with several safety concerns. In 2000, evidence emerged of pharmacokinetic and pharmacodynamic interactions between St John's wort (*Hypericum perforatum*) products and certain prescription medicines, including warfarin and the oral contraceptive pill (Henderson *et*

al., 2002). Reports of such interactions continue to be received by the yellow card scheme for ADR reporting. The most commonly reported herb-drug interactions relate to St John's wort and the oral contraceptives, which has lead to therapeutic failure - including unplanned pregnancies (MHRA, 2007).

Another safety issue involved Kava (*Piper methysticum*), used for anxiety, which was prohibited in unlicensed medicines in January 2003 (The Medicines for Human Use, 2002) following reports of liver toxicity ranging from abnormal liver function test results to liver failure requiring transplant in some cases. The ban followed a period of voluntary withdrawal during which the RPSGB instructed pharmacists to remove Kava products from sale in their pharmacy. Other safety concerns have been described, many of which have arisen because of problems with the pharmaceutical quality of unlicensed herbal medicines (Barnes *et al.*, 2002). Worldwide, 75 cases of hepatic adverse reactions associated with Kava have been reported. These included cases of liver failure resulting in 8 liver transplants and 4 deaths. In the UK, there have been 4 reported cases of liver toxicity associated with Kava (MHRA/CSM, 2003).

More recently the MHRA has received a total of 12 reports related to a possible interaction between cranberry juice and warfarin. Of these, 8 cases involved increases in INR and/or bleeding episodes, thus a caution was issued in Oct 2004 (MHRA/CSM, 2004). There have also been isolated reports associated with the use of two other popular herbs; ginkgo (Barnes *et al.*, 2002) and black cohosh (MHRA/CSM, 2004).

1.5.5 Regulation of herbal medicines

As outlined in section 1.2.3, the borderline between herbal medicinal products and foods is not very clear cut (Schilter *et al.*, 2003). For example, garlic can be considered into both categories. It is interesting to note that there has also been recent interest in the post-marketing surveillance of food products (Van Puijenbroek, 2007).

Each category is governed by different bodies within the UK. If a herbal medicine is considered to be a medicinal product, it needs to receive a marketing authorisation, in a similar manner to any other licensed medicine as outlined in section 1.2.3. In the UK there are about 500 herbal medicines with a UK marketing authorisation or product license (MHRA, 2007).

Most of these products were available before the Medicines Act licensing system came into force in 1971 and were granted a Product License of Right (PLR). Those that were indicated for minor or self-limiting conditions were given a PLR and were then granted a Product Licence (PL) on the basis of acceptable bibliographic evidence of efficacy *i.e.* no clinical trials were required to be conducted. Such products had to include the statements 'A traditional herbal remedy for the symptomatic relief of'...and 'If symptoms persist consult your doctor'. Those products that were indicated for more serious conditions required evidence from clinical trials in order for a licence to be granted.

The Medicines Act (1968) contains important exemptions from licensing and makes provisions for further exemptions to be included in Statutory Orders. One important exemption applies to herbal medicines. Products exempt from licensing include herbal medicines which satisfy the conditions laid down in Section 12 of the Medicines Act 1968. The Act defines herbal medicines as:

> "*... 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 substance.*"

Section 12(1) allows a person to make, sell and supply a herbal remedy during the course of their business provided the remedy is manufactured or assembled on the premises and that it is supplied as a consequence of a consultation between the person and their patient. Section 12 (2) allows the manufacture, sale or supply of herbal remedies where:

i. the process to which the plant or plants are subjected consists only of drying, crushing or comminuting;
ii. the remedy is sold without any written recommendation as to its use; and
iii. the remedy is sold under a designation which only specifies the plant(s) and the process, and does not apply any other name to the remedy.

The use of certain potent and hazardous plants *e.g. Digitalis*, Aconite, *Rauwolfia*, is restricted by medical practitioners under the Prescription Only Medicines Order 1977, and the sale of

certain other potentially hazardous plants are controlled by the The Medicines (Retail Sale or Supply of Herbal Remedies) Order 1977 *e.g. Areca, Aconitum, Ephedra* (MHRA, 2007).

Most herbal medicines are sold in the UK as 'unlicensed' herbal medicines or food supplements. Under these conditions, manufacturers are not required to consult the MHRA before marketing their product. Manufacturers opt for this method as they do not have to undergo expensive clinical trials or rigorous testing of their product, as there are no stringent regulations to prove the safety, efficacy or quality of these products. Thus for many herbal medicines there is a lack of information on the constituents, pharmacokinetics, pharmacological properties, toxicology, adverse effects, interactions (with other herbs, drugs, food, alcohol), use in special patient groups, contraindications *etc* as most of this information would be identified in the pre-marketing phases of a medicine (Ernst, 2000). This makes the necessity for post-marketing surveillance for herbal medicines greater than that required for conventional medicines. However, for unlicensed herbal medicines this is solely dependent on the spontaneous reporting of suspected ADRs, as only marketing authorisation holders of licensed herbal medicines are required to comply with the Directives (2001/83/EC) pharmacovigilance regulations.

Due to the current regulatory system for herbal medicines, illegal unlicensed products (which should have complied with section 12.2 of the Act) are able to make their way on the market. The majority of the problems associated with unregulated products are related to the quality (MHRA, 2007). Problems include adulteration, contamination, substitution and differences between label claims and actual contents. Examples in the UK include (MCA, 2002);

1) steroids in topical herbal preparations for eczema;
2) fenfluramine in a slimming product;
3) other prescription medicines (sildenafil, glibenclamide, warfarin, alprazolam) in herbal products;
4) substitution of *Aristolochia manshuriensis* for the stem of *Clematis* and *Akebia* species resulted in end-stage renal failure of two patients.

Herbal medicines contain numerous chemical constituents, which are often unknown or are partly explained (Barnes, 2002; Ernst, 2000). Furthermore, the chemical constituents can vary within different species of plants, the plant part used in the preparation (*e.g.* root, stem *etc.*) and

depending on conditions in which the plant was cultivated and harvested (Schilter *et al.*, 2003; Liang *et al.*, 2004). Thus herbal products containing the same ingredient not only differ between manufacturers but also display significant batch to batch variation with products from the same manufacturer (Glisson *et al.*, 2003; Gilroy *et al.*, 2003).

1.5.6 Traditional Herbal Medicinal Products Directive

Section 1.5.2 to 1.5.5, show that there is clear recognition at several levels for the need to develop ways of enhancing pharmacovigilance of herbal medicines. At the national level, the House of Lords' Select Committee report on Complementary/Alternative Medicine (House of Lords Select Committee on Science and Technology, 2000) recommended that the Government should continue to advocate a new regulatory framework for herbal medicines that would ensure medicinal quality and safety standards (which includes monitoring safety). Such a framework came into force in October 2005 under the new EU Directive on Traditional Herbal Medicinal Products (Directive 2004/24/EC). Under this framework, manufacturers of herbal medicines are required to satisfy the licensing authorities (*i.e.* the MHRA in the UK) of the quality and safety of their products and provide evidence of traditional use to demonstrate efficacy, in order to obtain product registrations (see table 1.3). At the time of submission of this thesis (April 2007), a total of 79 applications had been submitted within 12 member states and 8 herbal medicinal products had been granted a traditional herbal registration (THR) in three member states. The first in the UK being granted to Bioforce (UK) Ltd on the 8th November 2006 for Atrogel Arnica Gel (MHRA, 2007).

Table 1.3 Summary of the Traditional Herbal Medicines Directive (Directive 2004/24/EC)	
Key dates	
30 October 2005	Member States were required to take measures to comply with the Directive
30 April 2011	Member States must apply the Directive to products that have benefited from the transitional period.
Requirements for safety, efficacy and efficacy	
Quality	Pharmaceutical dossier required Addition of heavy metals, conventional drugs, non-herbal active ingredients (apart from vitamins/minerals) are not permitted Compliance with good manufacturing practice (GMP) standards
Safety	Bibliographic review and expert report on safety Composition will be declared Patient Information Leaflet/labelling Pharmacovigilance requirements
Efficacy	Based on longstanding use; 30 years bibliographic evidence in the EU or 15 years in EU plus 15 years in other specified territories.

Under the new scheme, registration of products are restricted to herbal medicines that are intended to be used without the supervision of a medical practitioner, that they are not for diagnostic purposes and that they do not require monitoring or a prescription (MHRA, 2007). Preparations will be limited to oral formulations, external use or products for inhalation. The scheme also allows for herbal medicines to be combined with vitamins and minerals, where there is evidence of safety and the vitamin/mineral are ancillary to the herbal active ingredient. However, products containing other non-herbal ingredients other than the excipients are not covered and products which are manufactured from isolated chemical constituents of plants would not be regarded as a traditional herbal medicinal product and would not be registered. Furthermore, the scheme only covers products that are classified as a medicine *i.e.* if a product is currently sold legally as a food, cosmetic or general consumer product, the company can continue to sell their product under these regimes.

After the full transitional period of the new scheme which ends on 30 April 2011, it is the Governments intention that, Section 12 (2) of the Medicines Act would cease to provide a

regulatory route by which manufactured OTC herbal medicines can reach the market place without a product licence (MHRA, 2007).

1.5.7 Pharmacovigilance of herbal medicines

At present the yellow card ADR reporting system is the main mechanism for the pharmacovigilance of herbal medicines. In spite of the increase in the number of reports from the inception of the scheme, the overall number of yellow card reports of suspected ADRs associated with herbal medicines received by the MHRA remains low, particularly in comparison to conventional medicines.

The WHO recognises the limitations of the spontaneous reporting of herbal medicines and has established a project on the ADR monitoring of herbal and traditional medicines, to stimulate reporting in this area and to standardise information on herbal medicines. The project has produced guidelines on safety monitoring and pharmacovigilance of herbal medicines which calls for strengthening the pharmacists' role in herbal safety monitoring and for consideration and inclusion of consumer reporting (WHO, 2004). It has also produced a template ADR reporting form which includes specific details on the reporting of herbal medicines.

Despite the WHO's efforts to harmonise the international pharmacovigilance of herbal medicines, a further implication is that the status/use of herbal medicines and terminology used to categorise herbal medicines is likely to vary in different countries. A report (Farah *et al.*, 2000) on the international monitoring of adverse health effects associated with herbal medicines looked at the different types of reports received by the UMC on herbal medicines and reported that it was difficult to classify and interpret the reports due to the myriad of names for herbal products (lay names, product names, scientific names).

1.5.8 Other UK spontaneous reporting systems for herbal medicines

Extending ADR reporting to traditional healthcare professionals is a logical choice as under the Medicines Act (Section 12.1) herbalists are able to compound their own preparations and at present there is no information on the potential ADRs that can result from these

preparations. Also, the WHO guidelines on safety monitoring of herbal medicines in pharmacovigilance systems states that:

> *"If adequate coverage of herbal medicines is to be achieved, national reporting schemes should be developed to include all providers of herbal medicines and providers of traditional, complementary and alternative medicine, according to national circumstances."*
>
> (WHO, 2004)

Despite these recommendations, at present the UK's yellow card scheme does not include any CAM practitioners as recognised reporters. However, within the UK, several independent practitioner-initiated schemes exist. In 1994, the National Institute of Medical Herbalists (NIMH) started up an independent yellow card reporting scheme, specifically for herbal medicines prescribed by herbal practitioners. Since the inception of the scheme to April 2006, a total of 42 NIMH yellow card reports have been received (Kayne, 2006). The Register of Chinese Herbal Medicines (RCHM) has also set up a similar scheme to the NIMH. The scheme was initiated in 1987 and has more than 500 members. In a recent symposium 3% of these practitioners were stated to have completed ADR reports (Kayne, 2006).

Both the NIMH and RCHM schemes are restricted to reporting by herbal practitioners. There are additional schemes such as Phytonet (2006), which includes all healthcare providers and the public as responder groups as well as the British Herbal Medicine Association (BHMA), which represents the manufacturers of unlicensed herbal medicines; however neither scheme has contributed a large number of reports. Although all of the above schemes (NIMH, RCHM, Phytonet and BHMA) feed data to either the MHRA or UMC, these are not desirable as for effective pharmacovigilance there should be a single centralised reporting scheme, so that signals can be rapidly generated.

1.5.9 Current problems with the spontaneous reporting of ADRs associated with herbal medicines

At present it is not known whether the low numbers of suspected ADRs associated with herbal medicines are due to the fact that herbals are not associated with ADRs or whether gross under-reporting is prevalent. This matter remains an ongoing debate (Mills, Article in

Press). However, considering the nature of some of the herbal safety concerns identified to date (*e.g.* St John's wort, Kava-kava), together with the problems associated with their safety, efficacy and quality, herbal medicines do make a case for greater vigilance.

Regarding possible reasons for under-reporting, a number of studies have shown that there is a lack of awareness amongst reporter groups that the yellow card scheme applies to (licensed and unlicensed) herbal medicines (Green *et al.*, 1999a; Wingfield *et al.*, 2002). Secondly (as outlined above in section 1.5.3) users of herbal medicines tend to have a positive belief concerning the safety of herbal products and are reluctant to inform their GPs (Barnes *et al.*, 1998; Giveon, 2004) or their pharmacists (Bouldin *et al.*, 1999) regarding usage or suspected ADRs. This is supported by findings from a study conducted by Gulian *et al.* (2002) where face-to-face interviews were conducted with users of herbal medicines and it was found that such users consulted mainly non-pharmacy, non-professional sources of information on their herbal medicines such as family members and friends. Hence, ADRs experienced by such consumers may not be reported to healthcare professionals as the initial usage relied on testimonials and anecdotal evidence.

At present, for those suspected ADR reports submitted in association with herbal medicines, the completeness of the data required to make an assessment may not be captured using the current yellow card. For example, the only emphasis for herbal medicines is under the concomitant medication section, which was added in October 2000 (See Appendix 1 for copy of yellow card). The "suspected drug" section also only requests for a product brand name instead of the ingredient. For herbal preparations exempt from licensing under the Medicines Act section 12.2 (1968) it is not permissible for manufacturers to use a brand name, thus it would be more appropriate to request for both the herbal ingredient name and brand (manufacturer/supplier/distributor).

Herbal ADRs also pose additional complications as the herbal constituents may vary significantly between manufacturers (see section 1.5.5) due to different species or parts of the plant being utilised by the manufacturer. In addition, batch to batch variation can occur as factors such as when the plant was harvested and how the plant was stored have been identified to alter the quality of the final product (Schilter *et al.*, 2003; Liang *et al.*, 2004). Thus, the genus, the species, plant part, batch number and manufacturers details are essential details

to be recorded in the yellow card to allow for follow-up and assessment of a suspected ADR report associated with a herbal medicine (Barnes, 2003). The UMC have also identified the following nomenclature criteria as important for the pharmacovigilance of herbal products (Farah *et al.*, 2006):

- the name should indicate only one species of plant
- the source for this name must be authoritative
- the name should indicate which part of the plant is used

Coupled with this, herbal preparations can contain multiple ingredients making it difficult to assign which herb is responsible for an ADR and to ascertain if there is a synergistic effect or an interaction occurring. Thus, more space is required on the yellow card to list each of the ingredients contained in the preparation. However, due to the limited space on the UK's yellow card, the necessity for the inclusion of this information is not fully stipulated and is presented in the guidance notes only. Though the existence of separate reporting forms for different categories of medicines may lead to confusion amongst healthcare professionals and the public, in case of herbal medicines, if not a separate form then at least modification of the current form is warranted.

1.6 Role of the community pharmacist in the ADR reporting of herbal medicines

Evidence suggests that community pharmacists are in an ideal position to advise patients/consumers on herbal medicines, monitor their usage, identify and report herbal ADRs, which was the main reasoning for the inclusion of community pharmacists as official reporters to the UK's yellow card scheme in 1999. Community pharmacists are specifically encouraged to report ADRs on conventional OTC and herbal medicines; evaluation has shown that a greater proportion of herbal ADR reports are submitted by community pharmacists in comparison to GPs, but numbers are still low (see figure 1.6; MHRA, 2007)

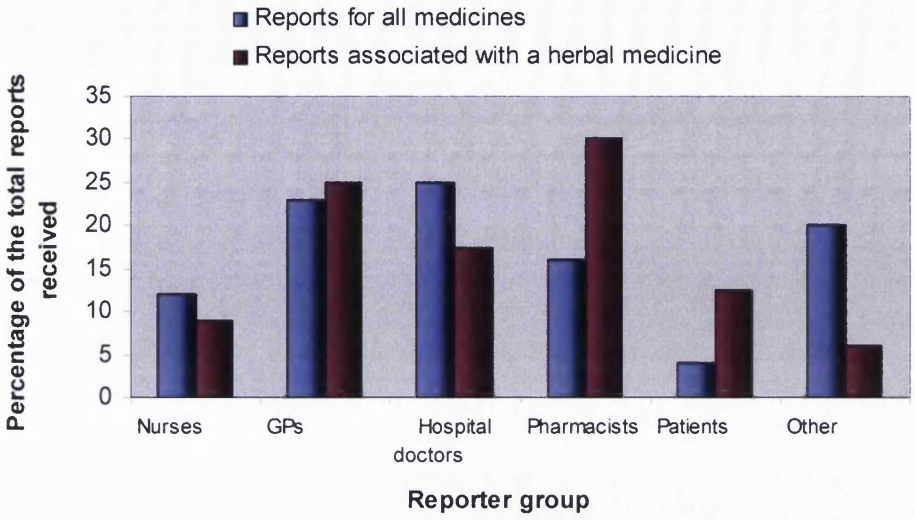


Figure 1.6 Proportion of reports submitted to the MHRA by each reporter group in 2005

Previous work has criticised pharmacists for their lack of knowledge on herbal medicines and on the ADR reporting system, which could contribute to under-reporting by pharmacists in this area (Barnes and Abbot, 1999; Chang *et al.*, 2000). Thus the issue on the extent of pharmacists' knowledge and training in herbal medicines is raised. Most UK schools of pharmacy include teaching on spontaneous ADR reporting in their undergraduate pharmacy programmes, but only one also teaches this subject with respect to herbal medicines (Cox *et al.*, 2004). In a survey of 112 community pharmacists in Glasgow, it was found that only 15% had received training in herbal medicines during their undergraduate pharmacy degree programme and that 79% of the respondents felt that they needed to learn more about herbal medicines (Quinn and Waterman, 1997).

It is possible that consumers are reluctant to disclose the use of herbal medicines to community pharmacists, as was found to be the case with GPs (Barnes *et al.*, 1998). Bouldin *et al.* (1999) also suggests possible reasons for this *e.g.* patients may be embarrassed as they may perceive pharmacists to be a stringent representative of "conventional" medicine and who might disapprove of the use of herbals or perhaps patients have the perception that herbal products are safe and their use does not need to be mentioned to the pharmacist. However, further work is required to establish this, as previous work has also shown that pharmacists are asked for information and advice on these products (Barnes and Abbot, 1999), which could indicate willingness of the public to disclose herbal medicine use to community pharmacists.

Further work is also required to establish the types of questions asked and the pharmacists' ability to answer them using appropriate information sources. Training on herbal medicines and their pharmacovigilance as part of the undergraduate curriculum or as postgraduate education should be further investigated.

As yellow card data cannot estimate the frequency of adverse effects and as there are few clinical trials for most herbal medicines (which in any case only have the statistical power only to detect common acute adverse events), there is a need to explore and demonstrate the safety profiles of specific herbal medicines in other ways. The implementation of an intensive monitoring scheme is another possible method to increase herbal ADR reports, which has been successfully used to increase reporting of HIV medicines (*Pharm J*, 1998) and paediatric medicines (Clarkson *et al.*, 2001). .At present, no such intensive monitoring scheme exists for herbal medicines or for the inclusion of additional reporters. Also it is not known if prompts for herbal information on ADR reporting forms would encourage or improve reporting for these preparations. Another approach, based on PEM concepts (see section 1.3.3), is to use community pharmacists to recruit all individuals who purchase a specific herbal product. Individuals, pharmacists and GPs could then be followed up for data on adverse events. The feasibility of using a community-pharmacy-based method to collect adverse event data has been demonstrated for a conventional OTC medicine, ibuprofen, purchased from pharmacies (Sinclair *et al.*, 1999; Layton *et al.*, 2002), but similar methodology has never been applied to OTC herbal medicines. In addition, it should not be assumed that previous findings, particularly relating to consumer recruitment and data collection with regard to OTC conventional medicines, would apply equally to herbal medicines

1.7 Summary

It is widely recognised that the need for further vigilance of herbal medicines is required and that community pharmacists could play a key role in this area. At present the yellow card ADR reporting system is the main mechanism for the pharmacovigilance of herbal medicines. Signals for both St John's Wort (*Hypericum perforatum)* and Kava-kava (*Piper methysticum)* were generated *via* this method. Whilst these are examples of success with current spontaneous reporting scheme, herbal medicines still remain an area of low reporting, despite their increased popularity. A recent article 'A model for the future conduct of pharmacovigilance' draws on the need for more efficient ADR signal detecting systems as under-reporting will always remain an issue with the current system (Waller and Evans, 2003). However, the yellow card scheme is at an infancy stage regarding the pharmacovigilance of herbal medicines and there remains a great potential to increase reporting in this area. Therefore, the focus of the research presented in this thesis was to examine the role of the community pharmacist in the pharmacovigilance of herbal medicines.

Chapter 2
AIMS OF THE RESEARCH

2.1 The development of research questions

Herbal medicines are widely used in both developed and developing countries. It is the common belief that these products are 'natural' and therefore 'safe' that is in part responsible for their popularity. Despite this, herbal medicines have been associated with several safety concerns. For example, St Johns' wort (*Hypericum perforatum*) has been associated with pharmacokinetic interactions leading to therapeutic failure, including unplanned pregnancies, and Kava-kava (*Piper methysticum*) has been associated with cases of liver failure. Thus, it is widely recognised that the need for further vigilance of herbal medicines is required.

Presently the spontaneous reporting system (yellow card scheme) is the main mechanism for the pharmacovigilance of herbal medicines (see section 1.5.7). However, such schemes have inherent limitations, particularly under-reporting of suspected ADRs, which are likely to be even more significant for herbal than for conventional medicines.

In the UK, community pharmacists have been identified as having key roles in the identification and reporting of adverse drug reactions associated with the use of herbal medicines. However, the number of reports submitted to the MHRA by pharmacists remains low and the majority of herbal reports are said to be from sources other than pharmacists (MHRA, 2007). Education and lack of training of community pharmacists have been postulated as contributory factors.

Therefore, the purpose of this thesis is to examine the role of the community pharmacist in the pharmacovigilance of herbal medicines and to explore and concentrate on the following areas:

- Identify community pharmacists current practices in and awareness of the pharmacovigilance of herbal medicines
- How to improve community pharmacists' ADR reporting of herbal medicines
- Developing methods for enhancing pharmacovigilance of herbal medicines through community pharmacy.

2.2 The principal research questions

i. What are the current practices of national pharmacovigilance centres with regard to the spontaneous reporting of suspected ADRs associated with herbal medicines?

ii. What are the deficiencies in the current UK's yellow card for the collection of suspected ADRs associated with herbal medicines?

iii. What are community pharmacists' attitudes, perceptions, knowledge and training needs concerning herbal medicines?

iv. How extensively are pharmacognosy and its related fields taught at UK schools of pharmacy?

v. Can adverse event data for herbal products be collected systematically from consumers using a community-pharmacy-based method of recruitment?

2.3 Principal hypotheses

i. Current practices of national pharmacovigilance centres towards reporting ADRs associated with herbal medicines vary even across members of the WHO-UMC programme.

ii. Few ADR reporting forms and guidelines are designed for the collection of suspected ADRs associated with herbal medicines.

iii. Community pharmacists require further education and training in herbal medicines and their pharmacovigilance.

iv. Current levels of undergraduate teaching on herbal medicines are not sufficient to adequately prepare future pharmacists on the safe, effective and appropriate use of herbal medicines.

v. The community pharmacy setting can be used to recruit consumers of herbal medicines for the collection of data on ADRs.

2.4 Operationalisation of the principal hypotheses

To test the above hypotheses the following aims and objectives were used:

Chapter	Aim	Objectives
4	To explore the current activities of national pharmacovigilance centres with regard to spontaneous ADR reporting for herbal medicines	1. To describe how herbal medicines are defined and classified by national pharmacovigilance centres 2. To evaluate what proportion of national pharmacovigilance centres accept reports for suspected ADRs associated with herbal medicines 3. To determine whether national pharmacovigilance centres specifically encourage the reporting of suspected ADRs associated with herbal medicines and if so, how this is done 4. To explore national pharmacovigilance centres' views on the suitability of their respective spontaneous reporting forms for reporting of ADRs associated with herbal medicines
4	To make recommendations for a modified UK's yellow card to effectively collect data on suspected ADRs associated with herbal medicines	1. To determine how many ADR forms and guidelines from national pharmacovigilance centres specifically mention the term herbal medicines 2. To identify all of the relevant data items required for an ADR associated with a herbal medicine 3. To make recommendations for the design of a new yellow card that meets the need for collecting data on suspected ADRs associated with both conventional and herbal medicines
5	To explore community pharmacists' experiences with and views on herbal medicines, using qualitative techniques	1. To identify issues relating to herbal medicines that are of concern/importance to community pharmacists 2. To explore pharmacists' attitudes, perceptions and knowledge with regard to various aspects of herbal medicines 3. To analyse qualitative data on which to base the design of a questionnaire to explore these areas in a quantitative study
5	To explore community pharmacists' experiences with and views on herbal medicines, using quantitative techniques	1. To determine how community pharmacists define, describe and classify herbal medicines and how these compare with a recognised definition 2. To identify criteria used by community pharmacists in selecting herbal medicines to be stocked in their respective pharmacies 3. To determine how frequently pharmacists receive requests for information on herbal medicines and identify what information sources are available 4. To determine how competent pharmacists believe they are in advising patients and the public on the safe and effective use of herbal medicines 5. To determine the level and extent of training and education pharmacists have received on herbal medicines 6. To determine if pharmacists have ever identified or received a suspected ADR associated with a herbal medicine and what action they took 7. To identify the criteria pharmacists use before submitting a yellow card report for a suspected ADR associated with a herbal medicine 8. To determine pharmacists' views on the current issues surrounding herbal medicines *e.g.* the supply of herbal medicines from pharmacies 9. To use qualitative data in the design of a questionnaire to explore pharmacists' experiences with and views on herbal medicines in a quantitative study

Chapter	Aim	Objectives
6	To investigate trends in the teaching of pharmacognosy/ natural products, herbal medicine and complementary/alternative medicine: a cross-sectional survey of UK schools of pharmacy	1. To determine the proportion of 'old' and 'new' schools of pharmacy including teaching of pharmacognosy on their core and elective programmes 2. To determine the inclusion of areas related to pharmacognosy, namely herbal medicines and aspects of complementary and alternative medicines (CAM), in the curriculum 3. To identify the method of delivery and extent of teaching in these areas 4. To explore respondents' views on the teaching of pharmacognosy and related areas
6	To assess the effect of pharmacy undergraduate teaching in the pharmacovigilance of herbal medicines	1. To assess students' existing knowledge of pharmacovigilance and specifically for herbal medicines 2. To see if the educational intervention could increase scores 3. To determine if quality of ADR reports written improved after an educational intervention
7	To develop and assess a new method for monitoring the safety of herbal medicines purchased OTC using community pharmacists	1. To conduct a literature search of studies utilising community pharmacies to recruit subjects 2. To develop a paper model for the active surveillance of herbal medicines through community pharmacy 3. To determine if adverse event data for herbal products can be collected systematically from consumers using a community-pharmacy-based method of recruitment 4. To present an evidence-based argument on whether or not this type of study is feasible in the community setting

Chapter 3

METHODS OF DATA COLLECTION AND ANALYSIS

3.1 Background

This chapter provides an overview of the research methods utilised in this thesis. It is divided into two main sections; qualitative and quantitative methods.

3.2 Quantitative methods

Quantitative methods are utilised for testing hypotheses, investigating frequencies and quantifying relationships between clearly defined variables (Smith, 2002). They encompass a broad range of techniques and instruments. Thus, for the purposes of this thesis, only survey and experimental trial techniques will be discussed.

3.2.1 Survey

Surveys involve collecting information from a sample of the population, either by face to face or telephone interviews, postal or other self-completion questionnaires or *via* diaries. Questionnaires are often a preferred method, as interviews can be expensive and time consuming and diaries often have a poor response rate (Bond and Bradley, 1996; Sinclair, 2001). In addition, questionnaires allow the research participant sufficient time to obtain answers for in-depth questions and participants may feel at ease particularly for sensitive questions.

Surveys can be designed to collect and describe the views, demographic details and activities of a population; these surveys are known as descriptive surveys. Descriptive surveys are unable to measure the direction of cause and effect on relationships (Bowling, 1997). Descriptive surveys are also known as cross-sectional because the data is collected from the population of interest at a fixed point in time. Most descriptive surveys are retrospective *i.e.* they request for information on past events and therefore may suffer from recall bias. Cross-sectional studies can be repeated to investigate changes over time; this method differs from longitudinal studies in that the research participants might vary from the initial survey.

Longitudinal surveys are used to analyse events at more than one time point potentially looking for effects of an intervention. The descriptive data generated from this method provides more robust information on the timing of events and the temporal relationship between variables; hence it is more powerful than cross-sectional studies and could be employed for active post-marketing surveillance (Smith, 2002). A further advantage is that most longitudinal surveys are carried out prospectively, thus reducing recall bias. The disadvantages of this method include the increased time required for conducting these studies, problems regarding follow-up and greater attrition rates.

3.2.2 Experimental trials

Experimental trial involves an experimental group which is exposed to an intervention and a control group. Both groups should be equivalent to minimise effects of confounding factors and investigated systematically under identical controlled conditions. Ideally pre- and post-intervention tests should be conducted to measure the effect of the intervention. Random allocation of the participants to each group can reduce the interference of confounding factors such as age and sex. Conversely, with a non-random distribution, it can not be assumed that any observed differences between the two groups are totally due to the intervention and in this instance it is essential to perform pre- and post- intervention tests.

3.3 Qualitative methods

Qualitative methods include interviews, focus groups, diaries, chronological accounts and field notes of observational research (Pope *et al.*, 2006). These methods are less obtrusive than quantitative methods as they aim to study people in their natural social settings. Furthermore, the openness and flexibility inherent in qualitative research makes it ideal for exploring and gaining insight into a subject area, particularly new areas. However, qualitative methods are not only limited to the developmental stages of research, but can be used to explore complex issues such as behaviour. The most common qualitative research used in pharmacy practice is the qualitative interview (Smith, 2002).

3.3.1 Interview

Interview based studies can be qualitative or quantitative (using a survey design), depending on the level of structure within the interview. The different interview structures are outlined in table 3.1. Interviews are valuable when in-depth information is required. This is particularly true for non-structured interviews as more complex issues can be explored. However, the disadvantages of this method are that considerable time is required for the collection and analysis of the data. Furthermore, it is expensive to conduct and therefore smaller samples are utilised which can reduce the representation of the data to the population of interest.

Table 3.1 Interview styles (Bryman, 2001)
Qualitative
Non-structured: Researcher has a brief topic guide, allowing considerable freedom within the interview. Interview takes the form of a conversation rather than a question-answer session **Semi-structured:** Researcher has an interview schedule with a list of themes and potential questions. Interview style is flexible, allowing for open dialogue that can extend beyond the parameters set by the interview schedule.
Quantitative
Structured: Researcher asks the same questions to each interviewee, offering the interviewee a fixed range of answers. This process is then followed by statistical analysis of the results. An example of this is a face to face survey.

3.3.2 Focus groups

Focus group discussions are often described as 'group interviews'. However, they differ in that the moderator will not demand every participant to answer each question. They can be used to explore participants' views and experiences with regard to a specific topic, or they can used to explore characteristics of the participants in a group.

There is more than one way of running or levels of moderating a focus group. Issues for investigation are identified through a systematic review of the literature. Often a schedule or topic guide is developed to guide the discussion and act as a memory aid. This should be flexible to allow emerging themes to be further investigated and analysed. The focus group itself is typically a relatively homogenous group of six to eight people and lasts between one-half to two hours (Smith, 2002). During the focus group session it is not necessary for people to reach a consensus, or for them to disagree, but it is the group dynamics that is of interest. As stated by Morgan (1988):

> *"The hallmark of the focus groups is the explicit use of the group interaction to produce data and insights that would be less accessible without the interaction found in a group"*

Data generated from focus groups can be used for a full range of evaluation purposes and either as a core element in qualitative research or used as part of quantitative research.

Focus groups are an efficient method of data collection; the sample size can be increased significantly in comparison to single interviews and it is easier to recruit subjects in comparison to questionnaires. Also unlike questionnaires, where the participant is limited to set answers, focus groups allow new ideas to be identified and explored. Group discussions provide a mechanism of quality control, as each participant is allowed time to reflect whilst others are contributing to the discussion and help to eliminate false or extreme views (Smith, 2002). In addition, the facilitator is able to clarify and confirm views.

One of the major disadvantages of focus groups include, that the response time to any given question is increased, due to the increased number of participants involved in the interview, therefore a limited number of questions can be administered (Smith, 2002). Further disadvantages include the requirement of a facilitator to manage the interview as participants can deviate from the subject area and certain participants can dominate the discussion.

3.4 Sampling methods

3.4.1 Sampling in quantitative research

A researcher's population of interest may contain too many subjects to study, as a result samples are taken and the findings are used to infer about the behaviour of the population (Bowling, 1997). Thus the method should allow for a representative sample of the total population, in order to make these generalisations. Ideally, random sampling should be conducted as it allows each individual within a population to have an equal chance of being selected *i.e.* individuals with a particular characteristic do not have a higher chance of being selected which may bias the outcome of the study. Random sampling consists of the following subtypes: unrestricted, simple, systematic, stratified and cluster sampling. For the purposes of this thesis; cluster and stratified sampling are briefly outlined below:

- Clustering involves the division of the population into naturally occurring clusters/groups *e.g.* geographical area, from which a number of participants are selected at random.

- Stratified sampling involves subjects being grouped into strata based on a particular characteristic related to the study outcome, and then a random selection of subjects is taken from each of the strata. The advantage of this method is that it avoids under- and over-representation of certain groups of the population.

Alternatively non-random sampling methods include quota and convenience sampling, which are used for their speed of recruitment and expediency:

- Quota sampling is a method of stratified sampling. It specifically selects a set number or proportion of individuals within different groups *e.g.* age and sex.

- Convenience sampling is also used for qualitative research and is therefore outlined below in section 3.4.2.

3.4.2 Sampling in qualitative research

Strategies used for sampling in qualitative research differ from quantitative research. Because of the detailed work qualitative studies involve, sample sizes are purposely small, thus statistical calculations and generalisation to the population of interest are inappropriate. Strategies often applied include purposive, representative, convenience and theoretical samples:

- Purposive sampling selects participants according to the projects goals *i.e.* individuals who share particular characteristics relevant to the study and whom the researcher believes will be the most informative. Focus groups depend on purposive sampling as the main objective of this approach is to gain insight and understanding by hearing from representatives from the target population and thus requires selecting a purposive sample that will generate the most productive discussions in the focus groups.

- Representative samples are employed when the researcher is unable to include a random sample, but requires a degree of representation to the target population. This is achieved by selecting a specific number of individuals in different categories *i.e.* age groups, gender.

- Convenience samples are employed for their ease, as they select the most readily accessible or willing participants. However, the main drawback of this method is that the sample may not be at all representative of the population of interest (Smith, 2002). A 'snowballing' effect can also be utilised where the participant can be used to identify other potential research participants (Bowling, 1997).

- Theoretical sampling is where the researcher recruits further research participants on the basis that they will provide further information or value to the study (Rutter *et al.*, 1998). The major drawback of this method is the risk of expanding the study beyond control, if there are no specified limits.

3.4.3 Sample size and statistical power

The bigger the sample, the more likely it is to reflect the whole population (although increasing the sample size does not reduce respondent bias). However, too many participants is often a waste of resources whereas too few participants is unethical as the data may not be reliable. Thus sample size calculations are used to justify the proposed study size and demonstrate that the study is capable of answering the research question.

The sample size can be statistically calculated using a power calculation. Power is the probability of the test to detect a real difference, if one exists. It depends on some estimation of the likely differences between groups. This estimation can be taken from data obtained from a pilot study or from extrapolation of data used within previous studies. In order to calculate the power of a test we set the significance level and calculate what sample size is required to get a significant difference. The 0.05 level of significance is usually taken, which equates to a 1 in 20 probability that the findings are due to chance. Although it is desirable to have a high level of significance this can produce relatively large samples and a lower power is sometimes used to obtain more realistic sample sizes.

Barbour and Kitzenger (1999) also identified nature of the research question, range of the people who need to be included and limitations imposed by time and cost as factors to consider when looking at sampling size and strategy. Other factors reported to be taken into consideration when calculating a sample size are the expected response and attrition rates in the case of longitudinal studies.

3.5 Establishing validity and reliability

As stated by Bowling (1997):

> *'Validity is an assessment of whether an instrument measures what it aims to measure'.*

Reliability of a study on the other hand refers to the reproducibility of the findings. To achieve both valid and reliable data, an appropriate and rigorous research method in line with the research objectives should be employed.

3.5.1 Validity and reliability in quantitative research

It is important that the survey instrument generates responses that are reliable and valid. With questionnaires there are many variables that can present problems. For example, variables such as attitudes, status and satisfaction levels, are subjective and may vary amongst different populations and settings.

The validation process involves testing the survey instrument; this can be done *via* a number of different methods:

- Face validity is generally the first form of validation conducted on an instrument. It involves the researcher to assess the presentation and relevance of the questionnaire (Bowling, 1997). Additionally the instrument can be piloted amongst potential research participants or colleagues and changed in accordance with their feedback.

- Content validity is similar to face validity and is usually carried out in the preliminary stages of research however, it is more systematic than face validity (Bowling, 1997). Content validity ensures that the instrument comprehensively covers the research area. For example, qualitative techniques such as exploratory interviews or focus groups can be used to identify the relevant issues.

- Responsiveness to change is concerned with whether or not the instrument can respond to changes which occur in an individual or population over a period of time (Bowling, 1997).

- Factorial validity is measured through factor analysis. This method takes correlated questions and recodes them into uncorrelated underlying values. Factorial validity can be inferred from whether the items tied into clusters form meaningful groups.

There are other forms of validation such as construct validity, criterion validity and precision (Smith, 2002). As outlined above, pilot work is useful in identifying questions that might be answered inaccurately and is also the first step to check reliability. In addition to this, there are three main statistical methods for reliability; internal, external and inter-rater.

- Internal reliability is also referred to as consistency, it is the ability of the instrument to assess one dimension or concept. This can be measured by either the split-half method or Cronbach's alpha. In split-half, the instrument is split into two parts and the correlation between them is computed, whereas with Cronbach's alpha an average correlation between the items and number of items in the instrument is computed (Bowling, 1997).

- External reliability is associated with the ability of the instrument to produce the same results over a period of time (Bowling, 1997). This can be assessed statistically by test-retest, here the instrument is administered to a sample of respondents on two separate occasions then depending on the type of data, a statistical test is used to determine reliability *e.g.* Cohen's kappa coefficient is used to test nominal data, weighted kappa is used for ordinal data and Pearson's correlation for interval data.

- Inter-rater reliability measures the level of agreement between two or more raters. The kappa test, Pearson's correlation, Spearman's rho and Kendall's tau may be used for the analysis. This method is also routinely used in qualitative analysis to check for reliability between coders.

3.5.2 Validity and reliability in qualitative research

Quantitative principles of reliability and validity cannot be applied to qualitative methods, as in qualitative research the objectives are exploratory. Thus as long as the interview is guided by the interviewee, the data will provide a true reflection of the respondents' views. Nevertheless preconceptions of the investigator, the willingness of the participant to share certain views and whether or not the interviewer is known to the participant have been identified as factors that can influence the study findings and introduce bias (Smith, 2002). In addition to this, transcripts are typically analysed by a single rater, hence the judgments may not be reproducible by other raters. A further disadvantage of using a single rater, is that they may not extract all of the themes contained in the transcripts. Investigator bias can be minimized by defining the systematic coding of data from each textual data and drawing inter-group comparisons. Also in some studies the coding procedure has been taken independently by two or more raters, however, it is questionable whether or not raters can consistently evaluate textual data (Weinberger *et al.*, 1998).

3.6 Other data considerations

3.6.1 Response

Response rates are an important aspect of study conduct. Response rates of 100% are rarely achieved (Smith, 2002). Lessler and Kalsbeek, (1992) reported that response rates can vary from 10% to 90%. Typically, the response rate for a postal survey might be 40% for the first mailing, increasing to a total of 60% after one reminder (Barnett, 1991). However, there is growing evidence that the volume of requests received by healthcare professionals is adversely affecting participation rates (McAvoy and Kaner, 1996) thus there is much debate as to what constitutes an acceptable response rate. For questionnaires, 3-4 reminders are often recommended, but increasingly ethics committees are viewing this as possible harassment of research subjects (Howell *et al*, 2003). Furthermore, there is also the question whether further responses do yield any meaningful data, as surveys with a low response may provide a representative sample of the population of interest (Asch *et al*, 1997).

Non-responders comprise those who refuse to participate in a study, people unable to respond and those unable to provide the required information (Smith, 2002). Non-response can also include missing data from poorly constructed questionnaires and in such instances the response rate for each question needs to be presented.

Non-response could introduce an element of bias to the data this is determined by the representation of the sample to the population of interest. It is often tested by comparing social and demographic characteristics of non-responders *versus* responders. Lessler and Kalsbeek (1992) suggest three ways of dealing with non-response when carrying out data analysis; do nothing; assess the potential for bias using auxiliary data and; compensate for the problem by weighting adjustments.

A number of factors influence the response rate such as the perceived relevance of the study, number of follow-ups of non-responders, time required, participants' perception of the research team, incentives (*e.g.* monetary), prior notification, personalisation of material, avoidance of administering the questionnaire during holiday periods and presentation of the questionnaire. The factors reported most consistently to have an impact was monetary incentives (Edwards *et al.*, 2002) and repeat mailings. Subject matter and prior notification have also been found to have favourable effects whereas, as questionnaire length increases the response rate decreases.

3.6.2 Quality assurance

Ideally data coding and data entry should be conducted independently by two of the investigators and then checked by a third person for any discrepancies between the two sets. However, this can be extremely time consuming and with limited resources may not be feasible. In this instance, typing errors from data input can be identified by scanning the data for 'unusual' values. For large databases a proportion of the inputted data should be randomly selected and compared against the original data source. However, sufficient wash-out periods between data entry and checking should be incorporated.

3.6.3 Missing values

Missing values can arise unintentionally when a question does not apply to the respondent or deliberately due to the respondent not wishing to answer the question. With the latter there are a number of reasons as to why this may arise: the question was ambiguous; or difficult; the question was too sensitive; the respondent did not know the answer; or it was skipped by the respondent as the questionnaire was too long (Smith, 2002). Although missing values are common in self-completed questionnaires and there are no recommendations on what is considered a tolerable level of missing values. However during analysis missing values need to be taken into consideration, as a high level can reduce the generalisation of the data to the target population.

3.6.4 Outliers

An outlier is an extreme data value that is non-typical of any other values in the sample. Outliers often bias the mean and increase the standard deviation of the data (Field, 2005). They can be detected by screening the data or visually from graphs such as box-plots. Outliers can be corrected by removing the case which can bias the sample, changing the score which can still result in an unrepresentative value and thus bias the statistical model or lastly by transforming the dataset (Field, 2005). Transforming the dataset is preferred, as it reduces the impact of the outlier without any statistical consequences; however, there are implications in interpreting the data (Grayson, 2004).

3.7 Methods of analysis

3.7.1 Quantitative data analysis

The objectives of the study, number of respondents, shape of distribution (normally distributed or skewed) and type of data (nominal, ordinal, interval and ratio) determine the statistical test that is appropriate for data analysis.

3.7.1.1 De scriptive analysis

Descriptive analysis forms part of the initial analysis strategy. It describes the findings in terms frequency distributions, statistics of central tendency (mean, mode and median) and dispersion (range and standard deviation). The distributions help to identify any recoding of the data that is required and also demonstrates any skewness and allows for reasons to be explored. In summary, it sets the baseline analysis.

3.7.1.2 Inferential statistics

Inferential statistics explore relationships (associations/correlations/differences) between the variables. Concerned with hypothesis testing and making statements about the population based on the sample. It involves testing for differences or relationships between variables. Depending on the distribution of the sample, parametric tests can be applied.

3.7.1.3 Parametric tests

There is some debate of when parametric rather than non-parametric tests should be used. It has been stated that parametric tests are appropriate when the data fulfils the following three conditions (Bryman and Cramer, 1997):

1. The level or scale of measurement is of equal interval or ratio scaling
2. The distribution of the population scores is normal
3. The variances of both variables are equal or homogenous

In general, if both distributions are not normal, or the size of the sample is small (under 15), non-parametric tests are appropriate (Bryman and Cramer, 1997).

Commonly used procedures include;

- t-test or analysis of variance (ANOVA) for comparisons of two or more groups, respectively
- Pearson's correlation coefficient for testing correlations between variables

- regression to summarise the nature of a relationship between variable and predicting values of the dependent variable within applicable limits.

3.7.1.4 Non-parametric tests

Non-parametric tests are ideal for nominal and ordinal data (Bryman and Cramer, 1997). Survey data on many variables are either nominal or ordinal (Smith, 2002), thus for such data non-parametric tests are appropriate. It is also may be more appropriate to use non-parametric tests when the size of the sample is small *e.g.* under 15.

When testing for associations between variables, chi-square for nominal data and Spearman's ranked based coefficient for ordinal data are used. There is a restriction on using chi-square when the expected frequencies are small. With only two categories if the expected frequencies are less than 5, then the binomial test should be used instead. With three or more categories, chi-square should not be used when any expected frequency is less than 1 or when more than 20% of the expected frequencies are less than 5.

Other commonly used procedures include Mann-Whitney U-test for comparison of ordinal data between two independent groups or a Kruskal-Wallis test for more than two independent groups. A Wilcoxon and Friedman test is used when related groups are being compared.

3.7.1.5 Factor analysis

Social science research often involves evaluating items that cannot be absolutely measured. These are known as latent variables, an example is job satisfaction. These latent variables are governed by a number of other characteristics *e.g.* emotion, previous exposure *etc.* Characteristics which go together constitute a factor and factor analysis is a method to identify groups or clusters of characteristics. Factor analysis differs from cluster analysis in that factor analysis groups variables such as perceptions whereas cluster analysis groups cases such as individuals and therefore characteristics. Factor analysis may be used to explore or to group items that seem to measure or evaluate the same concept and to assess the factorial validity of the questions that make up that scale.

3.7.2 Qualitative data analysis

The process of analysis begins during data collection, as the interview/discussion allows the researcher to clarify answers, probe, and pursue emerging avenues of enquiry *i.e.* data gathered dictates the ongoing data collection - a process known as 'sequential' or 'interim analysis' (Pope *et al.*, 2006). Once audio data is fully transcribed the data set undergoes a process of reduction. This is carried out by the reading and re-reading of data to discern any patterns, recurring themes and concepts and then indexing the data according to the categories identified. Initially some categories can be based on the interview schedule. These categories are further refined and reduced in number by grouping them together. Key themes and categories are then selected for further investigation. Emerging themes can then be arranged into matrices and explored for any patterns/differences. Quotes that capture the participants' knowledge, experiences and attitudes are presented to reflect the interview data. However, these should not be reported in a quantified manner (Brown and Sas, 1994).

Another method is the framework approach. This method involves five stages of analysis which are outlined in table 3.2. Typically the aims and objectives are set in advance and thus the data collection and subsequent analysis is more structured.

Table 3.2 Five stages of data analysis in the framework approach (Pope *et al*, 2000)
• Familiarisation Immersion in the raw data, in order to list key ideas and recurrent themes. • Identifying a thematic framework Identifying all the key issues, concepts, and themes by which the data can be examined and referenced. • Indexing Applying the thematic framework or index systematically to all the data in textual form by annotating the transcripts with numerical codes from the index, usually supported by short text descriptors to elaborate the index heading. • Charting Rearranging the data according to the appropriate part of the thematic framework to which they relate, and forming charts. • Mapping and interpretation Using the charts to define concepts, map the range and nature of phenomena, create typologies and find associations between themes with a view to providing explanations for the findings.

3.8 Study design

An overview of the whole study design is given here. Triangulated methods were employed as this ensured that the research area was comprehensively covered and the research questions were explored.

Chapter	Study	Method	Validity	Analysis
4	To explore the current activities of national pharmacovigilance centres with regard to spontaneous ADR reporting for herbal medicines	Quantitative - Questionnaire survey - Cross-sectional	Face validation - Internally by own reflection - Externally through expert opinion	Descriptive statistics Inferential statistics - Non-parametric
4	To make recommendations for a modified UK's yellow card to effectively collect data on suspected ADRs associated with herbal medicines	Quantitative - Data extraction	Face validation - Internally by own reflection	Descriptive statistics - Frequency - Percentages
5	To explore community pharmacists' attitudes, perceptions, knowledge and training needs concerning herbal medicines	Qualitative - Focus groups	Face validation - Internally by own reflection - Externally through expert opinion	Deductive analysis - Framework approach
		Quantitative - Questionnaire survey - Cross-sectional	Face validation - Internally by own reflection - Peer review - Pilot Content validation - Focus groups	Descriptive statistics Inferential statistics Factor analysis

Chapter	Study	Method	Validation	Analysis
6	To investigate trends in the teaching of pharmacognosy/ natural products, herbal medicine and complementary/alternative medicine: a cross-sectional survey of UK SOP's	Quantitative - Questionnaire survey - Cross-sectional - Longitudinal study	Face validation - Internally by own reflection - Externally through expert opinion. Responsiveness to change	Descriptive statistics Inferential statistics - Non-parametric
7	To develop and assess a new method for monitoring the safety of herbal medicines purchased OTC, using community pharmacists.	Quantitative - Questionnaire survey - Longitudinal (cohort) study	Face validation - Internally by own reflection - Externally through expert opinion. Content validation - Literature review Responsiveness to change	Descriptive statistics Inferential statistics - Non-parametric

Chapter 4

CURRENT PRACTICES IN PHARMACOVIGILANCE

4.1 Background

As outlined in chapter one there is an increasing awareness at several levels for the need to develop pharmacovigilance practices for herbal medicines; for example, the guidelines published by the WHO (2004). However, despite these initiatives there has been little investigation to date to further explore global pharmacovigilance practices with respect to herbal medicines in different countries.

Monitoring the safety of herbal medicines at an international level involves understanding and overcoming several complexities:

- Whether or not the countries monitor the safety of herbal medicines by including them as part of their national spontaneous reporting scheme.
- Whether or not national spontaneous reporting schemes for suspected ADRs specifically encourage reporting for herbal medicines by recognised reporter groups (*e.g.* pharmacists and patients).
- Whether or not reporting forms for ADRs are designed adequately to collect information on herbal medicines.
- The terminology used to refer to herbal medicines (*e.g.* common, Latin botanical, brand and lay names) within different countries.
- Whether or not the countries define herbal medicines or distinguish them from other medicines.
- How developed the national pharmacovigilance practices are for herbal medicines.

The WHO in 2002 conducted a worldwide survey on the regulation of herbal medicines (WHO, 2002b). They found that there were less than 70 countries worldwide that regulated herbal medicines and few countries had systems in place for the regulation of traditional health practitioners. Further to this, a study investigating the different types of herbal reports received by the WHO-UMC found that certain countries were more active in reporting than others (Farah *et al.*, 2000). For example, from a period of 1968 to 1997, ten countries were responsible for submitting just over 90% of the total reports received. The study concluded that there was limited data on possible adverse effects of herbal medicines. However, no comparisons were made between the national pharmacovigilance centres or attempts made to

understand why there is such a discrepancy between official member countries of the WHO-UMC programme.

There have been three independent studies (Griffin, 1986; Hughes *et al.*, 2002; Rabbur and Emmerton, 2005) comparing the ADR systems in different countries however, none of these studies make any references to herbal medicines and all were conducted with a small proportion of national pharmacovigilance centres. Thus, there was a need to establish the current pharmacovigilance practices with respect to herbal medicines on an international level.

4.2 Overall chapter aim and objectives

The diagram below summarises the aims and objectives in this chapter

Aim	Objectives	Method
To explore the current practices of pharmacovigilance with respect to herbal medicines at an international level	1. To identify the differences in practice between national pharmacovigilance centres towards the reporting for suspected ADRs associated with herbal medicines 2. To determine factors that may contribute to the different reporting rates between official member countries of the WHO-UMC programme	Cross-sectional survey of national pharmacovigilance centres Data extraction

4.3 Research approach

In order to meet the aims and objectives, this chapter is divided into two phases:

Research question	Phase	Approach
What are the current practices of national pharmacovigilance centres with respect to herbal medicines?	1	Cross-sectional survey of national pharmacovigilance centres
	2	An exploration of a modified UK's yellow card

The results for these two phases are presented separately (section 4.4.3 and 4.5.3) and discussed together (section 4.6) in line with the original aims and objectives.

4.4 Cross-sectional survey of national pharmacovigilance centres

The UK's yellow card scheme has over the years taken initiatives to encourage the reporting of suspected ADRs associated with the use of herbal medicines. These initiatives include:

- Extending the scheme to unlicensed herbal remedies, following on from a report by Guy's Hospital toxicology Unit on potentially serious ADRs associated with herbal medicines.
- Increasing the number of recognised reporter groups *e.g.* inclusion of community pharmacists and patients.
- Revision of the yellow card to include herbal medicines under the concomitant section.
- Revision of the guidelines to request for further details to facilitate assessment, for example the ingredients, source, the name and address of the practitioner and retention of a sample of the product in serious cases.

However, the current pharmacovigilance practices of other countries with respect to herbal medicines are unknown. Furthermore, the WHO in 2004 produced guidelines for the pharmacovigilance of herbal medicines, yet the degree to which these guidelines are adhered to by official member countries is unknown.

4.4.1 Aim and objectives of phase 1

Chapter	Aim	Objectives	Method
4	To explore the current activities of national pharmacovigilance centres with regard to spontaneous ADR reporting for herbal medicines	**1.** To describe how herbal medicines are defined and classified by national pharmacovigilance centres **2.** To evaluate what proportion of national pharmacovigilance centres accept reports for suspected ADRs associated with herbal medicines **3.** To determine whether national pharmacovigilance centres specifically encourage the reporting of suspected ADRs associated with herbal medicines and if so, how this is done **4.** To explore national pharmacovigilance centres' views on the suitability of their respective spontaneous reporting forms for reporting of ADRs associated with herbal medicines	Cross-sectional survey of national pharmacovigilance centres

4.4.2 Method for phase 1

4.4.2.1 Study design & sample

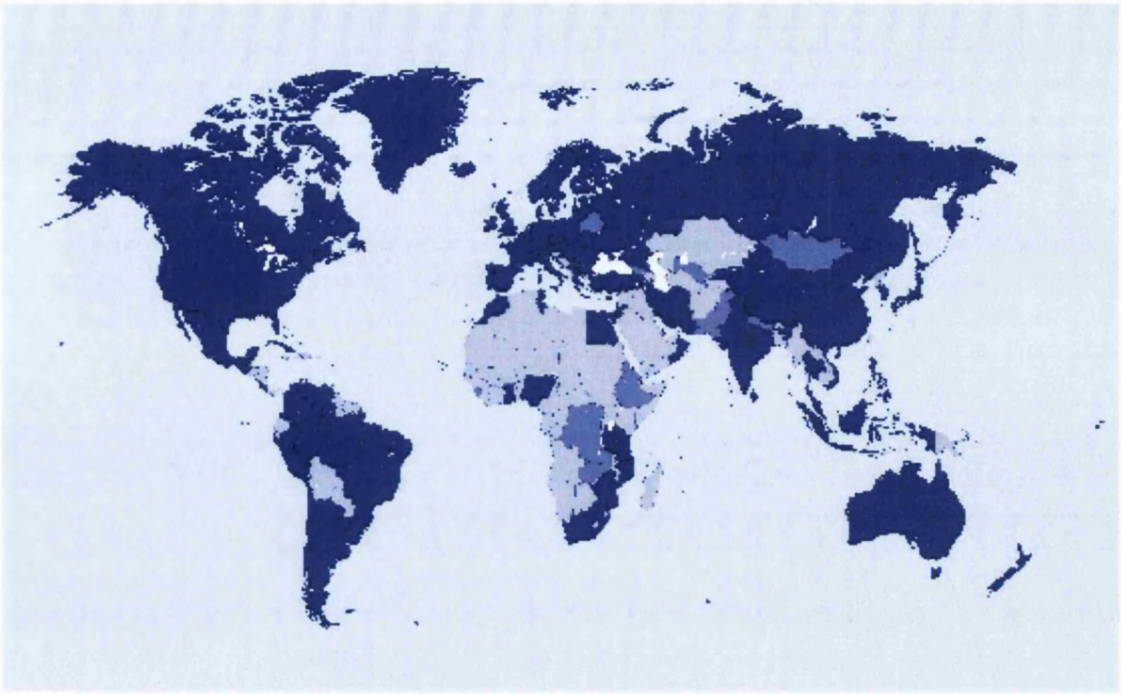
A cross-sectional survey of national pharmacovigilance centres was conducted. The sampling frame for the study comprised all full and associate member countries (n = 72 and 13, respectively) of the WHO-UMC. A list of the member countries is outlined below in Figure 4.1. Contact details were obtained from the UMC.

FULL MEMBER COUNTRIES

Argentina	**Fiji**	**Kyrgyzstan**	**Singapore**
Armenia	**Finland**	**Latvia**	*Slovakia*
Australia	**France**	*Macedonia*	**South Africa**
Austria	*Germany*	**Malaysia**	**Spain**
Belgium	**Ghana**	**Mexico**	**Sri Lanka**
Brazil	**Greece**	**Moldova**	**Sweden**
Bulgaria	*Guatemala*	**Morocco**	**Switzerland**
Canada	**Hungary**	**Netherlands**	**Tanzania**
Chile	*Iceland*	**New Zealand**	**Thailand**
China	**India**	**Norway**	*Tunisia*
Costa Rica	**Indonesia**	**Oman**	*Turkey*
Croatia	*Iran*	**Peru**	**Ukraine**
Cuba	**Ireland**	**Philippines**	**United Kingdom**
Cyprus	**Israel**	**Poland**	**U.S.A.**
Czech Republic	**Italy**	*Portugal*	**Uruguay**
Denmark	**Japan**	*Romania*	*Venezuela*
Egypt	*Jordan*	*Russia*	*Vietnam*
Estonia	*Korea, Rep Of*	**Serbia & Montenegro**	**Zimbabwe**

ASSOCIATE MEMBER COUNTRIES

Bahrain	**Eritrea**	**Malta**	**Nigeria**
Belarus	**Ethiopia**	**Mozambique**	*Pakistan*
Colombia	**Lithuania**	**Netherlands Antilles**	*Zambia*
Congo, Democratic Rep Of			



Official Member Countries (dark blue) **Associate Member Countries (medium blue)**
Non-member Countries (pale blue)

Figure 4.1 Countries participating in the WHO International Drug Monitoring Programme

4.4.2.2 Questionnaire

A six-page questionnaire was designed and developed to collect data in accordance with the objectives of the study. The questionnaire was comprised of mostly closed questions and was written in English. The questions were predominantly based on the UK's yellow card scheme to allow for comparisons to be made. A key part of the questionnaire sought information on how the national centre handle suspected ADR reports associated with herbal medicines and potential signals.

The questionnaire was tested for face validity two-fold; internally by own reflection; externally through expert opinion. Expert opinion was provided by three individuals working in the field of herbal safety. The questionnaire was amended in accordance with their comments (see Appendix 4 for final version of the questionnaire).

4.4.2.3 Procedures

A copy of the questionnaire was posted in March 2004 together with a covering letter explaining the study and requesting a copy of the national ADR reporting form and any other relevant material (*e.g.* reporting guidelines).

Seven follow-up mailings (2 postal, 4 electronic and 1 personal electronic mailing by the UMC) were sent to non-responders at 4-week intervals after the initial mailing. Data were entered into Microsoft Excel version 10 for analysis.

Responses were accepted for 3 months after the final follow-up to allow time for postal responses to arrive from developing countries.

4.4.2.4 Data analysis

Data were stored and analysed using SPSS version 13. A random check on 10% of the data was performed by the author after a set interval of 4 weeks. This was conducted by checking the hard copy of the questionnaire against the electronic record of the data to identify any discrepancies. This was conducted by the author after a period of 4 weeks from the initial data entry.

Descriptive statistics for the sample were calculated. Overall response rates and answers to specific questions for associate and official member countries and other categorical variables were compared using the Chi-squared test. Continuous variables were compared using appropriate statistical methods. Qualitative data were analysed using content analysis.

4.4.3 Results of phase 1

4.4.3.1 Response rate

In total, 89 mailings representing 85 countries were sent (4 countries had 2 points of contact). Of these, one country was excluded from the denominator due to an invalid address.

Figure 4.2 shows that responses from 65 were received; representing 62 countries (respondent countries are highlighted in bold in figure 4.1). For 3 countries, 2 contacts responded; only one from each was included in this analysis (one dealt only with vaccines, one was a regional monitoring centre and one dealt only with approved drugs), giving an eligible country response rate of 74% (62/84).

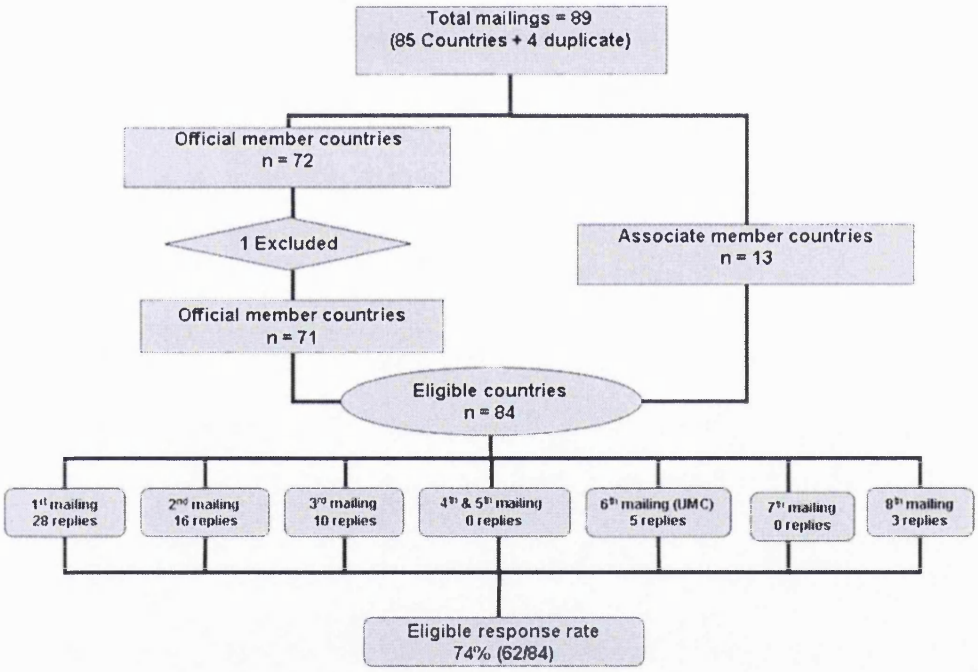


Figure 4.2 Response rate

Of the 62 countries that responded 10 were associate and 52 were official member countries of the WHO-UMC programme. There was no statistically significant difference between the proportions of respondents from associate and official member countries (10/13 *versus* 52/71 for associate and official member countries, respectively; $p = 1.00$; Fisher's exact test; 2-tailed) thus, implying that the sample was representative of the total population.

4.4.3.2 Characteristics of national pharmacovigilance centres

Table 4.1 shows the demographic characteristics of the respondents and non-respondents. There was no statistically significant difference in the characteristics (status, number of years as an official member, world region, median gross domestic product (GDP) *per* capita, total health expenditure as % of GDP) between respondents and non-respondents ($p>0.05$ for all; see table 4.1).

Table 4.1 Demographic characteristics of eligible respondents *versus* non-responders, n (%)†

Characteristic		Respondents n = 62	Non-respondents n = 22	Statistical test and *p* value
Status: Associate/Official		52/10 (83.9/16.1)	3/19 (13.6/86.4)	Fisher's exact test $p = 1.00$ (2-tailed)
Number of years as an official member	0-10	30 (48.4)	14 (63.6)	Chi-square = 3.51 $p = 0.32$
	11-20	15 (24.2)	6 (27.3)	
	21-30	4 (6.5)	1 (4.5)	
	> 31	13 (21.0)	1 (4.5)	
World region	Africa	10 (16.1)	3 (13.6)	Chi-square = 1.68 $p = 0.79$
	America	11 (17.7)	3 (13.6)	
	Asia	13 (21.0)	6 (27.3)	
	Europe	25 (40.3)	10 (45.5)	
	Oceania	3 (4.8)	0 (0)	
Median GDP *per* capita (Intl $, 2002)		9277.0 (10823.8)	6780.0 (3517.5)	Mann-Whitney U $p = 0.20$ (2-tailed)
Median GDP *per* capita (Intl $, 2002)	0<15,000	39 (62.9)	18 (81.8)	Chi-square = 2.41 $p = 0.30$
	≥15,000 <25,000	6 (9.7)	1 (4.5)	
	≥25,000	16 (25.8)	3 (13.6)	
Total health expenditure as % of GDP (2002)		7.0 (2.0)	6.1 (1.2)	Mann-Whitney U $p = 0.81$ (2-tailed)

† Percentages do not total 100 because of missing data

Figures 4.3 and 4.4 show that regardless of the number of years a centre has been an official member country of the WHO-UMC programme or the centre's world region categorisation there is a similar trend between the number of responders and non-responders. Again, this shows that the sample is representative of the total population. Figure 4.3 also shows that

there has been a particular growth in the number of official member countries over the last 10 years.

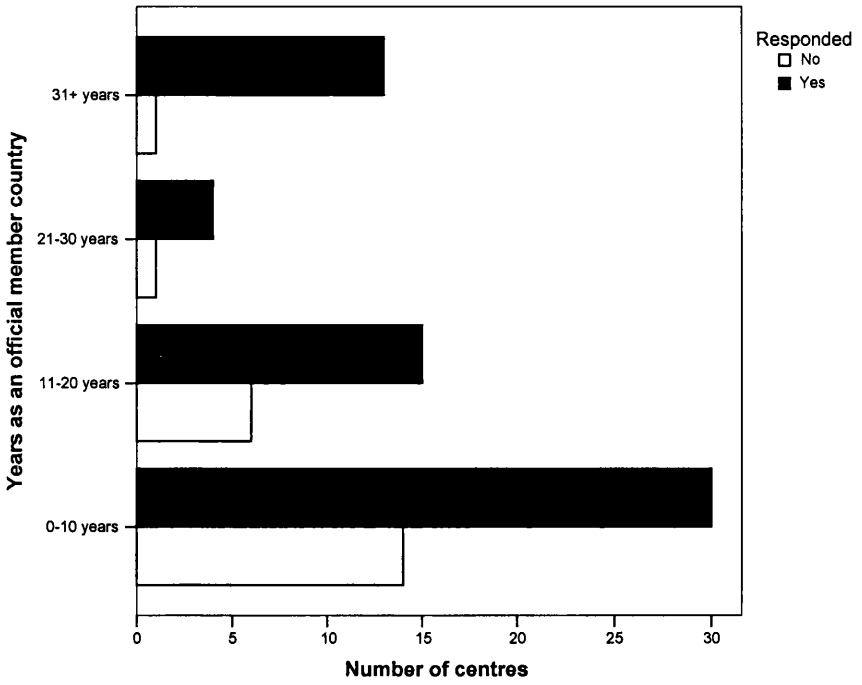


Figure 4.3 Number of years as an official member country of the WHO-UMC programme

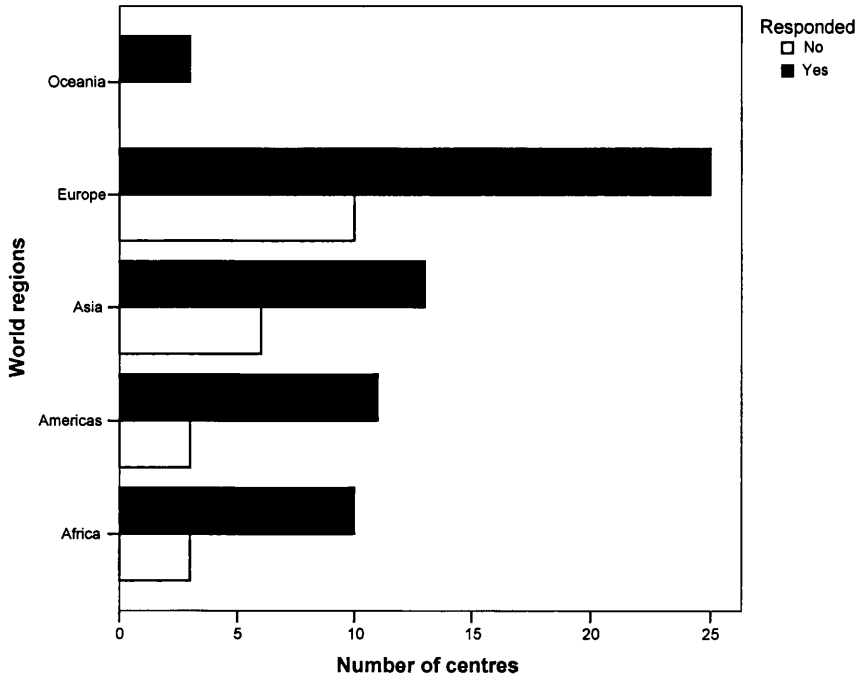


Figure 4.4 Number of national centres grouped according to their world region

4.4.3.3 Regulation of herbal medicines in respondent countries

Figure 4.5 shows that in the majority of the 60 associate and official member countries (missing data for 1 associate and 1 official member country); both licensed and unlicensed herbal medicines are available. There was no statistically significant difference between the regulatory types of herbal medicines available in each country and the number of years they had been as an official member of the WHO-UMC programme (Pearson's chi-square = 4.32, p= 0.63).

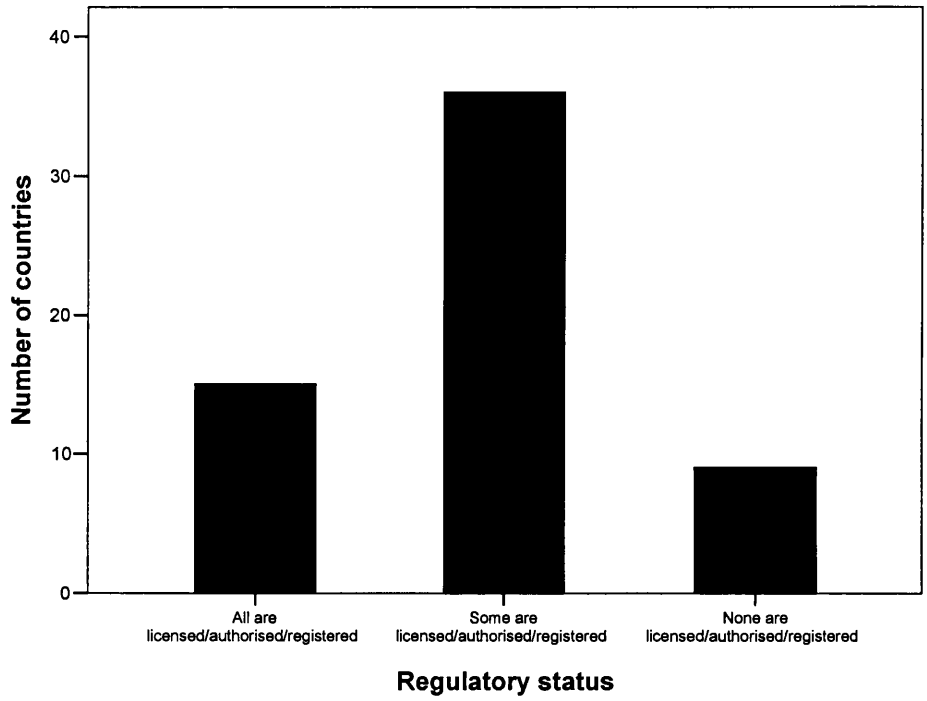


Figure 4.5 Regulatory status of herbal medicines in official member countries of the WHO-UMC programme

Similarly there was also no statistically significant difference between the regulatory types of herbal medicines available in each country and the different world region each member country was classified under (Pearson's chi-square = 7.48, p= 0.49). The median number and semi-interquartile range of the number of marketed herbal medicines that are licensed within the national centre's respective country was 150 and 254, respectively (see figure 4.6).

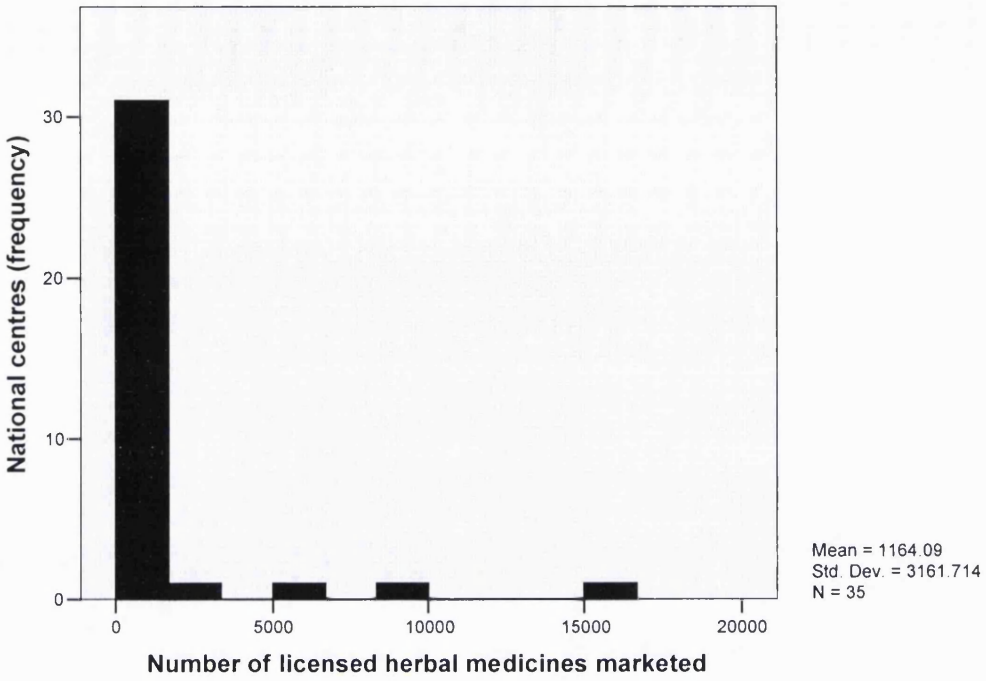


Figure 4.6 Histogram of the number of licensed herbal medicines marketed

4.4.3.4 Definition for herbal medicines

The WHO (2002a) defines herbal medicines as:

"herbs, herbal materials, herbal preparations and finished herbal products that contain as active ingredients parts of plants, or other plant materials, or combinations. In some countries, herbal medicines may contain, by tradition, natural organic or inorganic active ingredients that are not of plant origin (e.g. animal and mineral materials)"

Table 4.2 shows that despite all respondents being members of the WHO-UMC programme few (6% of responding associate and 27% of responding official member countries) used the WHO definition as stated above.

Table 4.2 Use of definitions for herbal medicines by national pharmacovigilance centres (n = 62), n (%) †		
Procedure	**UMC official members**	**UMC associate members**
Uses WHO definition	17 (27%)	4 (6%)
Uses own definition	17 (27%)	1 (2%)
Does not use a definition	18 (29%)	4 (6%)
† Percentages do not total 100 because of missing data		

Table 4.3 provides further details of the 18 countries that use their own definition for herbal medicines.

Table 4.3 Own definitions for herbal medicines used by national pharmacovigilance centres (n = 18)	
Definition used	**n**
EU definition	1
All Complementary medicines except minerals and vitamins	1
Traditional medicines	1
Vegetable origin	3
Naturally occurring substances	3
Plant based	4
Definition that includes herbal medicines	5

The majority used another definition that included the term herbal medicines. For example, Canada uses the term "natural health products" which includes:

"*herbal products, algae, bacteria, fungi, non-human animal material, vitamins, minerals, amino acids, essential fatty acids and probiotics.*"

Similarly the USA uses the term "dietary supplements" which includes:

"*vitamins, minerals, herbs or other botanicals, amino acids and substances such as enzymes, organ tissues, glandulars and metabolites.*"

However, it remains to be established how these national centres are able to correctly assign the above products without a correct definition for each of them.

4.4.3.5 Inclusion of herbal ADR reporting

In total, 55 (88.7%) respondents accepted suspected ADR reports for herbal medicines. The majority of these schemes were set up as the same system for non-herbal medicines. Of these national centres, 7 also receive suspected ADR reports for herbal medicines from other schemes (see table 4.4 for further details).

Table 4.4 Other schemes/organisations providing suspected ADR reports associated with herbal medicines

Country	Organisation
Brazil	Sentinel Hospitals Network
Italy	Center for national medicine of the S. Giuseppe Hospital in Tuscany – a public centre within the NHS
Malta	EMEA
Moldova	Drug information
Ukraine	As biological additions
UK	Register for Chinese medical herbalists, British Herbal Medicine Association, association and the National Institute of medical Herbalists.
Zimbabwe	Drug & toxicology information service run by the Department of Pharmacy at the University of Zimbabwe and the Expanded Programme on Immunisation. Run by the Ministry of Health and Child Welfare.

Of the 7 (11.3%) national centres that currently do not accept herbal ADR reports, none had an independent organisation in their respective country that administered suspected ADR reports for herbal medicines. Also, 5 (71.4%) of these national centres had plans for the introduction of accepting suspected ADR reports for herbal medicines in the future (table 4.5).

Table 4.5 Plans for the introduction of accepting spontaneous ADR reports for herbal medicines	
Country	**Plan**
Croatia	"Waiting for bylaws concerning medicinal products and herbal medicines."
Eritrea	"Not in the near future – new centre."
Mozambique	"After introducing the all disease control programme."
Nigeria	"Centre is to be launched in September 2004 and we shall take reports on herbal medicines if they come."
Serbia and Montenegro	"After the 1st of October 2004."

In total, 26 national centres stated that they accepted ADRs for all categories of herbal medicines and 16 national centres accepted spontaneous ADR reports for licensed herbal medicines only. Figure 4.7 shows the different regulatory categories of herbal medicines accepted by national pharmacovigilance centres. The majority of national centres accepted reports for licensed/authorised/registered herbal medicines. Fewer accepted reports for unlicensed/unauthorized/non-registered herbal medicines compared to licensed/authorised/registered herbal medicines. Least accepted reports were for banned/prohibited/illegal herbal medicines.

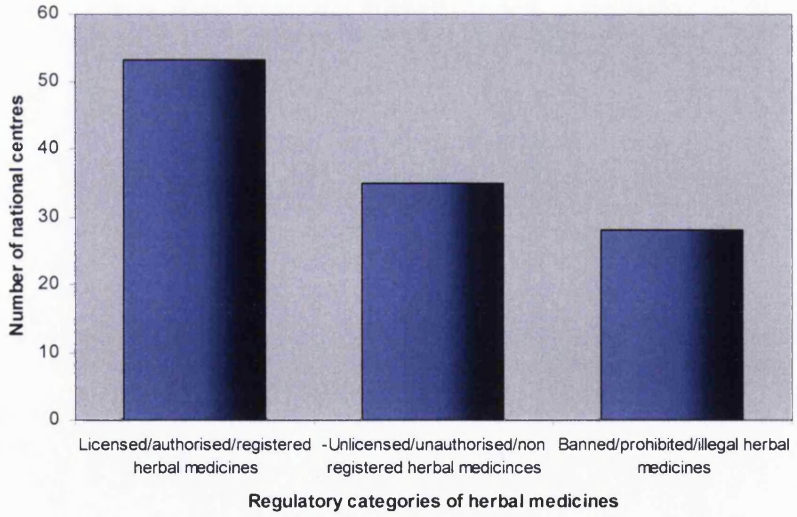


Figure 4.7 Number of national pharmacovigilance centres accepting reports for different types of regulatory categories of herbal medicines

4.4.3.6 Classification of products as herbal or non-herbal

Those national centres planning to or those already accepting ADR reports for herbal medicines (n=60) were asked to classify the following products listed in tables 4.6, 4.7 and 4.8. Table 4.6 and figure 4.8 show the classification of eight common herbal medicines.

Table 4.6 Classification of herbal products by national pharmacovigilance centres according to their definition for herbal medicines, n (%) †

Product	WHO definition (n=21)		Own definition (n=18)		No definition (n=20)	
	Herbal	Non-herbal	Herbal	Non-herbal	Herbal	Non-herbal
Aristolochia species	17 (8.1)	0 (0)	8 (44.4)	1 (5.6)	11 (55.0)	2 (10.0)
Cranberry juice	11 (52.4)	4 (19.0)	7 (38.9)	4 (22.2)	10 (50.0)	4 (20.0)
Digitalis leaf	16 (76.2)	1 (4.8)	9 (50.0)	3 (16.7)	12 (60.0)	3 (15.0)
Essential oils	2 (9.5)	0 (0)	3 (16.7)	1 (5.6)	1 (5.0)	1 (5.0)
Opium	8 (38.1)	5 (23.8)	6 (33.3)	7 (38.9)	6 (30.0)	6 (30.0)
Senna	15 (71.4)	1 (4.8)	10 (55.6)	2 (11.1)	13 (65.0)	1 (5.0)
St John's wort	18 (85.7)	0 (0)	12 (66.7)	1 (5.6)	13 (65.0)	1 (5.0)
Willow bark	13 (61.9)	1 (4.8)	10 (55.6)	1 (5.6)	8 (40.0)	1 (5.0)

† Percentages do not total 100 because of missing data

Only one national centre stated that they would classify all of the above eight products as herbal. Figure 4.8 shows the distribution of how many of the above eight products each national centre would classify as herbal.

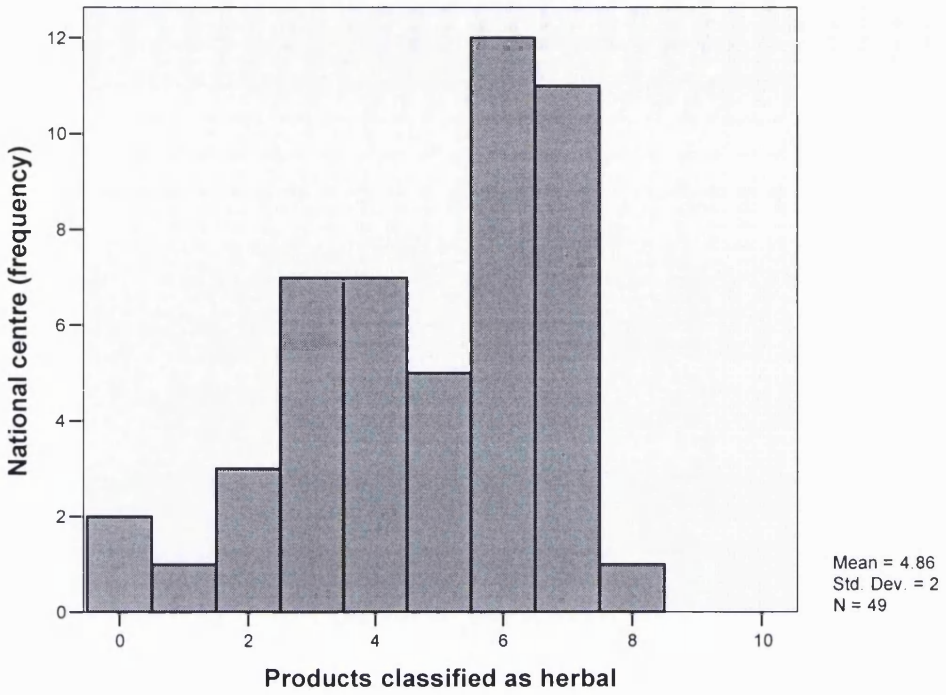


Figure 4.8 Histogram displaying the distribution for how many of the above 8 herbal products each national pharmacovigilance centre would classify as herbal

Table 4.7 and figure 4.9 show the majority of national centres classified the five non-herbal products as non-herbal in their scheme. In total, 18 national centres stated that their scheme would classify all five products as non-herbal.

Table 4.7 Classification of non-herbal products by national pharmacovigilance centres according to their definition for herbal medicines, n (%) †

Product	WHO definition (n=21)		Own definition (n=18)		No definition (n=20)	
	Herbal	Non-herbal	Herbal	Non-herbal	Herbal	Non-herbal
Animal product	1 (4.8)	12 (57.1)	3 (16.7)	5 (27.8)	1 (5.0)	12 (60.0)
Glucosamine	1 (4.8)	14 (66.7)	1 (5.6)	11 (61.1)	2 (10.0)	10 (50.0)
Melatonin	1 (4.8)	16 (76.2)	1 (5.6)	10 (55.6)	1 (5.0)	11 (55.0)
Minerals	0 (0)	19 (90.5)	0 (0)	12 (66.7)	2 (10.0)	11 (55.0)
Vitamins	18 (85.7)	1 (4.8)	10 (55.6)	2 (11.1)	13 (65.0)	1 (5.0)

† Percentages do not total 100 because of missing data

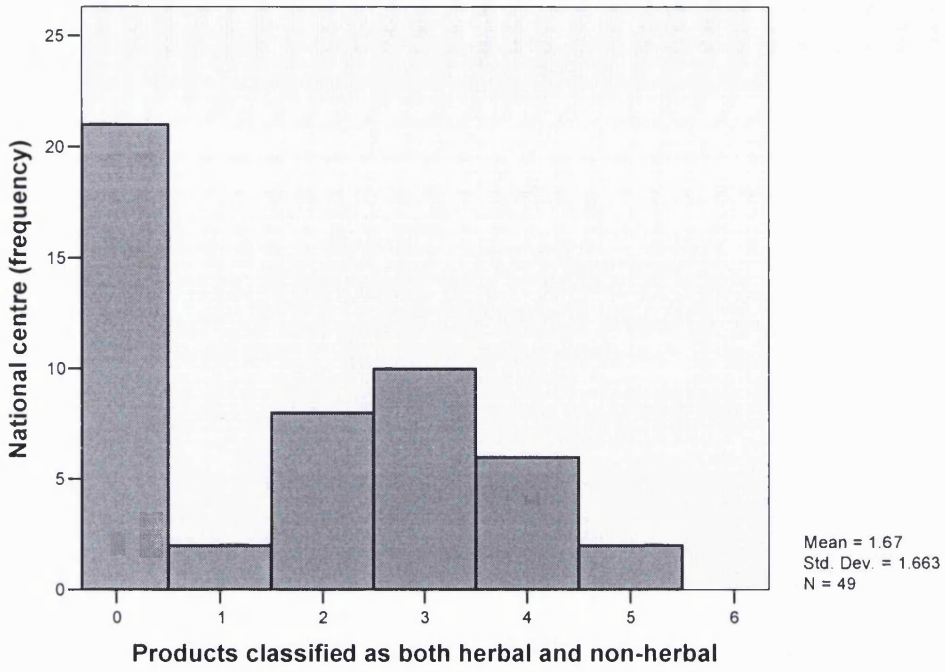


Figure 4.9 Histogram displaying the distribution for how many of the above 5 non-herbal products each national pharmacovigilance centre would classify as herbal

Table 4.8 shows that the majority of national centres classified Ayurvedic and traditional Chinese medicines as herbal and homeopathic remedies as non-herbal.

Table 4.8 Classification of products by national pharmacovigilance centres according to their definition for herbal medicines, n (%) †

Product	WHO definition (n=21)		Own definition (n=18)		No definition (n=20)	
	Herbal	Non-herbal	Herbal	Non-herbal	Herbal	Non-herbal
Ayurvedic remedies	7 (33.3)	2 (9.5)	6 (33.3)	3 (16.7)	5 (25.0)	2 (10.0)
Herb and mineral product	6 (28.6)	2 (9.5)	5 (27.8)	0 (0)	5 (25.0)	0 (0)
Herb and animal part product	6 (28.6)	2 (9.5)	4 (22.2)	1 (5.6)	3 (15.0)	1 (5.0)
Homeopathic remedies	2 (9.5)	8 (38.1)	3 (16.7)	7 (38.9)	4 (20.0)	8 (40.0)
Traditional Chinese medicines	9 (42.9)	1 (4.8)	3 (16.7)	2 (11)	6 (30.0)	1 (5.0)
† Percentages do not total 100 because of missing data						

The majority of national centres also stated that they would classify herb and mineral products

or herb and animal part products under both herbal and non-herbal. However, despite both Ayurvedic and traditional Chinese medicines often containing combination products of herbs and mineral and/or animal products few stated that they would include these types of preparations under both categories. Overall, only two national pharmacovigilance centres stated that they would classify all five types of products under both categories in their scheme. Figure 4.10 shows that few of the national centres would classify the above five types of products as both herbal and non-herbal under their scheme.

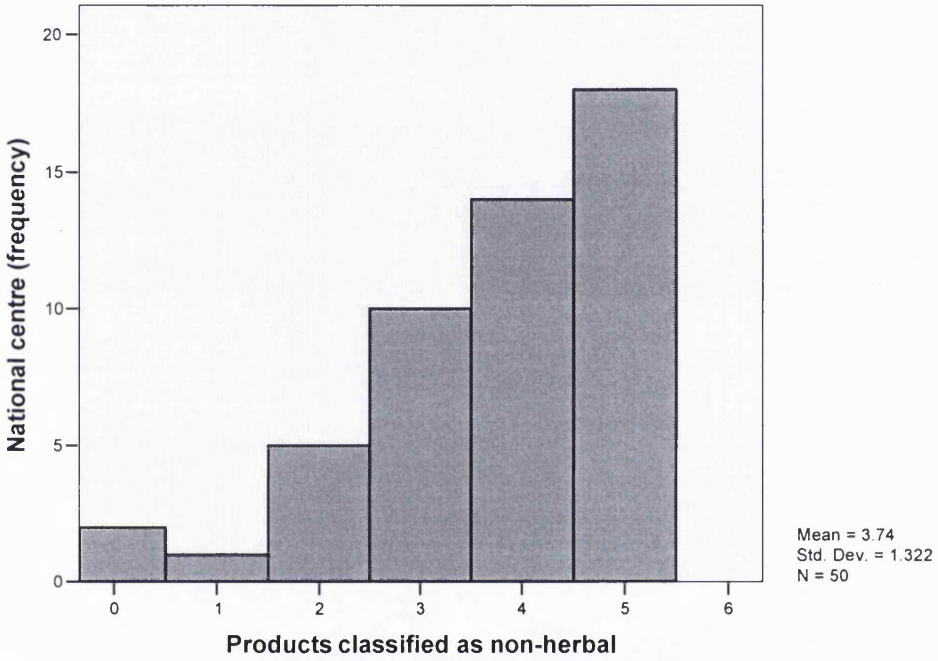


Figure 4.10 Histogram displaying the distribution for how many of the above 5 types of products each national pharmacovigilance centre would classify as herbal

Overall, there was little difference between the classification of the above 18 products and which type of definition the national centre used for herbal medicines.

4.4.3.7 Other terms used to define herbal medicines

In total, 30 national centres reported using other terms to refer to/describe herbal medicines. Figure 4.11 shows the different terms used by these national centres.

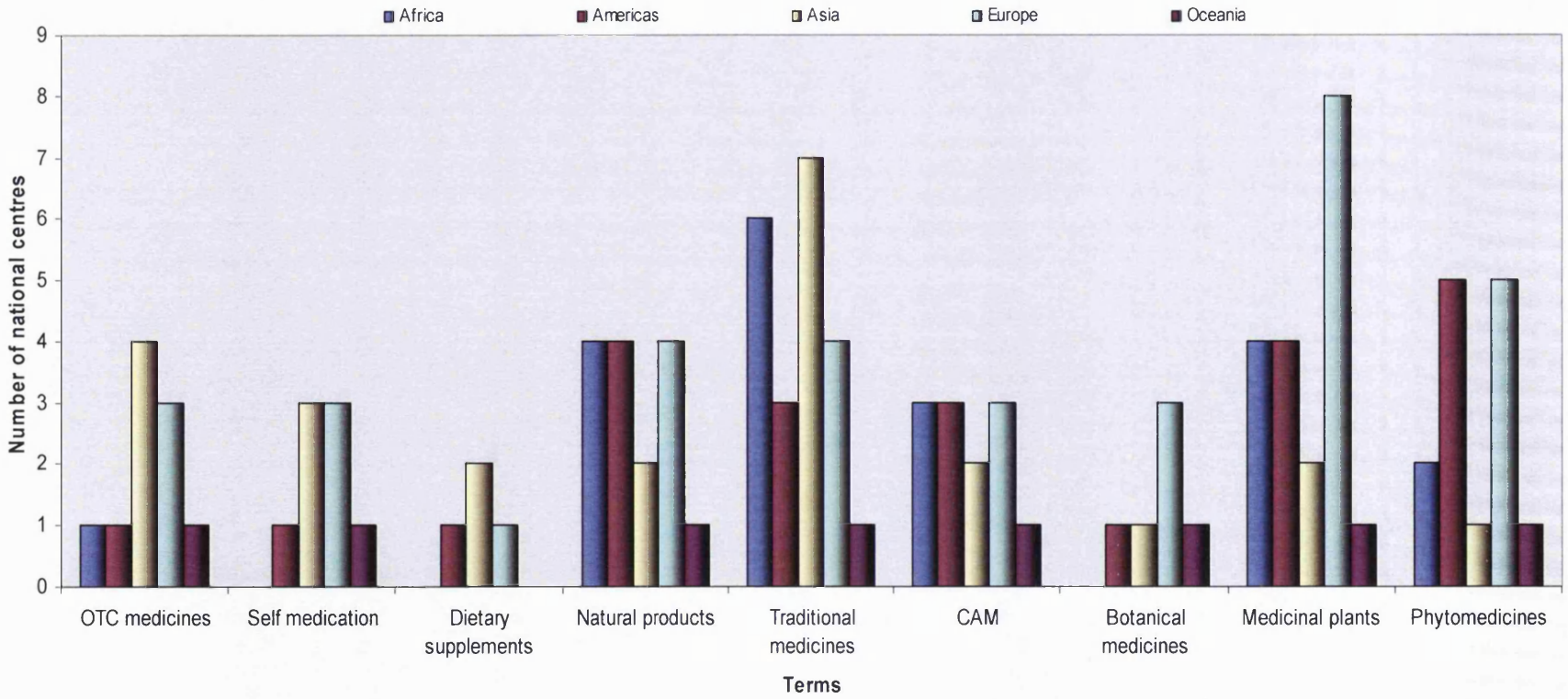


Figure 4.11 Other terms used to refer to/describe herbal medicines according to world region

The term medicinal plants, was most popular with European countries whilst term traditional medicines was popular within Asian and African countries.

4.4.3.8 Official reporter groups to the scheme

Table 4.9 and figure 4.12 show that the majority of national centres have a system of voluntary reporting rather than a mandatory system. The exception to this is for manufacturers of licensed products, where the majority of national centres have a mandatory system.

Table 4.9 Official reporter groups included in the scheme n=62

Reporter group		Reporter Status n (%)			
		Mandatory/ compulsory	**Voluntary**	**Pilot**	**Not a recognised reporter**
Medical doctors	GPs/family physicians	18 (29.0)	37 (59.7)	2 (3.2)	0 (0)
	Hospital physicians	20 (32.3)	36 (58.1)	3 (4.8)	0 (0)
Community pharmacists		13 (21.0)	38 (61.3)	4 (6.5)	3 (4.8)
Hospital pharmacists		15 (24.2)	37 (59.7)	3 (4.8)	3 (4.8)
Nurses/Midwives		9 (14.5)	36 (58.1)	3 (4.8)	8 (12.9)
Patients/Public/Consumers		0 (0)	20 (32.3)	5 (8.1)	29 (46.8)
Herbal-medicine practitioners	Statutory regulated	1 (1.6)	17 (27.4)	5 (8.1)	25 (40.3)
	Non-statutory regulated	0 (0)	20 (32.2)	2 (3.2)	24 (38.7)
Other CAM practitioners	Statutory regulated	2 (3.2)	18 (29.0)	5 (8.1)	23 (37.1)
	Non-statutory regulated	0 (0)	20 (32.3)	1 (1.6)	24 (38.7)
Manufacturers/ industry	Licensed products	32 (51.6)	20 (32.3)	2 (3.2)	5 (8.1)
	Unlicensed products	7 (11.3)	18 (29.0)	0 (0)	13 (21.0)
Other *e.g.* dentists, coroners		6 (9.7)	2 (3.2)	0 (0)	0 (0)

† Percentages do not total 100 because of missing data

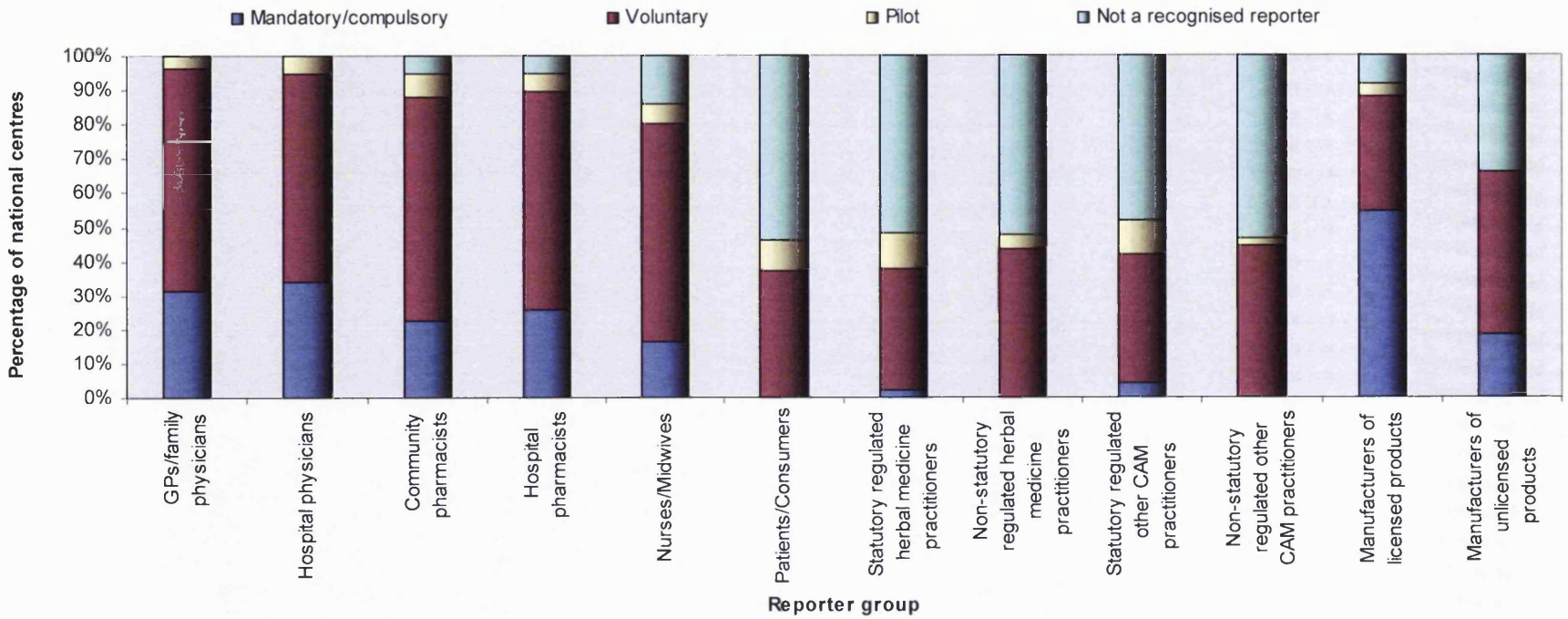


Figure 4.12 Status of reporter groups of official member countries of the WHO-UMC programme

Figure 4.12 also shows that a high proportion of member countries do not recognise patients or CAM practitioners as reporter groups, despite both groups being highlighted by the WHO (2004) as important sources for ADR reporting.

Of the 55 national centres that accept spontaneous ADR reports for herbal medicines, 16 (29.1%) specifically encourage certain reporter groups to report spontaneous ADRs associated with herbal medicines (table 4.10).

Table 4.10 Reporter groups specifically encouraged to report spontaneous ADRs associated with herbal medicines

Country	Reporter groups
Canada	Herbal-medicine practitioners, CAM practitioners, medical doctors, pharmacists
Fiji	All healthcare professionals
Ghana	Herbalists, physicians, pharmacists, nurses, patients
India	Health professionals
Indonesia	All healthcare professionals
Israel	Medical doctors, pharmacists
Malaysia	Health professionals, pharmacists
Malta	Doctors, pharmacists, dentists
Norway	Doctors, planning pharmacists from 2005
Oman	Hospital doctors, pharmacists and nurses
Switzerland	Traditional Asian medicine, homeopathic specialists
Tanzania	Doctors and pharmacist
Thailand	Community and hospital pharmacists
United Kingdom	All groups – community pharmacists
Uruguay	Medical doctors, nurses, pharmacists, consumers and herbal practitioners
Zimbabwe	All

4.4.3.9 Herbal pharmacovigilance activities of national pharmacovigilance centres

Figure 4.13 shows that the majority of national centres function as a single national centre. The two other organisational structures relate to Brazil and Mozambique. Brazil's national pharmacovigilance unit consists of a national centre, regional centres and a hospital network and Mozambique collaborates with its national disease control programme.

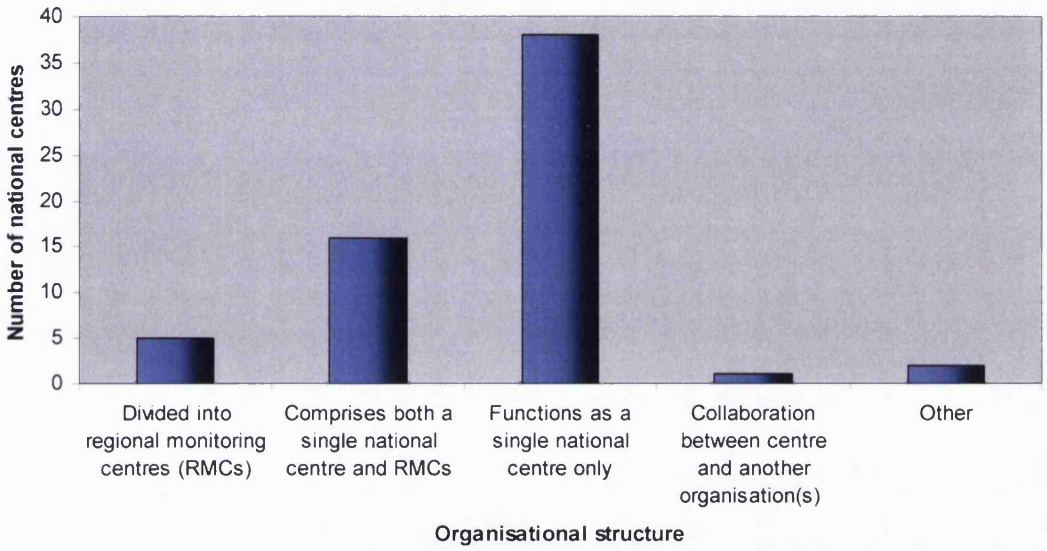


Figure 4.13 Organisational structure of national spontaneous ADR reporting schemes

Of the 22 countries stating they have regional monitoring centres, 20 provided further details. Figure 4.14 shows the distribution for the number of regional monitoring centre. The mode number of regional monitoring centres *per* country was 4 (range 3-31).

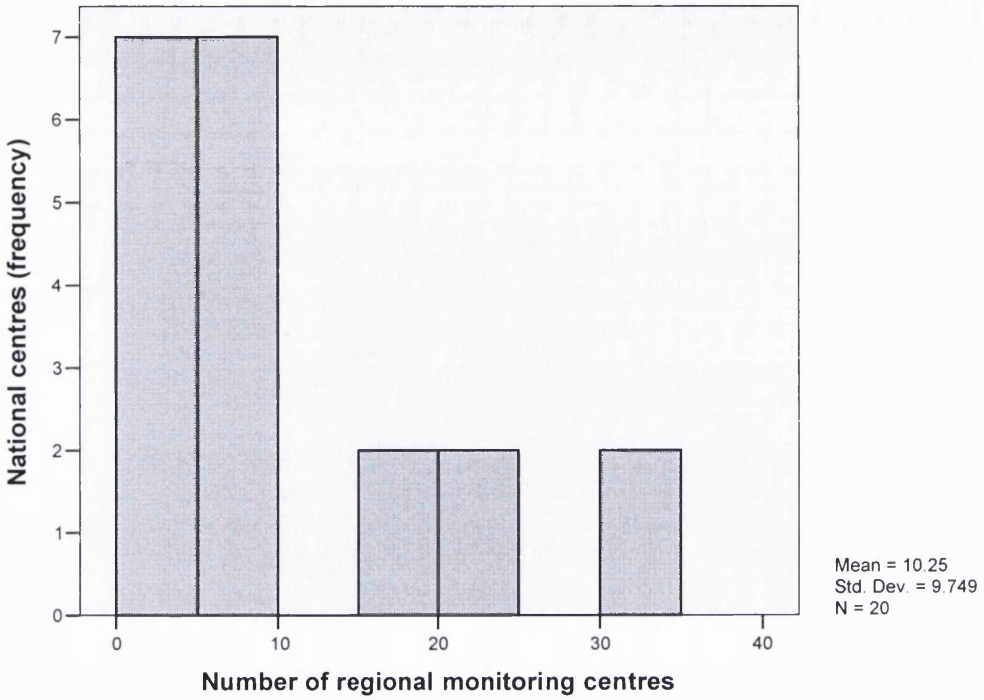


Figure 4.14 Histogram of the number of regional monitoring centre (n=20)

Of these 20 national centres, one (Switzerland) reported having a regional monitoring centre with a special focus on herbal medicines.

4.4.3.10 Management of reports

The management of ADR reports associated with herbal medicines was compared with those received for conventional medicines. Figures 4.15 and 4.16 show that there was little difference in the submission method and feedback provided for conventional and herbal ADR reports.

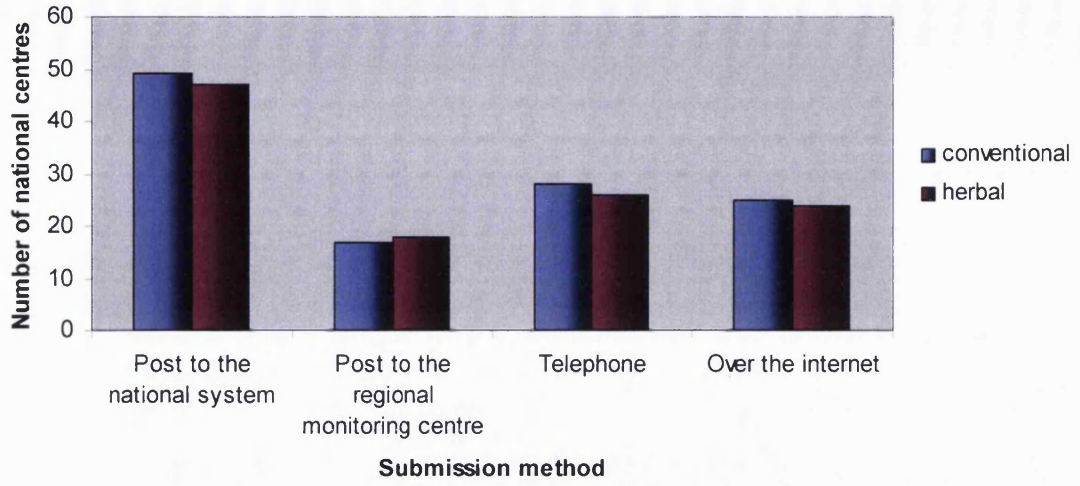


Figure 4.15 Submission methods for a spontaneous ADR report

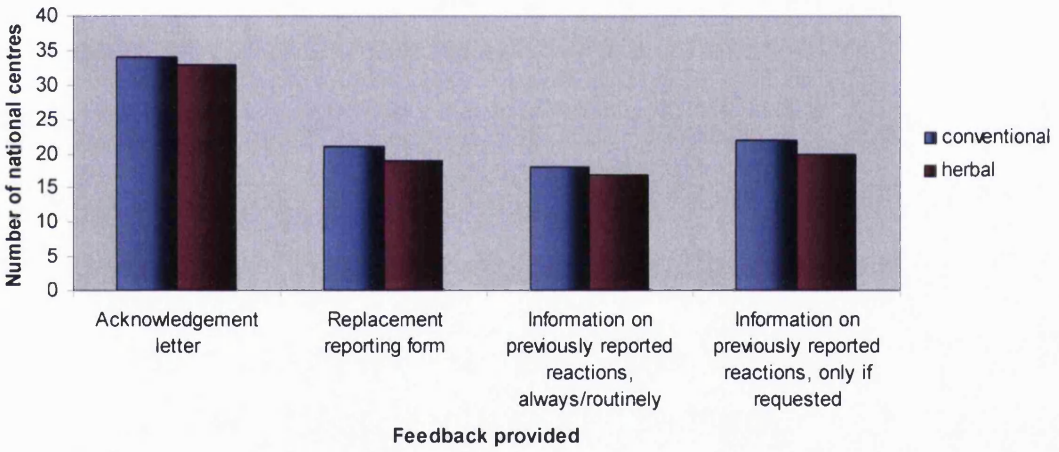


Figure 4.16 Feedback provided by national centre to the reporter for a submitted spontaneous ADR report

There was no statistically significant difference in either the method of submitting a report or feedback provided between conventional and herbal medicines (p=0.19 and 0.69, respectively; Wilcoxon signed rank test for two related samples).

4.4.3.11 Number of reports submitted

Table 4.11 shows the number of ADR reports received for both conventional and herbal medicines. Of the 55 national centres accepting ADR reports for herbal medicines there was a statistically significantly higher number of reports submitted for conventional medicines over herbal medicines (p=0.00; Wilcoxon signed rank test for two related sample).

Table 4.11 Number of spontaneous ADR reports received

		N		Median	Range	Percentiles	
		Valid	Missing			25	75
Total number of spontaneous ADR reports received since scheme first begun	Conventional	35	20	3918.00	2-162466	300.00	25600.00
	Herbal	23	32	5.00	0-1696	.00	240.00
Total number of spontaneous ADR reports received in 2003	Conventional	41	14	646.00	0-105509	68.50	2482.50
	Herbal	30	25	3.50	0-457	.00	33.50

Figures 4.17 and 4.18 show the distribution of the number of reports received for conventional and herbal medicines respectively. It is evident that there are certain countries that are more active in receiving spontaneous ADR reports than others. There was a statistically significant increase in the total number of spontaneous ADR reports received for both conventional and herbal medicines since the scheme first began and between the number of years as a member of the WHO-UMC programme (p=0.04 and p=0.00, respectively; Kruskal Wallis Test). This was also consistent with the findings for the total number of spontaneous ADR reports submitted for both conventional and herbal medicines in 2003 (p=0.00 for both; Kruskal Wallis Test) *i.e.* the older member countries (>31 years) submitted a higher proportion of spontaneous ADR reports.

Figure 4.19 shows that the majority of national centres considered that the data items stated below were essential for the assessment of a spontaneous ADR report associated with a herbal medicine however, few national centres were able to search these fields on their database.

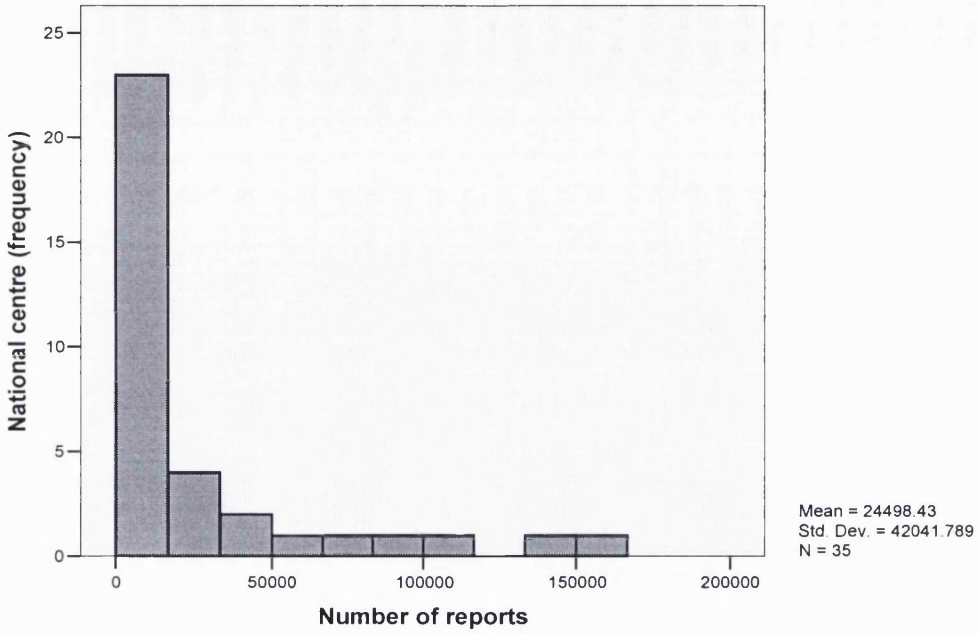


Figure 4.17 Total number of spontaneous ADR reports received since scheme first began for conventional medicines

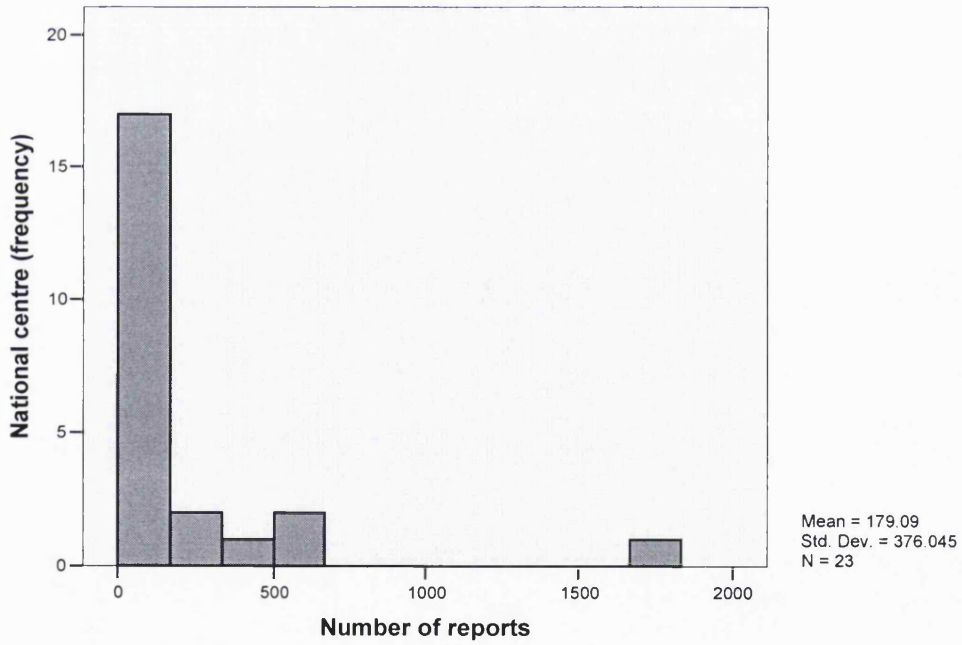


Figure 4.18 Total number of spontaneous ADR reports received since scheme first began for herbal medicines

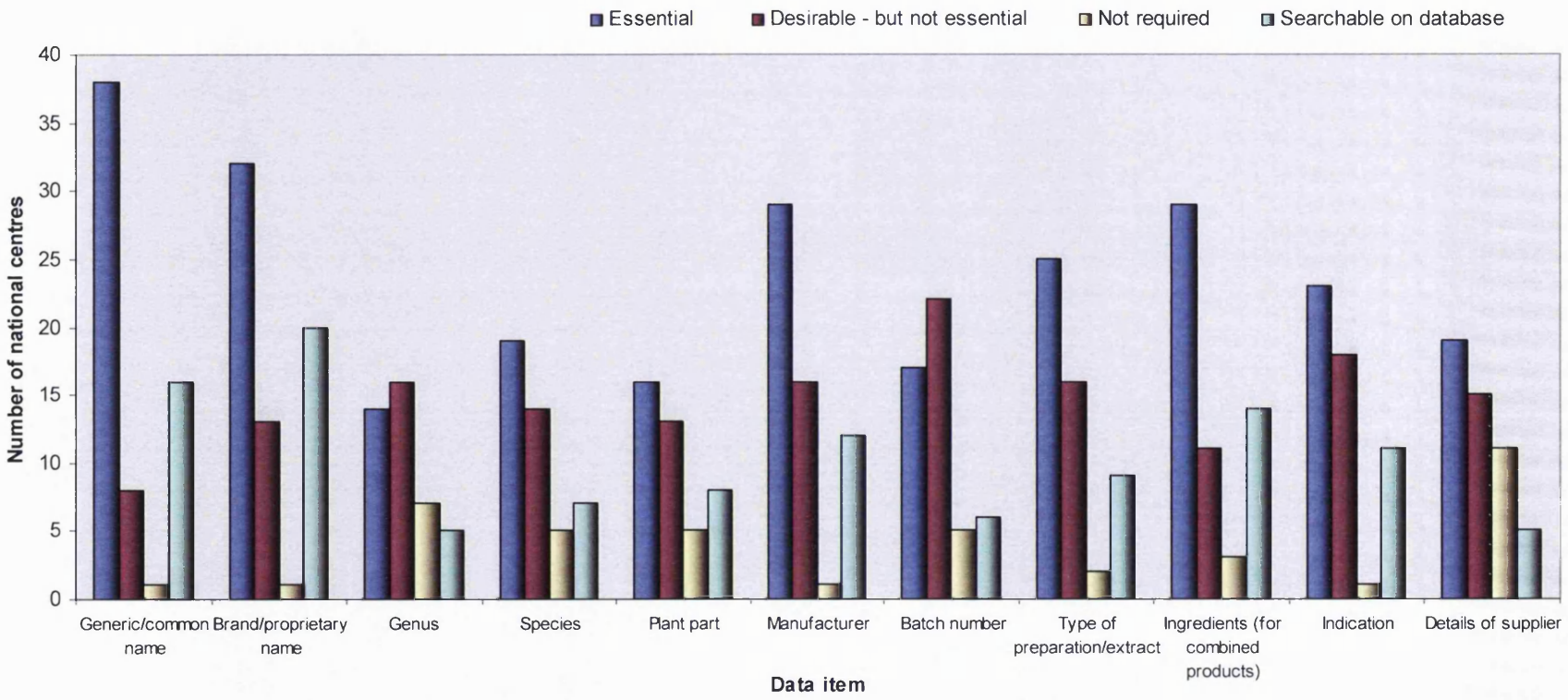


Figure 4.19 Data items on herbal medicines considered to be required for assessment of an ADR report

Figure 4.20 also shows that there is no marked difference between the screening method (manual and automated) used for both herbal and conventional medicines, which is consistent with the above findings.

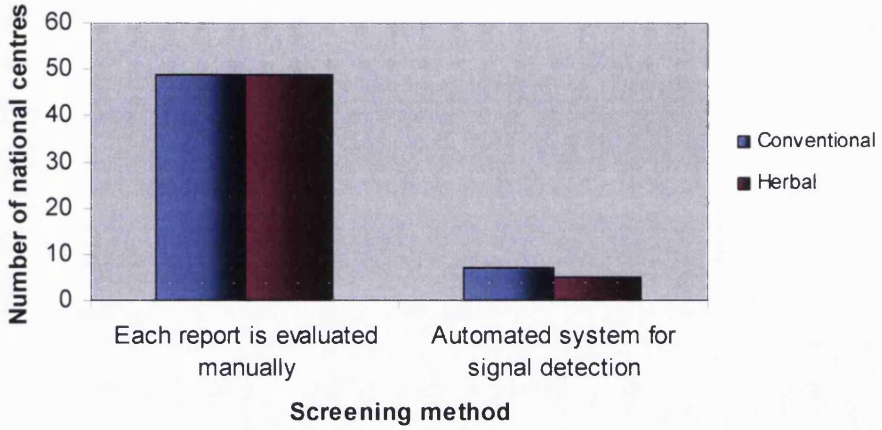


Figure 4.20 Screening method used for herbal and conventional medicines

4.4.3.12 Herbal safety concerns/signals

In total 20 national centres stated that they had detected signals of safety concerns associated with herbal medicines and 34 had received information on herbal safety signals detected elsewhere. Table 4.12 shows that kava kava and St John's wort were the most commonly detected herbal safety signals reported.

Table 4.12 Commonly detected herbal safety signals reported by each national centre

Herb	Frequency (% of total; n=77)
Kava kava (*Piper methysticum*)	20 (26)
St John's wort (*Hypericum perforatum*)	15 (19)
Aristolochia (*Aristolochia* species)	5 (6)
Ephedra (*Ephedra* species)	3 (4)

Figure 4.21 shows that the most commonly reported method used by national pharmacovigilance centres to communicate information on safety concerns to relevant groups was *via* direct national safety warnings and more specifically to recognised reporters.

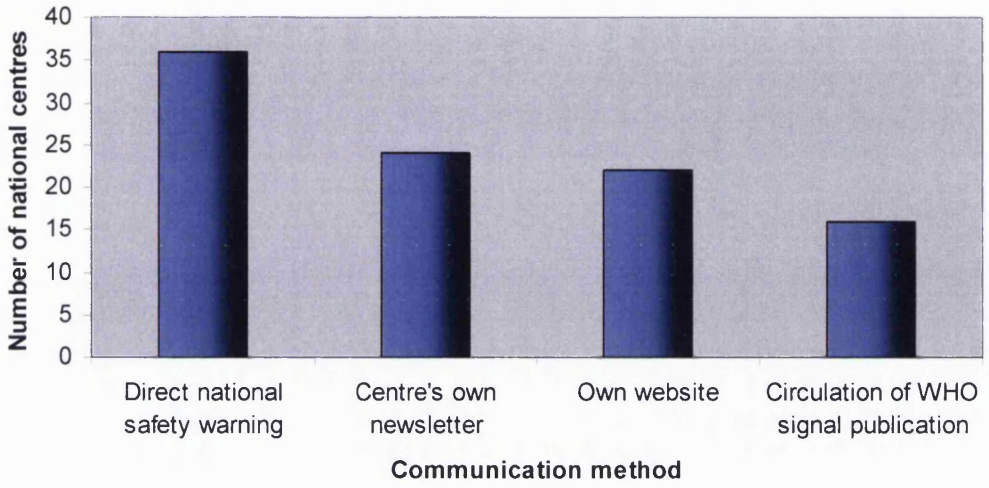


Figure 4.21 Methods used to communicate information on safety concerns to relevant groups

4.4.3.13 Views of respondents on spontaneous reporting for herbal medicines

Table 4.13 shows the respondent views on the spontaneous reporting for herbal medicines. In response to statements regarding herbal ADR reporting, the majority of respondents agreed/strongly agreed that their current ADR reporting form needs modifying in order to effectively collect data on suspected ADRs associated with herbal medicines. The majority of respondents (55%) disagreed/strongly disagreed with the statement that there should be a separate ADR reporting scheme for herbal medicines. This finding supports the proposal of a modified yellow card to effectively collect data on ADRs associated with herbal medicines (see phase 2 section 4.5).

Table 4.13 Views of respondents on spontaneous reporting for herbal medicines (n = 62), n (%) †			
Statement	**Agree/ strongly agree**	**Neutral**	**Disagree/ strongly disagree**
Your current ADR reporting form is suitable for collecting reports for suspected ADRs associated with herbal medicines.	34 (55%)	13 (21%)	13 (21%)
Your current ADR reporting form needs modifying to effectively collect data on suspected ADRs associated with herbal medicines.	35 (56%)	10 (16%)	12 (19%)
There should be a separate ADR reporting form for herbal medicines	15 (24%)	7 (11%)	34 (55%)
There should be a separate ADR reporting scheme for herbal medicines	11 (18%)	11 (18%)	34 (55%)
† Percentages do not total 100 because of missing data			

4.5 An exploration of a modified UK's yellow card

In phase one of this chapter, the current practices of national pharmacovigilance centres with respect to herbal medicines was explored. One of the key findings was that majority of the respondents (56%) strongly agreed or agreed that their current ADR reporting form needs modification in order to effectively collect data on suspected ADRs associated with herbal medicines.

It is not known if prompts for information on herbal and complementary medicines use on spontaneous reporting forms would encourage or improve reporting for these preparations. Currently the only emphasis for herbal medicines on the UK's yellow card is under the concomitant medication section, which was added in October 2000. The "suspected drug" section also only requests for the products brand name instead of the ingredient. For herbal preparations exempt from licensing under the Medicines Act section 12.2 (1968) it is not permissible for manufacturers to use a brand name (see section 1.5.5), thus it would be more appropriate to request for both the herbal ingredient name and brand (manufacturer/supplier/distributor).

Herbal ADRs also pose additional complications as the herbal constituent may vary significantly depending on a number of factors such as the genus, species, which part of the plant is used in the preparation, when the plant was harvested and how the plant was stored

(Barnes, 2002; Schilter *et al.*, 2003; Liang *et al.*, 2004). Thus, the genus, species, plant part, batch number and manufacturers details are essential for the identification and assigning of a herbal ADR. Coupled to this, a number of preparations contain multiple ingredients, making it difficult to determine which herb is responsible for the ADR or whether the ADR occurs as a result of a synergistic effect or an interaction with other medications. Therefore, more space is required on the yellow card to list each of the ingredients contained in the preparation. However, due to space limitations on the UK's yellow card, the inclusion of this information is restricted and is mainly presented on the guidance notes. Though the existence of separate reporting forms for different categories of medicines may lead to confusion amongst healthcare professionals and the public, in case of herbal medicines, if not a separate form then at least modification of the current form is warranted.

In recent years, there has been an international effort to harmonise the terms used to describe an ADR. Also the ICH has produced guidelines to harmonise the data elements required for the electronic transmission of ADRs (ICH, 2006). Together with this, the WHO-UMC programme pools data from over 70 countries in an agreed format (WHO, 2007). Despite this, information requested on individual national reporting forms varies substantially. Against this background, this study aims to explore the spontaneous reporting forms for ADRs and any accompanying guidelines used by national pharmacovigilance centres of the UMC programme.

4.5.1 Aim and objectives of phase 2

Chapter	Aim	Objectives	Method
4	To make recommendations for a modified UK's yellow card to effectively collect data on suspected ADRs associated with herbal medicines	1. To determine how many ADR forms and guidelines from national pharmacovigilance centres specifically mention the term herbal medicines 2. To identify all of the relevant data items required for an ADR associated with a herbal medicine. 3. To make recommendations for the design of a new yellow card that meets the need for collecting data on suspected ADRs associated with both conventional and herbal medicines	Data extraction

4.5.2 Method for phase 2

4.5.2.1 Procedure

All 84 eligible countries identified in phase 1 were also requested to provide a copy of their national ADR reporting form and any other relevant material (*e.g.* reporting guidelines) alongside their completed questionnaire.

4.5.2.2 Data Extraction from the ADR reporting forms and accompanying guidelines

Each ADR reporting form and any accompanying guidelines were translated into English (using contacts at the School of Pharmacy) and data extracted for background information on the scheme and more specifically to explore references to herbal medicines. Accuracy of the translations were confirmed using the WHO's online dictionaries.

Terminology accepted to act as a prompt for the reporting of herbal remedies included the following:

- OTC/self medication
- Alternative/complementary
- Natural health products
- Dietary supplements
- Traditional medicines
- Botanical/plant
- Phytotherapy
- Herbal medicines/remedies/products
- All other drug therapy

In each case the exact terminology used was recorded and further analysed.

4.5.3 Results for phase 2

4.5.3.1 Response rate

Of the 62 national centres that responded to the questionnaire 56 (90.3%) ADR reporting forms and one herbal ADR reporting form (from Congo) were received (see figure 4.22). Of these, 2 (Hungary and Lithuania) could not be translated and were excluded from further analysis (section 4.5.3.2, 4.5.3.3 and 4.5.3.4). In total, 4 (6.5%) centres reported having a separate ADR reporting form specifically for herbal medicines however, on closer inspection, one was in development (USA) and another one was run as a separate scheme (Italy). Regarding the guidelines, 46 respondents stated that they had guidelines available and in total 44 (95.7%) w ere obtained. Guidelines were also presented on 23 (41.1%) of the ADR reporting forms obtained.

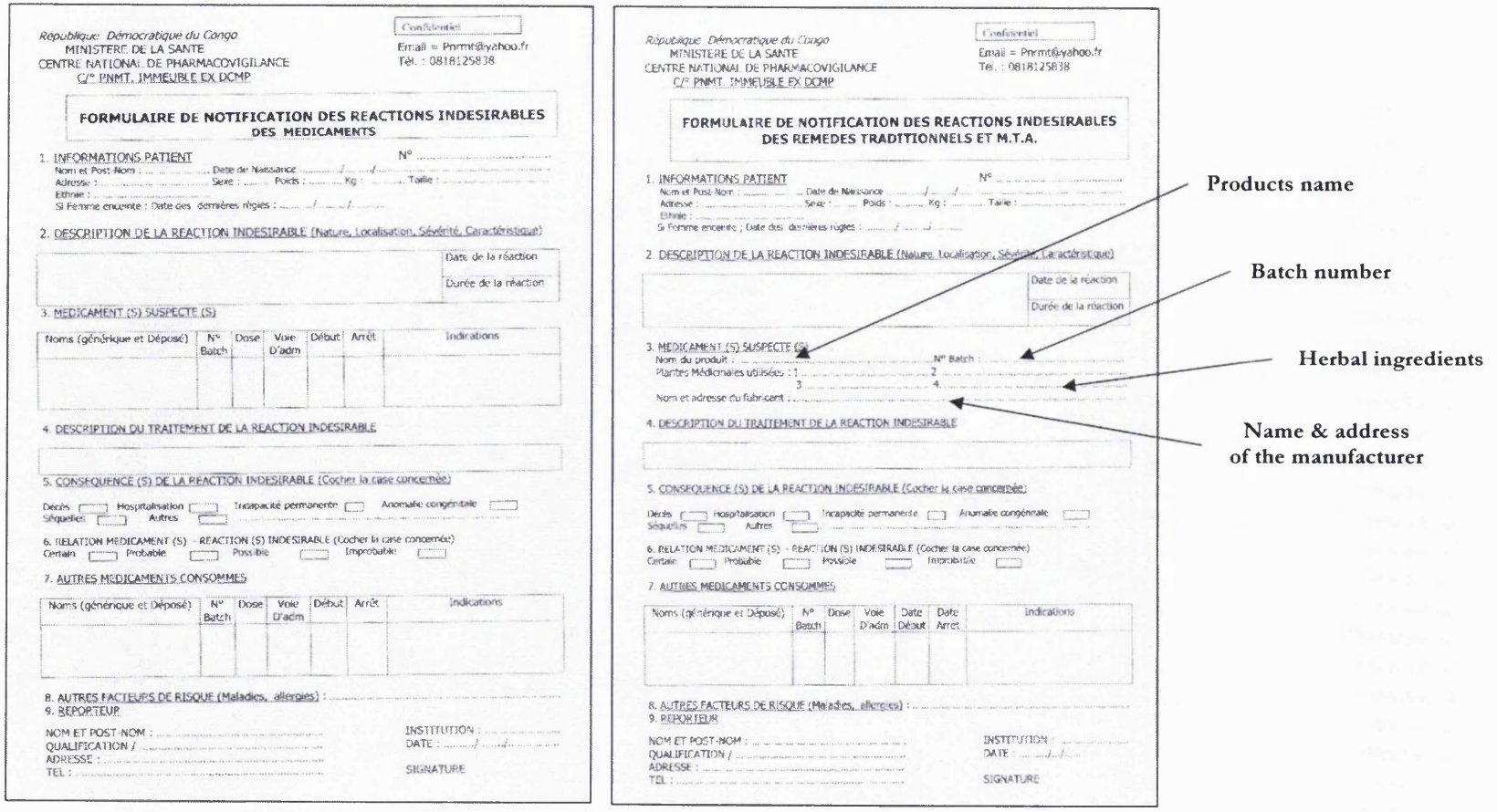


Figure 4.22 Congo's ADR reporting forms for conventional and for herbal medicines

4.5.3.2 Characteristics of ADR reporting forms

Table 4.14 shows that the majority of ADR reporting forms received were white (48.2%), a single A4 sheet in length (53.6%) or double A4 sheet in length (44.6%) and composed of both tick box and open ended questions (87.5%). Guidelines were also present on 42.9% of forms.

Table 4.14 Characteristics of ADR reporting forms (n=56)

Term		**Frequency n (%)**
Colour	White	27 (48.2)
	Yellow	25 (44.6)
	Blue	3 (5.4)
	Green	1 (1.8)
Length	A5	1 (1.8)
	A4	30 (53.6)
	2 *A4	25 (44.6)
Layout	Tick box questions only	0 (0)
	Open ended questions only	7 (12.5)
	Tick box and open ended questions	49 (87.5)
Guidelines	Yes	24 (42.9)
	No	32 (57.1)

Figure 4.23 shows that the majority of ADR reporting forms and accompanying guidelines were available from the national centre or on the internet.

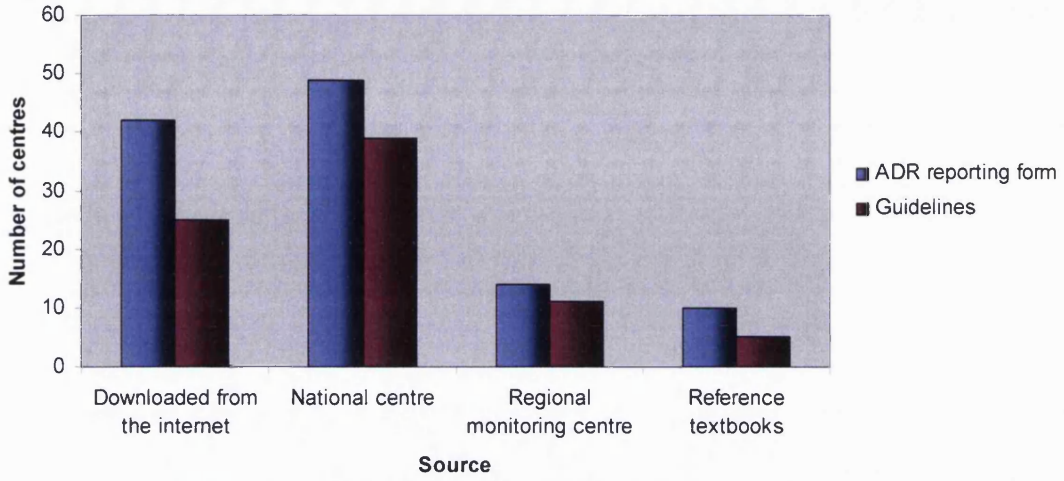


Figure 4.23 Availability of ADR reporting forms and guidelines

4.5.3.3 Data extraction of ADR reporting forms and guidelines

Of the 54 ADR reporting forms and 44 sets of guidelines obtained, 5 (9.3%) forms and 12 (27.3%) guidelines specifically mentioned the term herbal medicines. Table 4.15 provides details of the terms stated on both documents.

Table 4.15 Data extraction of ADR reporting forms and guidelines for terms that could refer to herbal medicines, n (%)

Term	Form (n=54)	Guidelines (n=44)
Alternative/complementary	2 (3.7)	7 (15.9)
Botanical/plant	0 (0)	0 (0)
Dietary/nutritional supplements	1 (1.9)	2 (4.5)
Herbal medicines/remedies/products	5 (9.3)	12 (27.3)
Natural health products	1 (1.9)	2 (4.5)
OTC/self medication	14 (25.9)	5 (11.4)
Phytotherapy	0 (0)	1 (2.3)
Traditional medicines	2 (3.7)	5 (11.4)
All other drug therapy	3 (5.6)	0 (0)
All terms	22 (40.7)	21 (47.7)

Figure 4.24 shows that the majority of the ADR reporting forms included the above terms within the concomitant medication section of the ADR reporting form.

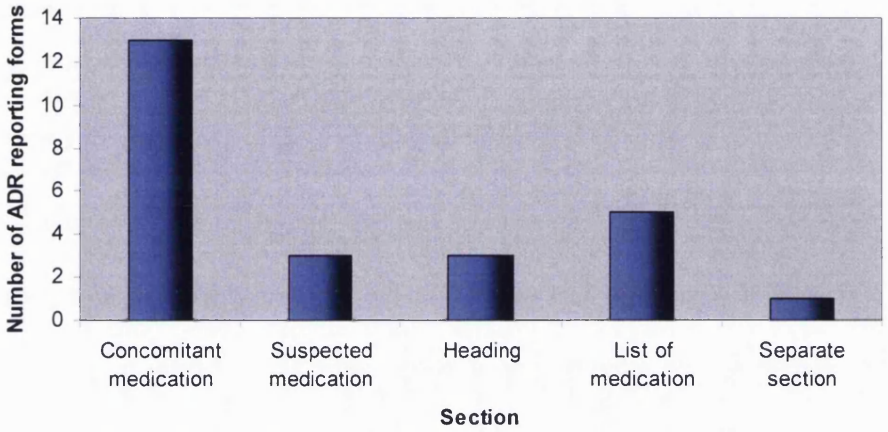


Figure 4.24 Appearance of terms that could refer to herbal medicines

4.5.3.4 Data fields on ADR reporting forms

Table 4.16 shows the frequency of data fields related to the patients demographics on the ADR reporting forms. Other data fields also included duration of side effect, country, nationality, allergies, medical history and reporter details.

Table 4.16 Frequency of data fields related to the patients demographics (n=54)			
Data field			**Frequency n (%)**
Patient demographics	Age		54 (100)
	Gender		53 (98.1)
	Ethnicity		12 (22.2)
	Weight		42 (77.8)
	Patient ID		33 (61.1)
	Other	Total	42 (77.8)
		Full name	20 (37.0)
		Address	8 (14.8)
		Height	8 (14.8)
		Hospital ID/treatment centre	14 (25.9)

Of the 54 ADR reporting forms received and translated, 17 (31.5%) grouped the suspected drug section with the concomitant drugs and asked to highlight the suspected drug with an asterisk. The majority (67%) provided an open box to write details of the suspected drug. Table 4.17 presents the specified data fields for the suspected drug. Other details specified included the strength, frequency, product registration number and source of product (*i.e.* self medication *etc*).

Table 4.17 Frequency of data fields related to the suspected drug (n=54)

Data field		**Frequency n (%)**
Suspected drug	Manufacturer	4 (7.4)
	Brand/proprietary name	10 (18.5)
	Generic/common name	4 (7.4)
	Batch number	5 (9.3)
	Formulation	5 (9.3)
	Indication	17 (31.5)
	Dose	16 (29.6)
	Route	15 (27.8)
	Date commenced	18 (33.3)
	Date stopped	18 (33.3)
	Rating of causality	2 (3.7)
	Other	4 (7.4)

Table 4.18 shows that the majority of the extracted data items on the suspected reaction, from forms collected from other countries are consistent with the UK's yellow card format. Other ADR reporting forms also included data items such as dechallenge/rechallenge (25.9%), laboratory data (14.8%), other risk factors (11.1%) such as an interaction, pregnancy, smoking *etc* and severity (7.4%).

Table 4.18 Frequency of data fields related to the suspected reaction (n=54)		
Data field		**Frequency n (%)**
Suspected reaction	Description of reaction	54 (100)
	Date reaction started	53 (98.1)
	Date reaction stopped	33 (61.1)
	Treatment received	26 (48.1)
	Outcome	51 (94.4)
	Rating of seriousness	48 (88.9)
	Other	28 (51.9)

Data for only the 37 ADR reporting forms with a separate concomitant section are reported in table 4.19. Other data items included frequency (10.8%), strength (10.8%) and a tick box to specify that no other preparations were taken (10.8%).

Table 4.19 Frequency of data fields related to the concomitant drugs (n=37)		
Data field		**Frequency n (%)**
Concomitant drugs	Manufacturer	2 (5.4)
	Brand/proprietary name	14 (37.8)
	Generic/common name	6 (16.2)
	Batch number	6 (16.2)
	Formulation	5 (13.5)
	Indication	26 (70.3)
	Dose	28 (75.7)
	Route	19 (51.4)
	Date commenced	32 (86.5)
	Date stopped	32 (86.5)
	Rating of causality	14 (37.8)
	Other	12 (32.4)

Similar to the "suspected drug" section, the majority (68.5%) of the "relevant additional information" section was an open ended box. Other details included if the manufacturers

were notified of the reaction, other risk factors (*e.g.* alcohol intake and smoking), hepatic and renal function and previous exposure to the drug.

Table 4.20 Frequency of data fields related to the relevant additional information (n=54)		
Data field		**Frequency n (%)**
Relevant additional information	Medical history	7 (13.0)
	Allergies	22 (40.7)
	Tests	15 (27.8)
	Pregnancy details	11 (20.4)
	Suspected drug interactions	3 (5.6)
	Rechallenge	9 (16.7)
	Outcome of rechallenge	8 (14.8)
	Outcome of dechallenge	9 (16.7)
	Other	24 (44.4)

4.6 Overall discussion

It is encouraging that there has been particular growth in the number of countries as official members of the WHO-UMC programme for international drug monitoring over the last 10 years, as most of them are developing countries and many people in such countries rely on medicinal plants as their main form of healthcare. However, from the findings in this chapter, it is evident that current practices of national pharmacovigilance centres towards reporting ADRs associated with herbal medicines vary even across members of the WHO-UMC programme. Although no studies to date have explored the pharmacovigilance practices of herbal medicines and it is not ideal to compare different studies, the findings reported here are consistent with the study by Hughes *et al.* (2002) as they found discrepancies in the general pharmacovigilance practices between different countries.

There are also clear differences in the pharmacovigilance practices between herbal and conventional medicines. For example, fewer national centres accepted ADR reports for herbal

medicines compared to conventional medicines. From a pharmacovigilance perspective the monitoring of herbal medicines should be the same as for conventional medicine. In fact as outlined in chapter 1 (sections 1.5.4 to 1.5.9), herbal medicines (particularly unlicensed herbal medicines) warrant the need for greater vigilance as there is limited data on their safety, efficacy and quality. However, even fewer national centres accepted reports for unlicensed herbal medicines compared to licensed herbal medicines. Though this finding is of concern, it is not surprising, as up until October 1996 the UK's yellow card scheme only accepted reports for licensed herbal medicines.

This chapter also highlights that "established" countries may not necessarily be further developed in terms of their regulatory or pharmacovigilance practices towards herbal medicines compared to less established countries. For example, there was also no statistically significant difference between the regulatory types of herbal medicines (licensed herbal medicines only, both licensed and unlicensed herbal medicines and unlicensed herbal medicines only) available in a country and the world region it was classified under, or the number of years the country had been an official member of the WHO-UMC programme. These findings are contrary to the assumption that European countries are likely to have a larger proportion of countries where all herbal medicines are licensed and that those countries that have been an official member country for a longer period are more likely to include reports for unlicensed herbal medicines.

As outlined in section 1.5.1 the definition of herbal medicines is critical to determine which products are included under this category. Findings from this study showed little difference between how each national centre classified 18 common products as herbal and non-herbal and which type of definition they used. However, it is evident from the different definitions for herbal medicines that they are open to interpretation, for example the WHO's (2002) definition adds that:

> "*....In some countries, herbal medicines may contain, by tradition, natural organic or inorganic active ingredients that are not of plant origin (e.g. animals and mineral materials)*"

Thus, those national centres using this definition would therefore be expected to classify mineral and animal products as herbal however, this was not the case. It is possible that inconsistencies occurred as certain products listed *e.g.* St John's wort may not have been available in some countries and thus they were unaware of how to classify them, which is a limitation of the study as the questionnaire was largely based on the UK's yellow card scheme. Also another potential shortfall of the survey method is that the response could reflect the respondent's knowledge rather than the organisation's practice. These inconsistencies in the classification of products raises concern on the ability to identify signals, as some may be overlooked due to them being incorrectly coded and highlights the need for a consistent definition for herbal medicines between member countries.

A number of countries used broader terms such as OTC, traditional, complementary/alternative and self medication to refer to herbal medicines. However, as observed within the UK, herbal medicines can span both conventional and alternative medicines and can be available on both prescription and OTC. Thus, potential signals could be missed *via* the incorrect classification of herbal medicines. The term medicinal plants, was most popular with European countries whilst the term traditional medicines was popular within Asian and African countries. This in part could be explained by local use, formulations available and the type of healthcare systems present in each country (*e.g.* traditional herbal practitioners *versus* conventional practitioners).

The majority of national centres have a system of voluntary reporting (excluding manufacturers of licensed products) and predominantly for established reporter groups such as GP's, pharmacists and nurses. As outlined in section 1.4 there is little evidence to suggest whether or not a mandatory system encourages reporting. Both Hughes *et al.* (2002) and Rabbur and Emmerton (2005) found that the majority of national centres operate on a voluntary basis and predominantly for healthcare professionals, which is consistent with the findings from this study. A number of national centres did include herbal medicine and other CAM practitioners as recognised reporters and there were several national centres piloting the extension of the scheme to these reporter groups, which is encouraging. Further work could

evaluate the contribution of these groups, particularly with respect to ADRs associated with herbal medicines.

In terms of specific reporter groups encouraged to report suspected ADRs associated with herbal medicines, the majority of national centres reported pharmacists to fulfill this role. Although within the UK, community pharmacists are specifically encouraged to report ADRs associated with herbal medicines, all reporter groups are also encouraged to do this. Hence both (all reporter groups and pharmacists) were reported in the questionnaire. This shows the susceptibility of questionnaires to the respondent's interpretation and the importance of phrasing the question correctly. Few national centres also carried out any further specific herbal pharmacovigilance activities, as there was only one regional monitoring centre that had a specific focus on herbal medicines and four that stated that they had a separate herbal ADR reporting form.

Overall there was little discrepancy between the management of ADR reports associated with herbal and conventional medicines. However, there was a large difference between the total number of ADR reports received for conventional and herbal medicines since the scheme first began, which indicates that there is either gross under reporting for herbal medicines or that there are few ADRs associated with herbal medicines. Given the nature of the ADRs associated with *St John's wort, Piper methysticum, Aristolochia* species and *Cimicifuga racemosa* the former can not be ruled out and the necessity to monitor all herbal medicines is maintained.

Both Hughes *et al.* (2002) and Rabbur and Emmerton (2005) also highlighted the increased use of the internet, which is also reflected by this study, as the majority of the national centres have an electronic format of their ADR reporting form available online and use the internet to communicate information on safety concerns to relevant groups.

All member countries receive a publication on signals generated from the WHO-UMC (Stahl *et al.*, 2003). The circulation of the WHO's signal publication was also outlined as a means to communicate information on safety concerns to relevant groups. Thus it is not surprising that

most member countries reported *Piper methysticum* and *Hypericum perforatum* as signals that they were aware of.

One of the key findings of phase one was that majority (56%) of the respondents strongly agreed or agreed that their current ADR reporting form is in need of modification in order to effectively collect data on suspected ADRs associated with herbal medicines. Data extraction of the national centres ADR reporting forms and accompanying guidelines (section 4.5.3.3) revealed that few specifically mentioned the term herbal medicines. However, a greater proportion mentioned broader terms such as OTC and self medication which could imply the use of herbal medicines.

Looking at the data items of ADR reporting forms, the majority of the data items presented on the UK's yellow card were also present on other national centre's ADR reporting forms, which is consistent with the findings from Hughes *et al.* (2002) as they reported that all 12 countries surveyed, requested for similar information on their ADR reporting forms. However, there were several data items for each section which could enhance the UK's yellow card for both conventional and herbal medicines without altering the card significantly. These are highlighted in table 4.21.

Table 4.21 Additional information that could enhance the UK's yellow card		
Section	**Data item**	**Justification**
Patient demographics	Height	This would allow for the patient's body mass index to be calculated and check if the dose taken by the patient was within a therapeutic range.
	Ethnicity	Different ethnic groups are known to react to medicines differently.
Suspected and concomitant drugs	List all drugs	Combining the suspected drug with the concomitant drug section and highlighting the suspected drug with an asterisk would allow greater space for other information without compromising the level of data required.
	Frequency	Needs to appear under the dosage as a number of medicines are taken more than once *per* day.
	Strength	As several strengths are available for the same preparation this information would be useful in assigning causality and determining the therapeutic dose required.
	Manufacturer	Aid in identifying the suspected product.
	Source of product	Valuable in identifying and if needed, the withdrawal of specific batches, particularly if adulteration or counterfeit products are suspected.
	Formulation	The bioavailability will vary according to the formulation thus further to this the ADR could be related to a specific formulation or due to a specific excipient.
	Severity	Though a reaction may not be serious, it can be classified as severe. A distinction between the two needs to be made.
Relevant additional information	Other risk factors	Tick box styled questions on smoking, alcohol, hepatic and renal function as these can impair the metabolism of the drug.
Separate section	Rechallenge/ dechallenge	Tick box styled questions to state if performed and then details of the outcome.
	Pregnancy	Although this appears in the "additional relevant information" section, this group forms an important care group in pharmacovigilance as limited data is available on the use of medicines within this group. Further details such as the trimester and date of last menstrual cycle could be requested using a tick box style question.

At the time of the study none of the national ADR reporting forms (excluding Congo's ADR reporting form for herbal medicines) included any specific data items relating to herbal medicines. Although one of the objectives of the study was to identify all of the relevant data items required for an ADR associated with a herbal medicine *via* the data extraction of all ADR reporting forms, this was only fully achieved for general data items. However, the majority of national centres considered the following herbal data items as essential/desirable for the assessment of a suspected ADR report associated with a herbal medicine:

- Manufacturer
- Ingredients
- Common/generic name
- Species
- Genus
- Plant part used in the preparation
- Type of preparation/extract

Further to this, the herbal ADR reporting form from Congo and the WHO's template of a model ADR reporting form (see appendix 1) both request the active ingredients and manufacturer's name, which supports that these data items would aid in the collection of suspected ADRs associated with herbal medicines. In addition both the RCHM's and NIMH's ADR reporting forms also request for specific details on the herbal medicine (see appendix 1). For example, the RCHM's ADR reporting form requests for a list of ingredients for the suspected herbal medicine or the brand name and the NIMH's ADR reporting form requests for details such as the full name of the herb or the brand name. It is likely that space limitations prohibit the inclusion of these details on the UK's yellow card. Also, it would not be ideal to radically change the current UK's yellow ADR reporting form and it is widely known that lengthy questionnaires can deter responses. The additional information required for herbal medicines presents a fine line between seeking sufficient evidence to establish causality and deterring healthcare professionals from reporting. Visually comparing the RCHM's ADR reporting form with the UK's yellow card, the RCHM's 3-page form appears to request more detailed information, although they contain similar questions. These additional

details could be included in the guidelines, yet the majority of accompanying guidelines (52.3%) failed to even mention any broad terms related to herbal medicines.

The investigation into the national ADR reporting forms highlighted the susceptibility of the UK's yellow card. For example, if no other drugs were being taken concomitantly by the patient or if no other information is available on the case, it is important that reporters state this, otherwise the pharmacovigilance centre can not rule out the possibility that the ADR resulted from another drug or through a possible drug interaction. However, there is no prompt for this on the UK's yellow card. Another example is that the dates as to when the reaction appeared relative to the time when the drug was administered should be spatially correct in order to establish the causality of the ADR, however in practice, the submission of a report containing incorrect information would not be identified, which highlights the susceptibility of the scheme.

Additional cards (see table 4.22) were obtained from the internet, though these were excluded from the main analysis as they were collected at a different time point to the questionnaire and the internet could not be relied upon providing the most up-to date version of the ADR reporting forms. Also, it was deemed inappropriate to use these additional ADr reporting forms in the analysis, as this was beyond the original study protocol. All additional cards consisted of tick box and open ended questions, with the majority (n=4) consisting of two A4 pages and containing some guidance on the form. None of the ADR forms specifically mentioned the specific term herbal medicines, however, under the other medicines section, 2 forms mentioned a broader term that could include herbal medicines.

Table 4.22 Additional ADR reporting forms

Card obtained	Argentina, Armenia, Austria, Germany, Singapore
Unable to translate card	Belgium, China, Croatia, Guatemala, Iceland, Slovakia
Unobtainable	Belarus, Colombia, Eqypt, Iran, Jordan, Macedonia, Moldova, Pakistan, Romania, Russia, Tunisia, Turkey, Venezuela, Vietnam, Zambia

The findings from this chapter indicate that there is a need for the UK's yellow card to be modified and extra data items, such as those highlighted in table 4.21, to be included. It could be argued that if all herbal medicines were regulated to the same degree as conventional medicines, that these additional details would not be required and simply the products batch number and brand name would be sufficient to identify the product, which could explain the reason as to why the German national ADR reporting form does not specifically mention the term herbal medicines on their ADR reporting form. Thus, with the implementation of the new directive on traditional herbal medicinal products it is possible that these additional pharmacovigilance challenges posed by herbal medicines will be minimised however, this remains to be established.

4.6.1 Limitations of the study

Although the study achieved a high response rate and there were no statistical differences in the characteristics between respondents and non-respondents, there were a couple of countries (*e.g.* Germany) who are known to be active in herbal pharmacovigilance that did not reply. Also due to language barriers, two ADR reporting forms were unable to be translated (Lithuania and Hungary) and were thus excluded from further analysis. For those national centres who responded, certain questions may have been misinterpreted as the questionnaire was only available in English.

4.6.2 Further work

Despite the above limitations it would be interesting to repeat the study after a set interval to see developments in national pharmacovigilance practices towards herbal medicines particularly in view of the release of the WHO guidelines on the pharmacovigilance of herbal medicines (2004) and with the implementation of the new European directive on traditional herbal medicines.

Results from this chapter have led to proposals for a modified yellow card for herbal medicines. The effectiveness of these modifications should be evaluated possibly by conducting a randomised control trial where one group receives the modified card and the other receives the current yellow card. Both groups could then be requested to complete the form according to a vignette and the quality of the reports could be assessed to see if there are any differences.

4.7 Overall conclusion

Current practices of national pharmacovigilance centres towards reporting ADRs associated with herbal medicines vary even across members of the WHO-UMC programme. Few national centres undertake activities specifically to encourage reporting of suspected ADRs associated with herbal medicines. Inconsistencies in classifying herbal products were evident between national centres and were shown to be independent of the centres' definition for herbal medicines. Few ADR forms and guidelines specifically mentioned the term herbal medicines. However, there is support from national pharmacovigilance centres for modifying existing ADR reporting forms to improve the collection of information on herbal medicines.

Even for conventional medicines there are deficiencies in the UK's yellow card which have been identified from the research conducted in this chapter. Specific proposals for the modification to the UK's yellow card to effectively collect ADRs associated with herbal medicines included:

- Brand/supplier/distributor/manufacturer of the herbal medicinal product
- Active ingredients in the product
- Common/generic name of the herb
- Type of preparation/extract
- Species, genus and plant part used in the preparation

The need for modification of ADR reporting forms is recognised by national centres and the above data items have been identified as essential/desirable for the assessment of herbal ADR

reports. These extra data items could thus add value to the UK's yellow card in terms of the quality and numbers of herbal ADR reports submitted. However, the effectiveness of such modifications should be evaluated.

Chapter 5

EVALUATION OF COMMUNITY PHARMACISTS' EXPERIENCES WITH AND VIEWS ON HERBAL MEDICINES

5.1 Background

Previous work has shown that the majority of all sales of herbal medicines are made from pharmacies and that community pharmacists are routinely asked for advice on their use (Barnes and Abbot, 1999). Thus, community pharmacists are in an ideal position to advise patients/consumers, monitor usage, identify and report herbal ADRs, which was the main reason for the inclusion of community pharmacists as official reporters to the UK's yellow card scheme in 1999. Chapter 4, has also identified that pharmacists as a specific reporter group are encouraged to report suspected ADRs associated with herbal medicines, by the majority of national pharmacovigilance centres, which provides further evidence of their importance in this area.

Community pharmacists still continue to submit low numbers of suspected ADR reports to the MHRA for which they have received wide criticism (Barnes and Abbot, 1999; Chang *et al.*, 2000; Cox, 2002). To date, no studies have specifically looked into the reasons for the low uptake of the yellow card scheme or in particular the low level of reporting of ADRs associated with herbal medicines by community pharmacists. Previous studies do suggest a lack of knowledge and understanding of the yellow card system (Houghton *et al.*, 1999; Barnes, 2001), particularly regarding the necessity to report suspected ADRs associated with herbal medicines (Green *et al.*, 1999a) and the inclusion of unlicensed herbal medicines in the yellow card reporting scheme (Wingfield *et al.*, 2002). Previous work has also shown that pharmacists receive insufficient training in herbal medicines (Quinn and Waterman, 1997) and that there is a disparity in levels of teaching of pharmacovigilance at schools of pharmacy (Cox *et al.*, 2004) which may contribute to low reporting.

Thus, as community pharmacies continue to sell and offer advice on herbal medicines there is a need to establish the types of questions community pharmacists are asked and the pharmacists' ability to answer them using appropriate information sources and based on training received as part of the undergraduate curriculum and as a qualified pharmacist. Further work is also required to determine issues that are of concern and importance to community pharmacists and their perceptions, attitudes, training and knowledge with respect to herbal medicines.

5.2 Overall chapter aim and objectives

The diagram below summarises the aims and objectives in this chapter:

Aim	Objectives	Method
To explore community pharmacists' experiences with and views on herbal medicines	1. To determine community pharmacists' experiences with and views on herbal medicines 2. To explore and understand the descriptive qualitative data generated 3. To validate the findings of the qualitative data through a quantitative approach	Focus groups Cross-sectional survey

5.3 Research approach

In order to meet the aims and objectives, this chapter is divided into two phases:

Research question		Phase		Approach
What are community pharmacists' experiences with and views on herbal medicines?	→	1	→	Focus groups of community pharmacists
	→	2	→	National survey of community pharmacists

The results for these two phases are presented separately (section 5.4.3 and 5.5.3) and discussed together (section 5.6) in line with the original aims and objectives.

5.4 Focus groups of community pharmacists

The protocol, themes for discussion, recruitment of pharmacies and the focus group sessions were developed and conducted by JB. The subsequent, data checks and analysis were conducted by AMA during the first phases of the doctorate training.

5.4.1 Aim and objectives of phase 1

Aim	Objectives	Method
To explore community pharmacists' experiences with and views on herbal medicines, using qualitative techniques	1. To identify issues relating to herbal medicines that are of concern/importance to community pharmacists 2. To explore pharmacists' attitudes, perceptions and knowledge with regard to various aspects of herbal medicines 3. To analyse qualitative data on which to base the design of a questionnaire to explore these areas in a quantitative study	Focus groups and content analysis

5.4.2 Method for phase 1

As outlined in section 3.3.2 focus groups are ideal for the collection of indepth data. However, due to the lower credibility often associated with qualitative data, this method was employed in the preliminary phase to identify key themes and then utilised to form the basis for further investigation (phase 2).

5.4.2.1 Themes for discussion

Based on published research and opinion on issues relating to community pharmacists and herbal medicines, a list of topical issues and themes were created for discussion at the focus groups. The list was circulated to individuals working in the field for their comments and input. Topics included the definition of herbal medicines, training and knowledge of pharmacists on herbal medicines, the professional role of pharmacists including their perceived role in ADR reporting of herbal medicines and lastly the perceptions and attitudes of pharmacists and consumers towards herbal medicines – all of which were thought to impact on the role of the community pharmacists. A finalised topic guide can be found in appendix 3.

5.4.2.2 Recruitment of pharmacists to the focus group

A letter describing the study was sent to the pharmacist proprietor/superintendent pharmacist of each pharmacy listed in the RPSGB Register of Pharmaceutical Chemists 2002. All recipients of the letter were asked to complete and return a short form indicating their willingness to participate. The form also included brief questions on the type of pharmacy they worked for, its local setting and some personal details about the pharmacist, such as their age and number of years as a registered pharmacist.

From the respondents, 50 pharmacists were selected based on the type of pharmacy they worked for. They were invited to attend an evening focus group session on a specific date. Pharmacists working in particular types of pharmacy (*e.g.* chain store) were grouped together. The last focus group session was a 'catch-all' session which included pharmacists whose views may not have been represented in the other groups, for example: locum pharmacists, practising academics, pharmacists working in specialist complementary medicine pharmacies; and pharmacists who were strongly opposed to herbal medicines.

All attendants were given a copy of the second edition of the reference text *Herbal Medicines; A guide for health-care professionals* (Barnes *et al., 2002)* as a token of appreciation.

5.4.2.3 Focus group sessions

The location and venue are known to influence discussions and therefore, it is vital that an appropriate and 'sympathetic' social environment is provided (Smith, 2002). For this study, the topic was not considered sensitive and would have minimal impact and the School of Pharmacy was selected for convenience.

Each focus group session was run by a facilitator (JB) who introduced the list of themes for discussion and invited participants to comment and express their views on each theme. An assistant moderator was also employed to make detailed field notes on each respondent and in particular to note their body language throughout the discussions. Each session was tape-recorded, transcribed, checked for any omissions using the field notes and amended.

5.4.2.4 Data analysis

Methods of qualitative data analysis are outlined in section 3.7.2. As the data collected was highly structured, a framework analysis was used to analyse the content of the data. Spreadsheets were used to form a matrix of responses to identify; differences in opinion, where consensus was achieved and how respondents' opinions changed on reflection/over the course of the discussions. Key themes emerging were also independently reviewed for consistency.

Once this was done, the final step of qualitative analysis involved revisiting the literature and seeking out conceptual tools that could explain the patterns emerging from the data. Hypotheses and constructs were developed and used to examine further cases. Quotes that capture the participants' knowledge, experiences and attitudes were selected to reflect the interview data. An encrypted copy of the raw data can be found in the sleeve of the back cover.

5.4.3 Results: phase 1

5.4.3.1 Response and characteristics of respondents

Table 5.1 shows that in total, 41 pharmacists participated and a total of 9 focus groups were held.

Table 5.1 Characteristics of respondents

Date	Area of employment	Number of participants
June 18th 2002	Multiple	5
June 19th 2002	Multiple	4
June 20th 2002	Locum	4
June 26th 2002	Multiple	3
June 27th 2002	Proprietors	5
July 2nd 2002	Catch all group	4
July 4th 2002	Retail pharmacy	4
July 9th 2002	Independents	5
July 10th 2002	Proprietors	7

5.4.3.2 What are herbal medicines?

This section includes pharmacists' definition for herbal medicines (section 5.4.3.2.1) and types of products/preparations/remedies they would consider as being herbal (5.4.3.2.2). The findings from these sections are summarised under section 5.4.3.2.3.

5.4.3.2.1 Definition for herbal medicines

As an opening question pharmacists were asked to express their view of what herbal medicines meant to them. A wide range of descriptive words such as 'pharmacognosy', 'natural', 'green', 'plants' and 'traditional' were expressed. However, when probed further, few pharmacists could correctly define herbal medicines, despite a series of articles on herbal medicines (Barnes, 2002) being published in The Pharmaceutical Journal.

In terms of defining herbal medicines, a number of misconceptions were held by pharmacists, which raises concern in whether or not pharmacists would be able to identify herbal medicines from other medicines and food supplements. For example, some pharmacists believed that the term encompassed other natural products, such as 'bacteria', 'fish oils' and other forms of CAM, which can be clearly identified by the following transcript:

"I think I would say obviously there are for example things from bacteria and things like that but I think those especially, I think mainly from plant, if we say 'herbal', I assume it's from plants." *[respondent 04D]*
"You've got the fish oil some things probably herbal or associated-" *[respondent 04B]*
"And homeopathy – tissue sorts and that sort of thing." *[respondent 04A]*

Other misconceptions included that some pharmacists viewed herbal medicines to be safer than conventional medicines and to have similar potencies to conventional medicines:

"No, I think herbal medicine, I would categorise more on similar to the normal mainline medicines except coming from plants. [similar] In terms of potencies probably but maybe with less side effects because of the, well combination of constituents." *[respondent 04B]*

"Plant products in the main – in realistic quantities as opposed to homeopathic quantities."[respondent 04A]

However, these assumptions have no scientific grounding as herbal medicines are known to cause side effects and many homeopathic preparations are herbal medicines which have been diluted as part of the formulation. A common example of a diluted herbal medicine is arnica homeopathic cream, obtained from the plant *Arnica montana,* which is used for bruising and swelling.

Many pharmacists viewed herbal medicines as complementary medicines:

"... they fall under the same umbrella insofar as they are 'complementary'." *[respondent 04A]*

"Herbal is a sub-section really, isn't it, of complementary –" *[respondent 04C]*

One pharmacist also expressed the unnecessary classification for herbal medicines:

"... to me herbal is part of the whole complementary set up and I do not need to look at herbal as a separate entity and I would actually look at it as a total set up of complementary health." *[respondent 04B]*

However, as outlined under chapter 1 (section 1.5.1), herbal medicines span across both 'conventional' and 'complementary medicines' and therefore should not be categorised under 'complementary medicines' only.

5.4.3.2.2 Types of products/preparations/remedies considered to be herbal

Pharmacists' views on whether or not they considered conventional medicines, homeopathy, essential oils, glucosamine and food supplements as herbal medicines are presented in this section. This was considered relevant as the classification of these products as herbal or non-herbal was identified as causing confusion at the level of national pharmacovigilance centres in studies conducted in chapter 4 (see section 4.4.3.6). Questions asked in this section were also used to gain an insight on pharmacists understanding and knowledge of herbal medicines.

5.4.3.2.2.1 Conventional herbal medicines

Many pharmacists made the assumption that conventional equated to non-herbal and felt that they had to classify products as either conventional or herbal:

"No, I think you have to differentiate between conventional medication which has got evidence based, standardised product licence but is herbally or naturally derived and other herbal complementary medicines for which the jury is still out. I mean St John's Wort and possibly Gingko has the potential to cross that border – you cross that border by being legal as it were." *[respondent 04A]*

Upon further discussion the consequences of these false boundaries (as herbal medicines can be both conventional and unconventional) was demonstrated as there was much confusion between the participants, which the following transcript suggests:

"Where do you put the boundaries, and like you say, you're basing it on clinical tests, but the boundary – because a lot of conventional, as you say – Quinine, Digoxin have come from the use of herbs, but they've just been taken that step further scientifically, so then you shift the boundaries from herbal, more on to conventional." *[respondent 26A2]*

"How it's used, and the amount of clinical trials that have been done on it, which makes it – takes it away from the herbal field into conventional therapy." *[respondent 26B]*

As previous work has highlighted that consumers are less likely to report an ADR associated with an 'unconventional' medicine compared to a 'conventional' medicine (Barnes *et al.*, 1998) the classification of all herbal medicines as unconventional suggests that fewer ADR reports could be submitted by even healthcare professionals. However, as herbal medicines have been associated with serious ADRs that have had an impact on the public health they need greater vigilance and to be viewed by pharmacist to the same degree as 'conventional' medicines.

Participants were further probed by specifically asking their views on how they would classify senna and digoxin. In general, many pharmacists considered digoxin as a conventional medicine as opposed to herbal. However, when probed for reasons as to how they came to that conclusion, a disparity in views was highlighted (summarised in table 5.2), again revealing a

lack of understanding of herbal medicines and their definition. For example, contrary to some of the pharmacists' belief, the following factors do not influence whether or not a product is herbal or non-herbal:

- Duration on the market
- Obtained a product licence
- If the product is standardised

Conversely, a product can not be classified as herbal if it satisfies any of the following factors:

- Synthetic/chemically changed
- Consists of a single constituent

There was much confusion surrounding the classification of senna as quoted by one pharmacist:

"It's a bit of a grey area really, isn't it?" *[respondent 02C]*

Some clearly defined senna as a herbal medicine, whilst also considering them as conventional medicines:

"Well I use it in my daily practice as a conventional medicine however it is strictly speaking I suppose a herbal medicine." *[respondent 20B]*

Whilst others clearly defined senna as non-herbal:

"We don't call Senna a herbal medicine though, do we?" *[respondent 04A]*

Reasons for regarding senna as a non-herbal and purely a conventional preparation are outlined in table 5.2.

Table 5.2 Reasons outlined in terms of categorising products as conventional as opposed to herbal

	Digoxin	Senna
Duration on market	*'There's always a grey area – you look at digoxin, you know, there's obviously a grey area bit where we see it, and something that's been that long made by that sort of company you would assume is more medical." [respondent 27C]*	*'I'd probably think conventional because it's been going for ages and ages, so you take it almost as first line." [respondent 02B]*
Synthetic/ chemically changed	*"...aspirin's a synthetic product, it's based on the original salicylic acid derivative that you get from willow and it's still synthesised, isn't it, the same as digoxin is synthesised. If you said to me digitalis tablets, then I would say yes, that's herbal." [respondent 27B]*	*'I tend to see it in herbal remedies as ones that are just taken from the plant and are not altered or changed. Whereas if you get stuff – if you're talking about a product like Sennacot, there has been this process of some chemical changes, I feel, or it's been changed in some way, so it's extracted, or you know, changed, so – and as you say, so many of our pharmaceutical products actually have started with plant material and then they've been developed on, haven't they –" [respondent 02C]*
Obtained a product licence	*"So is Digoxin [herbal], but it's got a product licence." [respondent 26C]*	*"...it's licensed, it's been quality controlled, everything, whereas herbal preparations, we don't know what sort of quality control it's got, it's had, we don't know how they've been extracted, what other ingredients are included in the preparation that they claim." [respondent 26C]* *'The thing about Senna, obviously they've made a preparation like Sennacot, and it's become a licensed medicine, and it's got indications for it, whereas, you know, if you look on a packet of say St John's Wort, it won't actually tell you what it's for, because it's got many indications, so – it's a conventional medicine because of the presentation, you know, and the way it's being used, although originally it's derived from plants, and so it many medicines on prescription, you've got Quinine, haven't you, which is also derived from plants – so – ". [respondent 26B]*
If they are standardised products	*'I suppose the difference is now Digoxin's all extracted and standardised isn't it. You don't have sort of powdered Digoxin tablets, we used to didn't we?" [respondent 26C]*	*"So there is a standardised – although it's a plant origin, you could think of it as medicine as well, conventional prescription medicine, because it definitely has a monologue in the BP, there's a standardised theme, whereas all the others are –" [respondent 27D]* *'I would view that as a medicine because it's standardised, its total sennacides so it's a drug. You talk about a drug or a herbal medicine, the drug to me is something that's standardised, of course I said earlier a lot of medications, digoxin, they all came from plants originally, lots of them did but they've become standardised and they're not necessarily made in the same way, they're synthesised or they're taken from plant extracts but they're scientific, they're standardised and therefore I would regard senna rather than a natural medicine that it may be, I would regard it as a drug". [respondent 19A]*
Constituents	*"...the way herbs work is that it's not just the active ingredient, it's what happens – what it comes with, all the other constituents, that's where it's working from, so taking it away from there, becomes – probably doesn't work as well – and that's probably what's Quinine and Digoxin, things that have been taken away from their original state.." [respondent 26B]*	*'That's a chemical compound with a structure and a function, you know what it does but with a lot of herbal medicines, the reason why there's two or three in there is because it's a plant, it's not just one drug." [respondent 19A]* *'Well, it's been adapted into – it's used a lot nowadays, you know, but then things like digoxin and aspirin, you know, plant sourced, so – so it's used conventionally – I don't know – it's just got one particular extract, the sennaside part, whereas in herbalism, there's about a few thousand constituents to it – so is it conventional – it's conventional in the sense that it's been very refined and they're just using one or two specific constituents to give an effect, so it's conventional in that way, but, you know, derived from obviously herbalism. So I don't know, so talking about it, a bit of both I would say" [respondent 02A]*

5.4.3.2.2.2 Homeopathy

When clarifying differences between herbal and homeopathic preparations, there was a disparity of views and confusion amongst pharmacists, illustrated by the following quote:

"It's not very clear cut between the two –" *[respondent 19D]*

"I always find there seems to be confusion as well, between herbal medicine and homeopathic medicine, because herbal medicine has got – I mean it's a different principle, isn't it?" *[respondent 18D]*

However, the majority of pharmacists viewed them as being separate sciences:

"I don't know how it works, whereas herbal medicine you can understand. I mean a lot of our medicines these days still stem from herbal medicines, I mean we still use Digoxin which obviously stems from Digitalis, you know, the logic is there and I can follow it, you know, I mean years ago they used to eat the bark of a willow because it contains hallucinates so you can understand all that, but homeopathic I will not class as herbal because I can't understand the same logic of it working, it doesn't work in the same way does it? I mean it's like for like and it's not, I don't think homeopathy is similar to herbal." *[respondent 10G]*

"I always thought of them as being separate, herbal medicine did not mean homeopathic for me." *[respondent 18C]*

"No, I view those separately, I don't consider them to be similar." *[respondent 27A]*

The difference between herbal and homeopathic preparations was attributed to the product's concentration (in the pharmaceutical formulation) by several participants, which raises the concern that pharmacists might be unaware that there can be homeopathic preparations of high and low potencies (Jutte and Riley, 2005):

"...the difference between homeopathic and herbal medicine is the dilution with homeopathic because you have different dilutions, sometimes you have 6C potency or 30C, with herbal medicine you don't have something like that, it's all in one." *[respondent 19B]*

"It's actually a different group, because although it may have active ingredients of herbs, but it's been diluted so much that it becomes a different formula altogether, so they are related but not – they're not herbs anymore, they become homeopathic preparations." *[respondent 26B]*

When specifically probed on how pharmacists would classify arnica (a specific herbal preparation which is also a commonly used homeopathic preparation) there was much confusion and difference in opinions between pharmacists, which is expressed by the following quotes:

"...although it's homeopathic, it's considered almost a herbal, so there's always grey areas and it's very difficult to know exactly where to put the divisive line." *[respondent 27C]*

"Especially with Arnica, because you've Arnica homeopathic and Arnica herbal – like, where do you go." *[respondent 18F]*

"I think that's more homeopathic, I don't know whether you class it as herbal." *[respondent 02B]*

"Arnica is a tincture, I'd say, it's a herbal – a herbal remedy – yes, definitely. *[respondent 02C]*

"Well actually they sort of fall between herbal and homeopathic I think." *[respondent 04C]*

The above again demonstrates the complexity of herbal medicines as they span across different complementary therapies and conventional medicines, thus much confusion exists amongst pharmacists when trying to force them into specific areas. Thus the removal of these false boundaries/terms might clear some of the misconceptions held.

5.4.3.2.2.3 Essential oils

Many pharmacists on impulse did not distinguish essential oils as herbal medicines and classified them under aromatherapy:

"I'd say that it was aromatherapy, I think that's different from herbal medicines, to me" *[respondent 04A2]*

Certain participants believed that this was the case due to the type of preparation being for external use:

"Yeah, I would say the same [essential oils are not herbal medicines], because they're not actually taken orally." *[respondent 26B]*

"Well, I see them as aromatherapy, I mean, or when consumers use them, or when customers use them, I think it's just – I mean they just inhale the – the oil and get the effect from that, or with herbal remedies you actually have the – I mean the medicine actually has been taken in, or maybe been rubbed on the body, and actually going into the system, to bring about an effect....." *[respondent 26A]*

"So I don't tend to – probably 'because they're not being, tend to be used – I mean they're used either directly externally, or to be used around perhaps a few drops on inhalation – something in that sort of nature, so I tend to see essential oils as in a different compartment really." *[respondent 02C]*

However, on deliberation, certain participants changed their view:

"I don't know, but when you sort of look at it, they're more – it could be under a bracket of herbal, isn't it – because it's – once again you think of Eucalyptus, which is – they've all come from plants, but in – in oil form." *[respondent 26A2]*

"What I view – generally I don't, obviously a lot of them are from plants we know that, but I don't regard them, when I'm thinking of for example herbals, I wouldn't – I mean unless I sort of look at in a scientific way and sort of sit down and say it's this scientifically, say if I was thinking normally I wouldn't think of it as a herbal medicine, yeah." *[respondent 04D]*

"Yeah, I think I agree, complementary – it's because they're classed as essential oils, if you do actually think about it, they are herbal aren't they? And I do recommend especially lavender and things, I do recommend a lot for relaxing stress." *[respondent 04C]*

It is encouraging that pharmacists are able to identify essential oils as herbal preparations but the initial delay in recognising them as herbal preparations raises the question on whether or not pharmacists question patients on the use of these types of products.

5.4.3.2.2.4 Food and dietary supplements

Despite knowing that glucosamine (a dietary supplement) is not from plant origin, certain pharmacists still claimed that they would classify glucosamine as a herbal medicine; as highlighted by the following quotes:

"You don't have to go that far, there's things like glucosamine and chondroitin, you would consider that a herbal though it's nothing to do with herbs, but it's that edge of just beyond manufactured medicines that we'd sort of put under that, that label." *[respondent 27C]*

"Yeah – although it's from the shellfish, I do consider it to be herbal in some way." *[respondent 09C]*

"It is a herbal medicine, yes, but there's enough research been done on it." *[respondent 10C]*

The unclear borderline between herbal medicines and food supplements was also noted by a couple of pharmacists:

"Well they sell garlic capsules, I suppose that's considered medicine but you go and buy garlic at the supermarket, that's food basically, yeah." *[respondent 19D]*

"Even as a professional, if someone said to you those two words, garlic and ginger, you would probably first think of them as foods rather than medicines even as a pharmacist, I know I would." *[respondent 19A]*

Many pharmacists viewed vitamins/minerals as separate to herbal medicines but stated that they would group vitamins, minerals and herbal medicines under the broader term 'food supplements':

"They're all food supplements, foods - ." *[respondent 09E]*

"No, we don't call them herbals, but maybe the public do, we just call them food supplements –"
[respondent 04C]

As the majority of herbal medicines are marketed as dietary supplements and are consumed within the diet it is not surprising that pharmacists are unclear on the difference between the two terms and therefore often view other products such as glucosamine under herbal medicines. Further work would be required to establish the degree to which pharmacists perceive certain food supplements as herbal and non-herbal and whether or not the classification of glucosamine as a herbal medicine is a widespread issue.

5.4.3.2.3 Summary of findings on asking pharmacists "what are herbal medicines?"

The summary of findings from sections 5.4.3.2.1 and 5.4.3.2.2 are listed in the box below:

Summary of findings on pharmacists views related to the definition of herbal medicines:

- Few pharmacists could correctly define herbal medicines.
- Some pharmacists believed that the term "herbal medicines" encompassed other natural products, such as bacteria, fish oils and other forms of CAM.
- There was much confusion over the classification of products such as senna and digoxin.
- The majority of pharmacists viewed homeopathic, vitamins and mineral preparations to be different to herbal medicines.
- Many pharmacists did not view essential oils as herbal medicines.

5.4.3.3 Stocking of herbal medicines in the pharmacy

There was a clear difference whether the pharmacy stocked mainly licensed or unlicensed products, which can be seen from the following quotes:

"I wouldn't sell it, I don't sell anything that's unlicensed because I think there's a deadline, I don't know if it's this year or next year, all the manufacturers have to have their products licensed if they're selling it as herbal remedies." *[respondent 10C]*

"It's very mixed actually, because some are licensed and some aren't –." *[respondent 09C]*

"I have to say I'm not actually sure. I don't know – I mean I've never actually looked for the little PL number on the side." *[respondent 09B]*

It also apparent that certain pharmacists were unaware of what products their pharmacy stocked which is concerning as the RPSGB Code of Ethics (2006) states that "pharmacists providing homoeopathic or herbal medicines or other complementary therapies have a professional responsibility to ensure that stocks of homoeopathic or herbal medicines or other complementary therapies are obtained from a reputable source of supply". For both multiples and independents, products stocked within the pharmacy were predominantly dictated by consumer demand. Where pharmacists had control, products were selected according to the manufacturers' reputation:

"I think as a proprietor I think we do find reps coming around. We are very selective on what we buy I mean obviously from the point of view whether we'll be able to sell the product or not. If it's a reputable company on a sale or return basis sometimes we buy them. I mean we personally think that we have to redeem them or if the public demands them we will stock." *[respondent 20C]*

Popular herbal products mentioned by pharmacists included Echinacea, St John's wort, Milk thistle, Ginkgo, Fever few and Calendula:

"Echinacea – in the last few years has really taken off hasn't it, become really – gingko – and St John's Wort, Milk Thistle." *[respondent 04C]*

" I mean we give out so much Calendula cream, literally day in and day out now for kids with eczema or they don't want to use E45 or they don't want to use anything, they want herbal and people are asking."
[respondent 10G]

Most pharmacists felt that the pharmacy was the appropriate place to sell herbal medicines:

"I think we should – if people want to have, use herbal medicines the first place they should try is a pharmacist. To safely recommend alongside the conventional medicines." *[respondent 27B]*

"And I would say that – I mean they feel more confident – a lot more confident if they've bought it from a pharmacy environment, where they can actually ask a few questions…" *[respondent 26A]*

However, some pharmacists felt they should have more input in the sales of herbal medicines:

"Of herbal medicines – I'm quite happy for it to be there, but providing I can have an input into it – I feel it would be better if I had more of an input and can, you know, make, either make some suggestions or comments about their choice, or give them an alternative of choice." *[respondent 27A]*

The majority of pharmacists held the opinion that herbal medicines are important to pharmacy/pharmacists as they play an integral part to patient care, which is encouraging:

"Yes, it's got a lot of potential I think to improve patient care." *[respondent 18D]*

"Again that's another opportunity there where you could be a real – what you call – a real healthcare team if you had the knowledge in herbals and complementary." *[respondent 04B]*

Summary of findings on pharmacists views on the stocking of herbal medicines in the pharmacy:

- There was a clear difference between pharmacies in terms whether they stocked mainly licensed or unlicensed products.
- Decisions to stock a product within a pharmacy were predominantly based on consumer demand.
- Popular products included Echinacea, St John's wort, Milk thistle, ginkgo, fever few and calendula.
- Most pharmacists felt that the pharmacy was the appropriate place to sell herbal medicines.
- The majority of pharmacists held the opinion that herbal medicines are important to pharmacy as they play an integral part to patient care

5.4.3.4 Recommendation of herbal medicines to patients/consumers

Pharmacists who had personally used herbal medicines were more willing to recommend them to their customers:

"I'm quite confident, especially in herbal medicines that I've tried myself and they've worked, and I'm very happy to sell them because I know – but I can't go round trying everything - ." *[respondent 18D]*

However, many pharmacists expressed a reluctance to recommend herbal medicines as they felt that they had insufficient information on the product:

"Well, I think it is quite important, like I keep saying, I think there's a lack of information, and that's my concern, and I think it's very important, it's a growing area, by consumers, and I'd just like more information, so I can feel confident in recommending it." *[respondent 26A2]*

"I think if you had a bit more information then you'd feel a bit happier to recommend it, even as, you know, first off as opposed to certainly some conventional, for some conditions. Or when you know the conventional ones aren't helping as much, then this might be a perfect alternative. But without that extra bit of knowledge, you sometimes, you stick to the conventional stuff because you know it more – it's a safer route."[respondent 02B]

One pharmacist also mentioned that the use of herbal medicines went against the principles of evidence-based medicine and was therefore reluctant to recommend herbal medicines:

"I find myself fighting my scepticism for herbal medicines. I think we've all been brought up on evidence-based medicine and the evidence on herbal medicine is hearsay, and as you say, it's in the newspapers, it's pushed, and I find I can't, I can't stand there recommending a herbal preparation to somebody if I know that I haven't got the evidence to back it up with." *[respondent 27B]*

Similarly another pharmacist could not understand as to why they should recommend herbal medicines due to unsubstantiated claims:

"Unsubstantiated claims, I wouldn't do them [recommend] for traditional medicines, so I don't see why I should do them for alternative medicines, and that doesn't exactly leave me with a lot of recommendations to make for herbals - ." *[respondent 09E]*

As a result of the lack of information available on herbal medicines, many pharmacists preferred to recommend conventional medicines over herbal medicines:

"If I had a choice of recommending between the two, conventional or herbal, I'd probably go for con – conventional more, because obviously I know much more about it, I'm much more confident in it – and herbal, I would like to recommend for those who don't want conventional therapy, that's how I would go about that." *[respondent 26B]*

However, some pharmacists did state that they would recommend herbal medicines when conventional therapy had 'failed':

"Sometimes if the conventional stuff hasn't worked, or you feel that they think that it's not helping as much, and that's an easy way to say: 'Why don't you try this?' as well." *[respondent 02B]*

Or they would supply them on the customer's requests:

'I don't go out of my way to say 'Right, we've got a herbal range, take this.', but if somebody comes to me and says 'What have you got in the herbal line?', and if there are no other, what I think are contraindications and they're fit and able and sound of mind, then yes, we can talk about certain things. But if they're pregnant or they've got other conditions, if they're depressed and they want something for depression then at least they know I am not happy." *[respondent 10E]*

Many pharmacists expressed the opinion that, where information is available on a product and they were familiar with the herb, they would recommend such items:

"If it's something that I'm sort of reasonably familiar in, that I've read about and been told about, then yes, if it's – I mean I think, for me as well, it tends to – it depends how much information the manufacturers give you as well, because a lot of them do give you some quite good reference manuals, so if it's a condition that somebody comes in with, that – I'm familiar with a herb that might actually help, and they want something alternative, then I will recommend it." *[respondent 09D]*

"The only one I have regularly recommended is sometimes Echinacea, I know a little bit more and I think it helps with colds. Other than that, I can't think of any other." *[respondent 10B]*

Also, one pharmacist felt that they had sufficient training in pharmacognosy to be able to determine which herbal medicines to recommend. However, considering that previous work has suggested a lack of training of pharmacists in herbal medicines (Barnes and Abbot, 1999; Chang *et al.*, 2000) and the fact that most information on herbal medicinal products is unknown (De Smet, 2002), it is difficult to understand on what basis this statement was made:

"I think we've done enough in pharmacognosy, when we do pharmacognosy, to be able to determine which ones you would be able to or which ones you wouldn't be able to recommend." *[respondent 10C]*

Summary of findings on pharmacist's views on recommending herbal medicines to patients/consumers:

- Pharmacists who personally used herbal medicines were more likely to recommend them.
- Many pharmacists expressed a reluctance to recommend herbal medicines due to insufficient information on the product.
- Some pharmacists stated that they would recommend herbal medicines when conventional therapy had failed or would supply them on the customer's requests.

5.4.3.5 Advising the public on herbal medicines

This section includes the frequency of enquiries made to pharmacists (5.4.3.5.1), types of questions asked on herbal medicines (5.4.3.5.2) and pharmacist's perceived role in advising on herbal medicines (5.4.3.5.3). The findings from these sections are summarised under section 5.4.3.5.4.

5.4.3.5.1 Frequency of enquiries made to pharmacists

Most of the participating pharmacists were asked for advice on herbal medicines however, the level varied between stores. Factors suggested by pharmacist included the geographical location of the pharmacy and demographics of the nearby population:

'I don't get that many [requests], it's only because of the area I work in – it's only one or two people who have found out about it via the internet, or for whatever reason have come in. But in general, in my area of work, there's not that many people because they don't speak English, they're less educated, etc, so from my point of view it's, you know, perhaps 1% of my time perhaps do I get asked, so -." *[respondent 02A]*

"...most of my customers are over-sixties, so just to give you a general idea of the general population I have, and nobody really asks anything about herbal medicine." *[respondent 18E]*

Certain pharmacies which were renowned for stocking a wide range of herbal medicines received a greater number of enquiries:

'We have a wide range of herbal and homeopathic remedies and we have a lot of queries and enquiries from European clients." *[respondent 10F]*

As outlined by one pharmacist, it is difficult to accurately assess the volume of questions asked on herbal medicines as a number of queries are dealt with by counter staff:

" I mean it's difficult to gauge because the staff are quite well versed in these things as well so the number of times I get consulted doesn't necessarily represent the number of consultations." *[respondent 04A]*

Also, enquires on herbal medicines formed a low percentage of the pharmacists' daily activities. However, this does not reflect the frequency of enquiries made and would require further investigation quantitatively:

'If I had to give a percentage it would be about five." *[respondent 27C]*

Many pharmacists noticed that they would receive an influx in questions on herbal medicines after a related article in the press:

"I notice it particularly on Mondays, after people have read the Sunday papers." *[respondent 18B]*

5.4.3.5.2 Types of questions asked on herbal medicines

Questions posed to pharmacists varied from general information based on the use of a specific product (*i.e.* dose, interactions, use in special groups, safety) to requiring recommendation of a herbal product for a specific condition:

"How to utilise it, dosage, whether it will interact with other medication that they are taking, how safe it is – just those sort of questions really." *[respondent 02C]*

"Most often, somebody comes in and says 'I've got this, and I want to take – I don't want to go to the doctor, I want to take something herbal, what can you recommend'?" *[respondent 09B]*

"We get asked a lot of questions – 'is it safe in pregnancy' and it's very, very difficult to find the answer, because you can 'phone the manufacturers and they haven't tested it, or they're not too sure, so you can't give a specific answer." *[respondent 09A]*

A number of pharmacists found that they would be asked for their opinion on specific products advertised:

"The most frequent one I get is 'I've read it in the paper or heard it on the radio, is it any good' - ."

[respondent 09C]

Some pharmacists also received referrals from health food shops on the suitability of a product:

"I've been a bit shocked that people have – perhaps I'm quite naive really about that – I've been quite shocked when people have come from Holland & Barrett – I believed that their staff at least had a fairly thorough knowledge of their products and often they do have a contra indication of something like that on the bottle, and

people have come in clutching something and saying: 'I bought this, but I've just noticed it says this – what do you think?" *[respondent 27E]*

5.4.3.5.3 Pharmacists perceived role in advising on herbal medicines

Many pharmacists believed that advising on herbal medicines is part of pharmacists' professional practice as they are the experts on conventional medicines and can assess potential interactions between conventional and unconventional medicines:

"But one thing we have in our favour is we know about conventional medical treatments and that's something that we can pick on. From my experience some doctors just would not take time to discuss herbal medicine with their patients, they just say, 'No, don't take anything'. So I think some patient need in-between and also there's nothing to stop them from self medication so I feel that we have a responsibility because we know how conventional therapies, side effect, in interaction very well." *[respondent 20A]*

However, many also felt that at present they did not have sufficient knowledge or information on herbal medicines to adequately fulfill this role, which confirms previous findings:

"...I would like to be able to give them professional advice and at the moment I don't feel I am."
[respondent 19D]

5.4.3.5.4 Summary of findings on pharmacists views on advising the public about herbal medicines

The summary of findings from sections 5.4.3.5.1, 5.4.3.5.2 and 5.4.3.5.3 are listed below:

Summary of findings on pharmacists views on advising the public about herbal medicines:

- Most pharmacists were asked for advice on herbal medicines however, the level varied between stores.
- Many pharmacists believed that advising on herbal medicines is part of pharmacists' professional practice as they possess the knowledge on conventional medicines, but at present they did not have the knowledge or information to fulfill this role.

5.4.3.6 Pharmacists' knowledge of herbal medicines and pharmacovigilance

This section includes pharmacists' perceived knowledge of herbal medicines (5.4.3.6.1), pharmacists' knowledge of licensing of herbal products (5.4.3.6.2), and pharmacists' knowledge of application of yellow card scheme for ADR reporting to herbal products (5.4.3.6.3). The findings from these sections are summarised under section 5.4.3.6.4.

5.4.3.6.1 Pharmacists' perceived knowledge of herbal medicines

The majority of pharmacists felt that their knowledge on herbal medicines was not adequate:

"Yeah, that's the most frustrating part, 'if you're taking any medicines, consult your pharmacist when you go', and they bring it into you, and – you know, you don't – you don't know." *[respondent 018D]*

"I get queries from GPs, and that is when I notice my inadequacy, because I won't be able to reply." *[respondent 18E]*

Some pharmacists felt that health food shops were a better source of information than pharmacies:

"I do feel that we are expected to be able to answer questions on these things, because they are considered to be medicines, and I think it's bad in some ways that we can't answer the questions, which people get an answer to from the health food shops in many case, and I think - ." *[respondent 09C]*

"So they (health food shops) probably know more than the average pharmacist does to our shame but then we haven't got time, we're already busy doing other things." *[respondent 10E]*

The majority of pharmacists were aware of common herbs and recent public health concerns associated with specific herbs such as St John's wort:

"Very important, I think it's very very important. I mean at the moment I remember if I dispense any of the contraceptive pills I make a point of asking the patient whether they are on St John's Wort or not or other – I

know that certain medical like epilepsy I would ask them and some people do tell me – 1 out of 10 says yes they are taking it – I say 'you've got to stop that 'because it's going to interfere'. So that has made the pharmacist aware and that awareness is going to the public so that is the best channel really for the public to be aware of the side effects and the things like that." *[respondent 20C]*

"About a year ago they published some of the herbal medicines in the journal with the known side effect, common one that a lot of people don't know that have side effects with other ones like gingko bilboa and warfarin and they mentioned quite a lot of it but that was about a year ago and I'm sure a lot of pharmacists want really to know that this herbal medicine are dangerous with this. They actually wrote a lot of the conventional medicine that interact with commonly used herbal medicine and I think that was quite useful." *[respondent 19B]*

Most pharmacists attained their knowledge from reading The Pharmaceutical Journal, which shows that it is an effective medium for conveying safety concerns to pharmacists:

'I think it really, you know, I mean if you work in different shops, or you don't work every day in your shop you can miss those things, and I think they have to go in The Journal, for me, personally, I do read it every week." *[respondent 09]*

5.4.3.6.2 Pharmacists' knowledge of licensing of herbal products

Most pharmacists were aware of the existence of licensed herbal medicines and could identify products with a licence:

"...– it's got a product licence number on the actual product." *[respondent 26B]*

However, there were some pharmacists who were completely unaware to the existence of licensed herbal medicines:

"I'm bound to show my ignorance, but I didn't realise there was such a thing as a licensed herbal product." *[respondent 27B]*

Irrespective of this, the majority of pharmacists were more confident recommending a licensed herbal medicine compared to an unlicensed herbal medicine:

"Yeah, I mean normally when I'm selling herbal preparations, I would prefer to use the phrase, it's got a product licence, so it is indicated for whatever, the thing is I know it's been rigorously tested, and – you know, they've applied for a licence, it does work, so – I feel more confident selling that and as well more confident in its quality, maybe because of the setting, in that it's in Boots, not in another store, but there again if you're in another store, you might feel confident selling your products there, so - ." *[respondent 18C]*

Some even expressed the view that pharmacies should only sell licensed herbal medicines:

"I mean definitely in a chemist you have to sell licensed products, you're not allowed to sell unlicensed products. We can give advice for unlicensed products, to tell people that they're dangerous and to educate the public to be aware of them, their existence and why some medication or some country have a relaxed rule on product claim about their use and even though it say so on a box doesn't mean that they actually do the same thing."

[respondent 20A]

Some pharmacists were frustrated over the fact that many herbal medicines do not state an indication:

"The other problem is when you do have herbal medicines it doesn't specifically say that it's for this purpose. Obviously they would and you take one or two but never say this is for that purpose. I don't know if that's – if it's licensing or what." *[respondent 10B]*

"That's right. To be quite honest, it makes me quite angry when manufacturers make things and do not supply even an information leaflet to say what they themselves think this product is supposed to be used for and occasionally they might just write on the label, 'Do not take if you're pregnant or if you're diabetic and if you experience any side effects see your pharmacist', I think it's just a cop out to cover themselves in case something goes terribly wrong." *[respondent 19D]*

This shows a lack of understanding of the current licensing system for herbal medicines, as unlicensed herbal medicines that are exempt from The Medicines Act section 12(2) cannot make any medical claims.

5.4.3.6.3 Pharmacists' knowledge of application of yellow card scheme for ADR reporting to herbal products

Most pharmacists did not consider submitting a yellow card report for a suspected ADR associated with a herbal medicine:

"With this herbal things, nobody's going to report anything. I mean when a patient comes to you and reports side effects with herbal medicines you don't report it to anybody do you? You just tell them to stop taking it." *[respondent 19D]*

Most pharmacists stated that if they suspected an ADR associated with a herbal medicine they would either contact the manufacturer or instruct the consumer to stop taking the product to see if their symptoms subsided:

"I think if I suspected an ADR, I'd probably contact the manufacturer, and take it from there, and if I suspected maybe an interaction with a conventional medicine, I'd contact the manufacturer of the conventional medicine, and see what information they hold." *[respondent 18H]*

"Well I would just say, 'Just stop taking it, that's the only way to find out is to stop taking it, if the side effects disappear then you can be sure it's because of the herbal medicine'." *[respondent 19D]*

However, when prompted, some pharmacists said they would submit a yellow card report if the reaction was serious, previously unreported or if they could assign causality, which again shows a lack of understanding of the current pharmacovigilance system:

"Well I think I would yellow card if there was a serious – or perhaps not even a serious one. I mean unfortunately being a locum I'm not in the same place every day, I tend not to get the feedback that other people get about medicines they're taking but certainly I mean I would yellow card now." *[respondent 20B]*

"Well, as long as it's been unreported, or even if it's serious, I'd send it off, because at least someone's got it on the database." *[respondent 09A]*

"I'd want to be fairly sure that it was attributable to that herbal medicine that herbal medicine that they'd taken – but if it was fairly obvious then yeah, I would send it." *[respondent 09D]*

5.4.3.6.4 Summary of findings of pharmacists' knowledge of herbal medicines and pharmacovigilance

The summary of findings from sections 5.4.3.6.1, 5.4.3.6.2 and 5.4.3.5.3 are listed in the box below:

Summary of findings of pharmacists' knowledge of herbal medicines and pharmacovigilance:

- The majority of pharmacists felt that their knowledge on herbal medicines was not adequate.
- The majority of pharmacists were aware of common herbs and recent public health concerns associated with specific herbs.
- Most had gained their knowledge by reading The Pharmaceutical Journal.
- Most pharmacists were aware of licensed herbal medicines and felt more confident recommending them compared to an unlicensed herbal medicine.
- Most pharmacists stated that if they suspected an ADR associated with a herbal medicine they would either contact the manufacturer or instruct the consumer to stop taking the product to see if their symptoms subsided.
- Few pharmacists considered submitting a yellow card report for a suspected ADR associated with a herbal medicine.

5.4.3.7 Pharmacists' views on the regulation of herbal medicines

With respect to the regulation of herbal medicines most pharmacists stated that there needed to be more stringent control of their quality:

"There should be obviously tighter regulations on that quality assurance, you know standardisation needs to be brought in." *[respondent 19E]*

Some expressed the view that their sales should be restricted to pharmacies only:

"I think what – what needs to happen first is for herbal medicines or such like to be reclassified, so that they are only sold from premises where people are trained and not supermarkets, that's the first thing that has to happen. And secondly, I feel we want the resources, we need the references, but are they available, do they exist, because – as we already said – yeah, you telephone the manufacturer from time to time, and sometimes they're not even aware of any side-effects, I mean – so I think first and foremost, before a product is released on to the market, a straight test of some sort, equivalent to the conventional medicines should take place, then they should be classified in a similar way to our P-medicines, because what we're trying to do is prevent them from being bought, and of course therefore causing harm to people, isn't it – that's what we're talking about here, so I think we need to sort of start at the top, rather than from the bottom up." *[respondent 18E]*

Most pharmacists were unaware of how herbal medicines were regulated at the moment:

"Under the Food Act, aren't they?" *[respondent 18F]*

"I think they are under the Food Act." *[respondent 18E]*

Summary of pharmacists views on the regulation of herbal medicines:

- Most pharmacists held the opinion that there should be tighter control of herbal medicines, particularly with respect to their quality.
- Some pharmacists viewed that the sales of herbal medicines should be restricted to pharmacies only.
- Most pharmacists were unaware of how herbal medicines were regulated at the moment.

5.4.3.8 Training of pharmacists in herbal medicines

This section includes pharmacists' perceived need for training in herbal medicines (5.4.3.8.1), the extent and type of previous training undertaken in aspects of herbal medicines (5.4.3.8.2), and methods for acquiring training on herbal medicines (5.4.3.8.3). The findings from these sections are summarised under section 5.4.3.6.4.

5.4.3.8.1 Pharmacists' perceived need for training in herbal medicines

Most pharmacists felt that they required training in herbal medicines, as they felt that they should be responsible for the products that they sell:

"To give us the information that, you know, we need – yeah, I think pharmacists should have more training in herbal medicines as it is becoming such a big and popular subject, if we're going to sell the products, then we should have the knowledge to sell them." *[respondent 09C]*

As expressed by one pharmacist, training required should be based according to their perceived needs and priorities:

"But I think I have a responsibility to the people that come in my shop, if they want information – to be able to find out about it or be able to tell them about it, where I practice at the moment I don't get asked very often, so I attach a fairly low priority to it – my immediate – my previous job I was asked fairly often and therefore I found out more about it at that stage. I think it really – I think your CPD should be directed by your perceived needs, and for me at the moment it's a fairly low CPD, because I'm just not asked very often."

[respondent 09E]

5.4.3.8.2 The extent and type of previous training undertaken in aspects of herbal medicines

Most pharmacists had received little undergraduate training in herbal medicines and had gathered their knowledge from general reading and from working in the pharmacy:

"You get taught very, very little when you're at college, so the knowledge you pick up is generally what you've read once you've qualified, so it's just what you've picked up, it's not – it's almost not a sound background."

[respondent 02B]

Those that had received undergraduate training mainly received it through the pharmacognosy component of the syllabus and felt that it was inadequate due to the fact it was not practice-based:

"But it has to be practice based, because – not like us I remember my pharmacognosy now, thinking back on it, we did have – I remember, sessions and giving us a whole display of all the pharmacy medicines which contain herbs in them, and we had to detect which herb was in what, and whatever – but not that sort of thing, which is fine, it's important to pass your exam, but more – more sort of interaction, more practice based."

[respondent 18E]

"Pharmacognosy was very unrelated to the products that are available I felt, it's more purist - ."

[respondent 09C]

Larger multiples offered in–house training in herbal medicines and many pharmacists had attended additional training sessions provided by certain manufacturers, but many felt that that the information was biased towards the companies own products:

"I went to a training session from Pharma Nord on their herbal medicines, and it was basically a sales pitch really – it was a little bit of training, we learnt a little bit, but basically the idea was to sell their products."

[respondent 27B]

5.4.3.8.3 Methods for acquiring training on herbal medicines

The majority of the pharmacists participating in the focus groups shared the opinion that the MPharm degree should contain training on herbal medicines:

"Certainly I think the pharmacists who are at university now definitely, definitely need to have some grounding and apart from that it could probably be an option but you would definitely need something in there as we certainly didn't get it, or I didn't get it, at university." *[respondent 19A]*

"I think it's very important that they need training, I mean when we came out of pharmacy training, we did not necessarily know each and every drug but we knew how to get information quickly and efficiently and in the same way if they are taught about the herbals, can be used as a, maybe in combination." *[respondent 04B]*

Many pharmacists also shared the opinion that training should be available as a continuing personal development programme for those pharmacists requiring additional training:

"A recognised course for pharmacists, not every pharmacist, but maybe a pharmacist who chooses – want to get involved in herbal medicines - ." *[respondent 26B]*

"Maybe not compulsory, but it should be up to the individual pharmacist, but something similar to the healthcare training assistants course, so you know at least somebody should know something about the medicines – well that might be a good – a good idea – yeah." *[respondent 09A]*

For post-graduate training, the preferred method of undertaking training was *via* a CPPE package, for the following reasons outlined below:

"So just a CPPE package or something like that, at least we could then choose whether we want to do it, and people can prioritise, but it's how often they prefer to do a stroke management training, as opposed to me, who'd do homeopathic or herbal." *[respondent 18B]*

Most pharmacists found that counter staff had variable training on herbal medicines and in some cases possessed the same level of knowledge as the pharmacist:

"Yes because obviously the amount of training that staff have is very variable. I think I would – you know unless people come in and ask for something by name and they ask have they used it before – yes – well I have to assume they know what they're doing with it otherwise I think I'd like them to be referred to me even if I don't have the knowledge, I sort of have the responsibility in a way whereas the counter staff don't have that." *[respondent 20B]*

"You find a lot of counter staff, their knowledge on herbals, it's the same as pharmacists, it's what they've used themselves, and family have told them – and hands on experience, they haven't received any training." *[respondent 18F]*

5.4.3.8.4 Summary of findings of pharmacists' views on the training of pharmacists in herbal medicines

The summary of findings from sections 5.4.3.8.1, 5.4.3.8.2 and 5.4.3.8.3 are listed in the box below:

Summary of findings of pharmacists' views on the training of pharmacists in herbal medicines:

- training in herbal should be provided in the undergraduate curriculum.
- postgraduate training should be voluntary and based upon the individuals need
- CPPE packages provided an ideal method for postgraduate training
- Training of counter staff in herbal medicines varied

5.4.3.9 Information sources on herbal medicines

This section includes information sources available to pharmacists (5.4.3.9.1), and information on herbal medicines required by pharmacists (5.4.3.9.2). The findings from these sections are summarised under section 5.4.3.9.3.

5.4.3.9.1 Information sources available to pharmacists

Many pharmacists stated that there are not enough information sources available to look up information on herbal medicines:

"No, there's nowhere to look up, you know, if you can or not, because if you've got your regular OTC like, you can look in the back, the BNF, ABPI and you can see whether it's alright to do it, you can make a judgment call then, but there's nothing herbal." *[respondent 18F]*

Locum pharmacists in particular, stated that it was much more difficult for them to obtain information:

"There is something about actually being a locum. It is much more difficult to find the information. If you work for a large multiple they very often provide education/information however as a locum you really have to source everything yourself so it is much more difficult. I think this is why I have this slightly negative attitude to availability of information. It's much more difficult to find you know I have no say over which references are kept in pharmacies that I work in so apart from carrying around a huge box myself you can't always guarantee the information will be there when you need it so it is difficult." *[respondent 20B]*

Many pharmacists as a result of this lack of information available contacted the manufacturers, despite knowing that the information supplied by manufacturers can be biased:

"Yes, I'm not saying whether it's right or wrong, but they usually get an answer of some kind, and I feel part of that is the lack of information that we can get, which is trustworthy, we have to rely on manufacturer's information, which we have to assume is correct, but it's always biased to selling their product, it's not necessarily just strict – whereas with like the data sheet information, we know that is done as part of a proper trial, and it's usually unbiased information that we can rely on, but when we ring up a manufacturer about the latest product they've just brought out, artichoke hearts, or something, in capsules, they're going to tell you that it's wonderful stuff, and they don't ever have pure clinical data, and it's very hard to give straight answers to customers – and it's also hard to find this stuff sometimes – you have to dig around to find who manufactures it, and then try and get hold of a 'phone number for them in Germany, or something – it would be nice to have a good source of information." *[respondent 09C]*

Pharmacists tended to rely on information from companies perceived to be more reputable, such as Solgar and Bioforce:

"Solgar also produce – and they run good seminars and things, so they're, they're very supportive. And some of the companies have very good technical sections, so if you have a particular problem you can phone them and I find them very useful." *[respondent 02C]*

"The manufacturers, whatever they give us, like I keep a lot of Bioforce, those tinctures and things, and they give you a pretty good -run of information on the various things." *[respondent 27D]*

Many pharmacists stated that they used the National Pharmaceutical Agency (NPA) as an information source and preferred this to the RPSGB's helpline and textbooks:

"I've got a couple of textbooks which I've bought on herbal medicines but to be honest with you it's just as easy to pick up the phone and ring up the NPA, it's so much easier than looking it up, it's just ease and convenience to pick up the phone and someone's on the other end of the line who will do it for you, that's probably yeah, the NPA is definitely the main thing." *[respondent 10G]*

"I've used the NPA, but not the society" *[respondent 26A]*

"No, not at all, I never use the Society, more NPA but never the Society." *[respondent 10B]*

Many pharmacists found The Pharmaceutical Journal informative particularly for herbal medicines. However, they mainly used it to browse through and read articles of interest rather than specifically searching for information on herbal medicines.

" I just read the pages to read when I get time and I have a chance to read them." *[respondent 10B]*

"Occasionally, if there's an article that catches my eye –." *[respondent 09C]*

Most pharmacists stated that they had gained their knowledge from The Pharmaceutical Journal, which implies that there could be greater emphasis on herbal medicines during the undergraduate degree:

"I qualified about nine years ago, and at that time there wasn't much herbal stuff on my course at all, it was something I had to pick up mostly through the PJ, from working hands-on really." *[respondent 18F]*

The majority of pharmacists were aware of books being available on the market but preferred to use other sources as the books contained monographs on specific herbs and were not product specific:

"I find that literature is a bit useless really, because even the pharmaceutical press herbal handbook, or whatever it's called, doesn't have many of the things that are on the shelf in any case, it's about ten years out of date, and it's just not terribly helpful – ." *[respondent 09C]*

"It's got a monograph, whatever it's called, on each thing like perhaps artichoke, fennel – it may list some of the preparations, but it doesn't really give you information on products – you have to sort of look at Kalms and think valerian, calamine, whatever, and go to about six pages and be quite good at your pharmacology – it's quite good, but it's written in very pharmacological effects with cautions, and you have to sort of weigh it up and then take a bit of a gestimate, which is a dicey business, and this time, there's a time implication and a legal implication." *[respondent 27C]*

Many pharmacists mentioned the use of Stockley for the identification of interactions and Martindale for common herbs:

"You're stuck like – there's Stockley for interactions, and that's it, that's frustrating." *[respondent 18F]*

"I mean the Martindale has a couple of references, more common ones, but there isn't what you call a specific, like a formal compendium on herbal medicines." *[respondent 18G]*

5.4.3.9.2 Information on herbal medicines required by pharmacists

Information that pharmacists were particularly keen on obtaining was around interactions. General information similar to conventional medicines *e.g.* indication, contraindications, use in special groups, side-effects, efficacy were all requested for by many pharmacists.

Many pharmacists suggested a quick reference book that has been independently produced, something similar to the BNF:

"I'd like the BNF of herbal medicine please I would, I'd like a really concise, easy to use reference of the whole lot you know and a table with interactions so we don't have to search through every monograph you know." *[respondent 20B]*

Other suggestions included having a specific website, helpline or a medicines information centre specifically for herbal medicines:

"I would like to have a helpline, maybe I don't know, from the Pharmaceutical Society or something like that and because we can get through the internet in all our stores, if you can phone someone on a helpline then maybe they can get into the internet and at this time you can get the answer, it will be a good idea." [respondent 19C]

"As we have Drug Information Centre, I think there should be Herbal Information Centre where pharmacists can access information." *[respondent 19B]*

5.4.3.9.3 Summary of findings of pharmacists' views on information sources on herbal medicines

The summary of findings from sections 5.4.3.9.1 and 5.4.3.8.2 are listed in the box below:

Summary of findings of pharmacists' views on information sources on herbal medicines:

- most pharmacists held the opinion that not enough information available on herbal medicines and relied on information supplied by the manufacturers, despite knowing that the information supplied may be bias.
- most pharmacists would like a quick reference book similar format to the BNF is required for herbal medicines.

5.4.4 Conclusions from the focus group discussions (phase 1)

As outlined in chapter 3, focus group discussions are an ideal method to gain a vast amount of indepth data on a particular topic from representatives of a target population. In phase 1 of this chapter the following broad topics were investigated:

- What pharmacists perceive as herbal medicines
- Stocking of herbal medicines in the pharmacy
- Recommendation of herbal medicines to patients/consumers
- Advising the public about herbal medicines
- Pharmacists' knowledge on herbal medicines and pharmacovigilance
- Regulation of herbal medicines
- Training of pharmacists in herbal medicines:
- Information sources on herbal medicines

From analysis of the data gained the following areas were highlighted for further quantitative investigation (phase 2; section 5.5):

- Definition of herbal medicines and classification of products.

- Criteria used by community pharmacists in selecting herbal medicines to be stocked in their respective pharmacies.
- How frequently pharmacists receive requests for information on herbal medicines and the nature of these requests.
- Information sources on herbal medicines available to and used by community pharmacists.
- How competent pharmacists believe they are in recommending and advising the public on the safe and effective use of herbal medicines.
- Knowledge of pharmacists on herbal medicines and associated areas.
- The level and extent of training and education pharmacists have received on herbal medicines.
- Pharmacovigilance practices of community pharmacists with respect to herbal medicines.

5.5 Cross-sectional survey of community pharmacists

Qualitative research has been criticised lack of reliability and reproducibility, which is largely due to biases that can be introduced by the; investigator, location, venue, sample selection and analysis of the data. The themes can not be generalised to a population therefore, the above findings (phase 1; section 5.4) need to be applied to a national sample and confirmed in a quantitative approach, which forms the basis for phase 2 of this study.

5.5.1 Aim and objectives: phase 2

Aim	Objectives	Method
To explore community pharmacists' experiences with and views on herbal medicines, using quantitative techniques	1. To determine how community pharmacists define, describe and classify herbal medicines and how these compare with a recognised definition 2. To identify criteria used by community pharmacists in selecting herbal medicines to be stocked in their respective pharmacies 3. To determine how frequently pharmacists receive requests for information on herbal medicines and identify what information sources are available 4. To determine how competent pharmacists believe they are in advising patients and the public on the safe and effective use of herbal medicines 5. To determine the level and extent of training and education pharmacists have received on herbal medicines 6. To determine if pharmacists have ever identified or received a suspected ADR associated with a herbal medicine and what action they took 7. To identify the criteria pharmacists use before submitting a yellow card report for a suspected ADR associated with a herbal medicine 8. To determine pharmacists, views on the current issues surrounding herbal medicines *e.g.* the supply of herbal medicines from pharmacies 9. To use qualitative data in the design of a questionnaire to explore pharmacists' experiences with and views on herbal medicines in a quantitative study	Cross-sectional questionnaire survey

5.5.2 Method for phase 2

5.5.2.1 Study design

A cross-sectional questionnaire survey of community pharmacists in England was conducted, using names and addresses from the RPSGB 2005 pharmacy workforce census database.

5.5.2.2 Questionnaire

A structured questionnaire was designed and developed from the above focus group data (phase 1; section 5.4) and published research and opinion on issues relating to community pharmacists and herbal medicines. The questionnaire requested for information on the following areas:

- types of herbal products and preparations stocked in the pharmacy
- criteria used in selecting herbal medicines to be stocked
- how frequently community pharmacists receive requests for information on herbal medicines and the nature of these requests
- what information sources on herbal medicines are available and used
- the level and extent of training and education community pharmacists have received on herbal medicines
- pharmacists' experiences of identifying or receiving reports of suspected ADRs associated with herbal medicines and their knowledge of the application of the UK's yellow card scheme to herbal medicines
- pharmacists' views on the current issues surrounding herbal medicines *e.g.* the supply of herbal medicines from pharmacies

The last section collected general demographic data on the characteristics of the respondent, including details such as gender, age, year of registration as a pharmacist and other qualifications, to explore relationships between demographics and perceptions.

Face validation was ensured using self reflection, comments received from experts in pharmacy practice research and by piloting the questionnaire on five practicing pharmacists known to the researcher (AA). The five pharmacists involved in the pilot were excluded from the final sample. The questionnaire was also externally peer reviewed by an expert in ethics. A copy of the comments received can be found in appendix 3. Modifications to the questionnaire were made in line with the comments received.

5.5.2.3 Sample size

Few studies have been carried out with community pharmacists around herbal medicines. Of the three studies that have involved community pharmacists, the response rate has varied from 49% to 75% (Barnes and Abbot, 1999; Green *et al.*, 1999a; Wingfield *et al.*, 2002). In general, response rates for studies involving community pharmacists can vary from as low as 20% to over 90%. Thus, based on this data, an average response rate of 50% was taken into consideration for the overall sample size.

A 3% random sample of pharmacists who reported they were working as a community pharmacist at the time of the 2005 census (n = 18, 243) was selected to provide a total of just over 500 community pharmacists. It was not possible to stratify the sample into locum and full-time community pharmacists, but the representativeness of the sample was checked by comparing the census data with the respondents.

5.5.2.4 Study procedures

Each pharmacist selected at random was sent a postal questionnaire, an information leaflet providing full details of the study and a covering letter inviting them to complete the questionnaire. A copy of the questionnaire can be found in Appendix 3. In total, 2 follow-ups of non-responders were carried out at set intervals of 3 weeks. The study was closed after 12 weeks of the initial mailing and all responses received before this period were included in the study.

5.5.2.5 Data analysis

Data was entered and analysed using SPSS version 13. A random check on 10% of the data was performed by checking the hard copy of the questionnaire against the electronic record of the data to identify any discrepancies. This was conducted by the author after a set period.

Descriptive statistics for the sample were calculated. Overall response rates and responses to specific questions for locums and community pharmacists and other categorical variables were compared using the Chi-squared test. Responses to open questions were explored using content analysis. The level of agreement and consistency of pharmacists' views to Likert scale questions were explored using factor analysis.

5.5.3 Results

5.5.3.1 Response rate

Figure 5.1 shows the response rate for the questionnaire. In total, 203 questionnaires were returned. Of these, 33 were excluded and 3 taken as non-responders to give an overall eligible response rate of 33.6% (167/497).

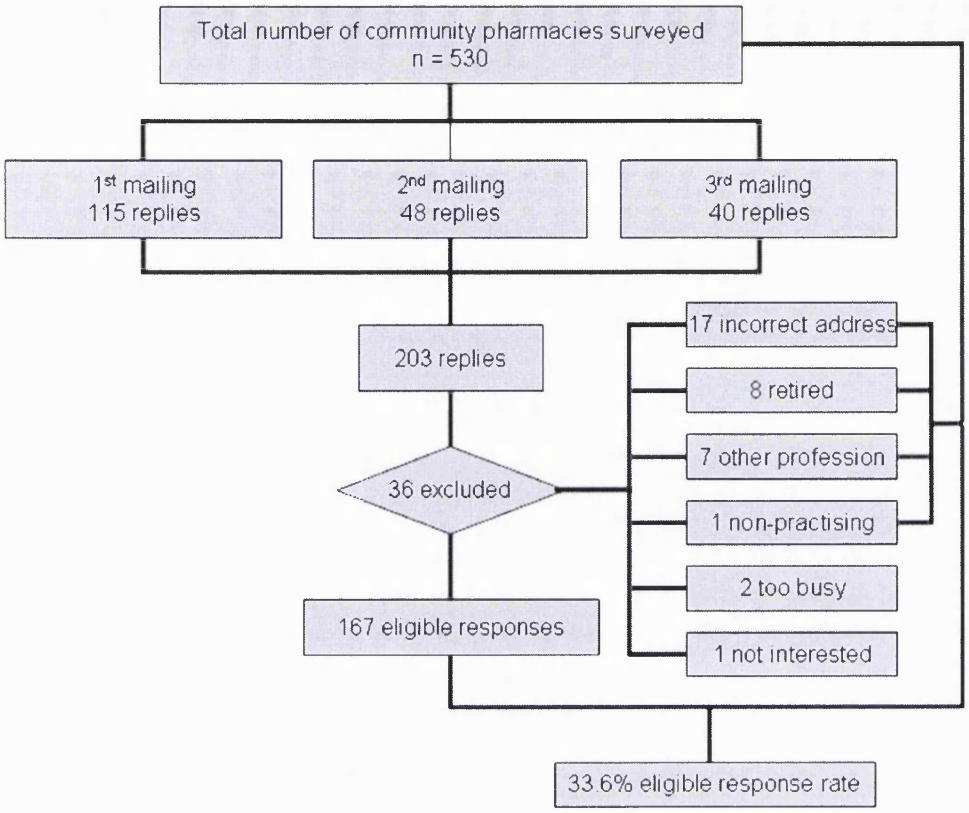


Figure 5.1 Questionnaire response rate

5.5.3.2 Representativeness of sample

Table 5.3 outlines baseline data for both the census and the survey respondents. There was no statistically significant differences between the census and survey respondents (p = 0.109; Wilcoxon Signed Rank Test for two related samples).

Table 5.3 Baseline data to judge the representativeness of the sample

	Census	Survey respondents
Respondents actively employed	27,344 (85.0%)	177 (87.2%)
Respondents are employed as pharmacists	26,027 (80.9%)	170(83.7%)
Locum pharmacists	6760 (35.5%)	44 (26.3%)

5.5.3.3 Characteristics of respondents

Table 5.4 summarises the characteristics of the respondents according to location. There were some regional differences in respondents' characteristics. A higher proportion of females responded from Scotland in contrast to England and Wales. Also, a greater proportion of respondents from Wales had been on the register for fewer years and had practised for fewer years as a community pharmacist compared to the other countries.

Table 5.4 Demographic characteristics of eligible respondents n (% of that location)†

Characteristic		All n = 167	England n = 140	Scotland n = 20	Wales n = 7
Gender: Male/Female		84/83 (50.3/49.7)	73/67 (52.1/47.9)	7/13 (35.0/65.0)	4/3 (57.1/42.9)
Age (years)	21-30	43 (25.7)	34 (24.3)	6 (30.0)	3 (42.9)
	31-40	29 (17.4)	24 (17.1)	4 (20.0)	1 (14.3)
	41-50	37 (22.2)	33 (23.6)	3 (15.0)	1 (14.3)
	51-60	32 (19.2)	28 (20.0)	4 (20.0)	0 (0)
	> 60	26 (15.6)	21 (15.0)	3 (15.0)	2 (28.6)
Ethnicity	White	121 (72.6)	97 (69.3)	19 (95.0)	5 (71.4)
	Asian	38 (22.8)	37 (26.4)	1 (5.0)	0 (0)
	Black	2 (1.2)	2 (1.5)	0 (0)	0 (0)
	Chinese	3 (1.8)	3 (2.1)	0 (0)	0 (0)
	Mixed	2 (1.2)	0 (0)	0 (0)	2 (28.6)
	Other	1 (0.6)	1 (0.7)	0 (0)	0 (0)
Years on register	0-10	49 (29.3)	39 (27.9)	6 (30.0)	4 (57.1)
	11-20	25 (15.0)	21 (15.0)	4 (20.0)	0 (0)
	21-30	40 (24.0)	36 (25.7)	3 (15.0)	1 (14.3)
	31-40	33 (19.8)	28 (20.0)	5 (25.0)	0 (0)
	> 40	20 (12.0)	16 (11.4)	2 (10.0)	2 (28.6)
Years worked as a community pharmacist	0-10	66 (39.5)	51 (36.4)	10 (50.0)	5 (71.4)
	11-20	31 (18.6)	30 (21.4)	1 (5.0)	0 (0)
	21-30	34 (20.4)	30 (21.4)	3 (15.0)	1 (14.3)
	31-40	25 (15.0)	20 (14.3)	5 (25.0)	0 (0)
	> 40	9 (5.4)	7 (5.0)	1 (5.0)	1 (14.3)

† Percentages do not total 100 because of missing data

5.5.3.4 Characteristics of respondents' workplace

Table 5.5 summarises the characteristics of the respondents' workplace. As expected the majority of pharmacists worked full time, for large nationals and in either the village or town high street. This was consistent for all three locations.

Table 5.5 Demographic characteristics of eligible respondents n (% of that location)†

Characteristic		All n = 167	England n = 140	Scotland n = 20	Wales n = 7
Type of pharmacy	Independent	38 (22.8)	34 (24.3)	2 (10.0)	2 (28.6)
	Small (2-15)	34 (20.4)	29 (20.7)	4 (20.0)	1 (14.4)
	Medium (16-25)	2 (1.2)	2 (1.4)	0 (0)	0 (0)
	Large (26-100)	15 (9.0)	13 (9.3)	1 (5.0)	1 (14.3)
	National (100+)	73 (43.7)	59 (42.1)	11 (55.0)	3 (42.9)
Local setting of pharmacy	Village high street/village centre	37 (22.2)	31 (22.1)	4 (20.0)	2 (28.6)
	Town high street/main shopping street	61 (36.5)	50 (35.7)	8 (40.0)	3 (42.9)
	Out-of-town shopping centre	6 (3.6)	5 (3.6)	1 (5.0)	0 (0)
	Rural *e.g.* area without other shops	6 (3.6)	5 (3.6)	0 (0)	1 (14.3)
	Supermarket	14 (8.4)	13 (9.3)	1 (5.0)	0 (0)
	Health centre/doctor's surgery	12 (7.2)	12 (8.6)	0 (0)	0 (0)
	Housing estate	15 (9.0)	12 (8.6)	2 (10.0)	1 (14.3)
	Other	10 (6.0)	8 (5.7)	2 (10.0)	0 (0)
Hours of employment *per* week	0-10	22 (13.2)	16 (11.4)	4 (20.0)	2 (28.6)
	11-20	23 (13.8)	18 (12.9)	4 (20.0)	1 (14.3)
	21-30	19 (11.4)	17 (12.1)	1 (5.0)	1 (14.3)
	31-40	50 (29.9)	43 (30.7)	7 (35.0)	0 (0)
	> 40	46 (27.5)	40 (28.6)	3 (15.0)	3 (42.9)
Years working in the pharmacy	0-5	88 (52.7)	73 (52.1)	11 (55.0)	4 (57.1)
	6-10	24 (14.4)	19 (13.6)	4 (20.0)	1 (14.3)
	11-20	25 (15.0)	24 (17.1)	1 (5.0)	0 (0)
	> 20	20 (12.0)	15 (10.7)	3 (15.0)	2 (28.6)
Role in the pharmacy	Superintendent pharmacist	14 (8.4)	13 (9.3)	1 (5.0)	0 (0)
	Area manager	3 (1.8)	2 (1.4)	0 (0)	1 (14.3)
	Store manager	43 (25.7)	37 (26.4)	4 (20.0)	2 (28.6)
	Owner	14 (8.4)	13 (9.3)	0 (0)	1(14.3)
	Pharmacist	44 (26.3)	40 (28.6)	4 (20.0)	0 (0)
	Locum	44 (26.3)	32 (22.9)	9 (45.0)	3 (42.9)
	Other	6 (3.6)	6 (4.3)	0 (0)	0 (0)

† Percentages do not total 100 because of missing data

5.5.3.5 Definition of herbal medicines

Most pharmacists described herbal medicines as derived from plants, for example:

"*Any medicine derived from in part or entirety from plant material*" [female respondent 3]

Some pharmacists also stated that herbal medicines are of plant origin. This is not necessarily correct as there are medicines that have originated from plants but are not classified as herbal medicines as they fall outside the Medicines Act 1968 definition. For example, digoxin and aspirin have originated from plants, but as they are now both synthetically produced they are no longer classified as herbal medicines.

"*Medicines of plant origin which are not conventional medicines*" [female respondent 222]

Again there were misconceptions held by some pharmacists with the terms conventional (see quote above) and homeopathic (see quote below):

"*Medicines that are produced with the minimum of synthesis from naturally occurring plant or animal extract. In concentrations above homeopathic doses*" [male respondent 259]

There were also misconceptions over the licensing status and formulation concentration of herbal medicines:

"*Made from plant, mineral or animal. Measurable amounts of specified ingredients. No product licence.*" [female respondent 295]

"*Herbal medicines are derived from plants and plant extracts. They are usually dilute preparations which have a negligible pharmacological effect on the human body.*" [female respondent 70]

5.5.3.6 Product characterisation

Tables 5.6 and 5.7 show that, the majority of participants were able to correctly assign products as either herbal or non-herbal. Items that caused confusion included colpermin capsules (peppermint oil), fybogel sachets (isphaghula husk) and senokot syrup (senna). All three of these products are herbal medicines and are used in mainstream therapeutics.

Table 5.6 Correct assignment of herbal medicines, n = 167 (%) †

Product	Correct	Incorrect	Don't know
Dried root of *Aristolochia fangji*	122 (73.1)	0 (0)	37 (22.2)
Colpermin capsules	49 (29.3)	113 (67.7)	3 (1.8)
Cranberry juice	113 (67.7)	46 (27.5)	6 (3.6)
Dried leaf of *Digitalis lanata*	135 (80.8)	15 (9.0)	16 (9.6)
Fybogel sachets	67 (40.1)	94 (56.3)	5 (3.0)
Capsules containing garlic powder	157 (94.0)	4 (2.4)	4 (2.4)
Senokot syrup	74 (44.3)	88 (52.7)	2 (1.2)
St John's wort herb extract	162 (97.0)	4 (2.4)	1 (0.6)
Willow bark extract	152 (91.0)	7 (4.2)	8 (4.8)

† Percentages do not total 100 because of missing data

Table 5.7 Correct assignment of non-herbal products, n = 167 (%) †

Product	Correct	Incorrect	Don't know
Aspirin	153 (91.6)	8 (4.8)	4 (2.4)
Chondroitin	94 (56.3)	45 (26.9)	28 (16.8)
Digoxin	146 (87.4)	19 (11.4)	1 (0.6)
Glucosamine	105 (62.9)	44 (26.3)	17 (10.2)
Melatonin	103 (61.7)	31 (18.6)	30 (18.0)

† Percentages do not total 100 because of missing data

Figure 5.2 shows that the scores for the above questions were approximately normally distributed: the mean score for correctly assigning the above 14 products was 9.77 (standard deviation = 2.3).

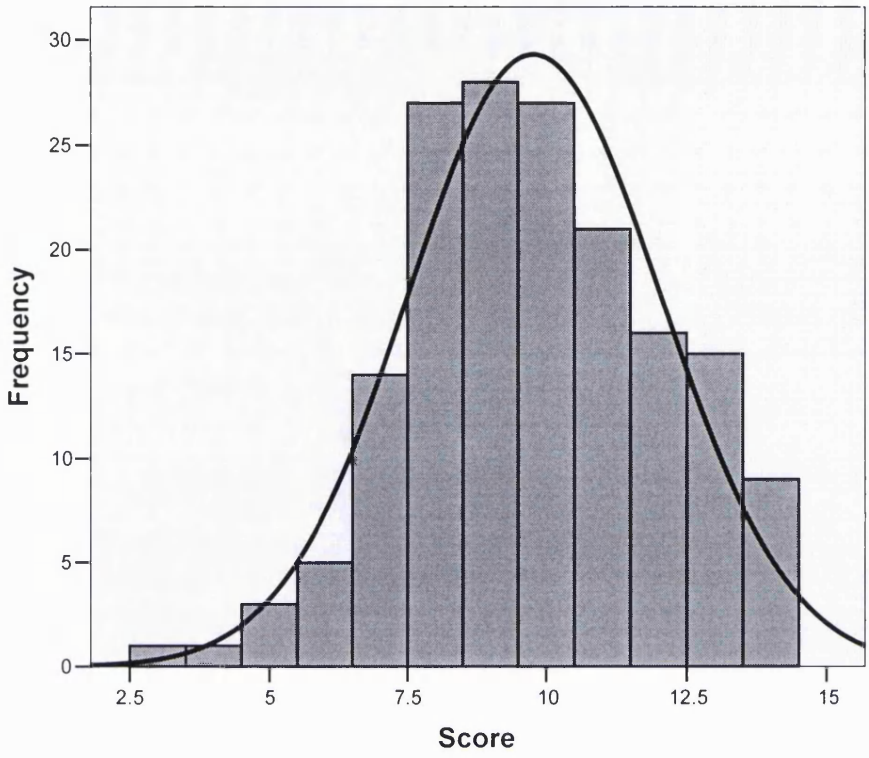


Figure 5.2 Histogram of overall scores for correctly assigning the above products

Tables 5.8 and 5.9 show that, the majority of pharmacists were able to correctly assign different types of preparations as either herbal or non-herbal. Homeopathic preparations of plant material, however, were incorrectly assigned by the majority of pharmacists.

Table 5.8 Correct assignment of herbal preparations, n = 167 (%) †

	Correct	Incorrect	Don't know
Dried or fresh raw or crude plant material	157 (94.0)	3 (1.8)	5 (3.0)
Extracts of plants or plant parts (*e.g.* leaves, roots)	160 (95.8)	5 (3.0)	2 (1.2)
Essential oils	96 (57.5)	55 (32.9)	15 (9.0)
Homeopathic (*i.e.* highly dilute) preparations of plant material	74 (44.3)	87 (52.1)	5 (3.0)

† Percentages do not total 100 because of missing data

Table 5.9 Correct assignment of non-herbal preparations, n = 167(%) †			
	Correct	**Incorrect**	**Don't know**
All complementary/alternative medicines	145 (86.8)	15 (9.0)	3 (1.8)
All homeopathic (*i.e.* highly dilute) remedies	135 (80.8)	24 (14.4)	5 (3.0)
Homeopathic (*i.e.* highly dilute) preparations of non-plant material	145 (86.8)	14 (8.4)	6 (3.6)
Non-plant dietary supplements *e.g.* Co-enzyme Q_{10}	138 (82.6)	15 (9.0)	13 (7.8)
Minerals	152 (91.0)	10 (6.0)	4 (2.4)
Vitamins	152 (91.0)	9 (5.4)	5 (3.0)
† Percentages do not total 100 because of missing data			

Figure 5.3 displays the distribution of scores. The overall mean score for correctly assigning the above 10 preparations was 8.11 (standard deviation = 1.4).

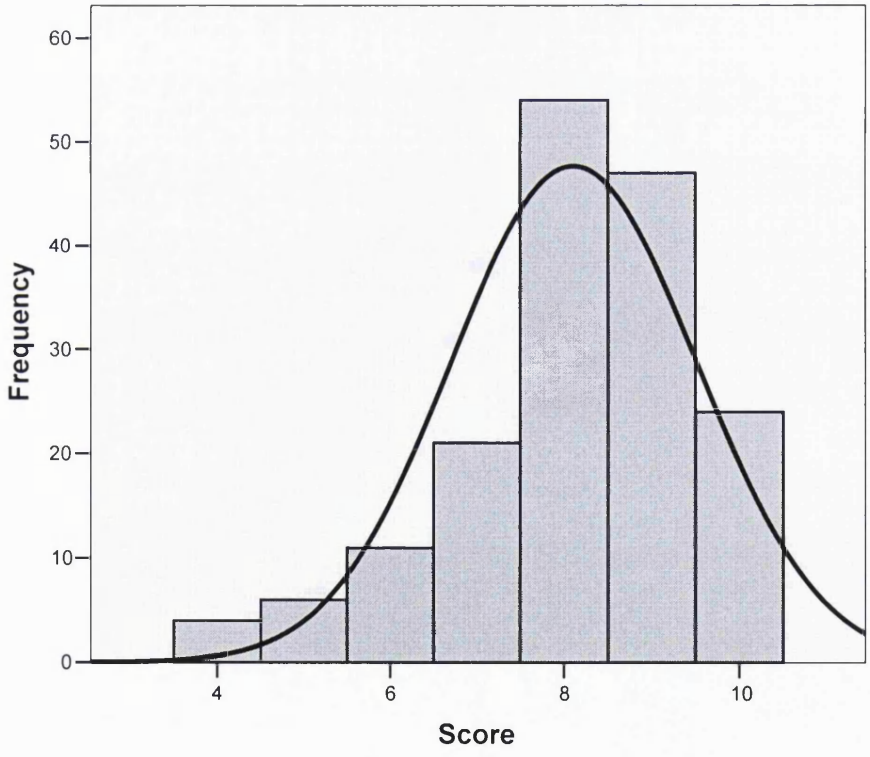


Figure 5.3 Histogram of overall scores for correctly assigning the above 10 types of preparations

5.5.3.7 Herbal medicines sold in the pharmacy

In total, 145 (86.8%) pharmacies sold herbal medicines. Table 5.10 summarises details of the types of herbal medicines stocked in the pharmacy.

Table 5.10 Details of herbal medicines presented in the pharmacy, n = 145 (%)

Categories of herbal medicines sold in the pharmacy	Licensed herbal medicines only	75 (51.7)
	Both licensed and unlicensed herbal medicines	56 (38.6)
	Unlicensed herbal medicines only	0 (0)
	Don't know	13 (9.0)
Types of herbal medicines sold in the pharmacy	Tablets/capsules	145 (100.0)
	Herbal tinctures	64 (44.1)
	Essential oils	114 (78.6)
	Herbal teas	31 (21.4)
	Crude/loose dried or fresh herbs	8 (5.5)
	Topical preparations of herbal medicines	102 (70.3)
	Other (juices & liquid)	2 (1.4)
Person in charge of deciding which herbal medicines are stocked in the pharmacy.	Headquarters	80 (55.2)
	Superintendent pharmacist	41 (28.3)
	Non-pharmacist manager	13 (9.0)
	Pharmacist in charge	54 (37.2)
	Other	16 (11.0)

Other members involved in the selection of herbal medicines included healthcare assistants or general staff predominantly through requests from patients. Two pharmacies had specialists involved, one had a health aid assistant and another had a qualified homeopath.

Figure 5.4 shows that community pharmacists predominantly stock licensed herbal medicines only.

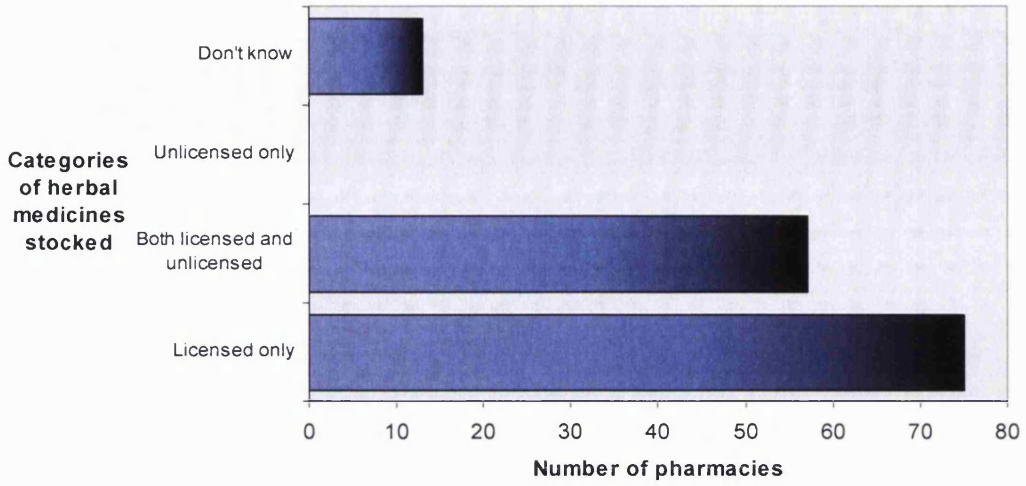


Figure 5.4 Categories of herbal medicines stocked in the pharmacy

In total, 41 (28.3%) pharmacists were involved in the selection of herbal products stocked in the pharmacy. The three main criteria used to select products were:

- consumer demand
- cost
- efficacy

However, none of these three criteria fit with the RPSGB code of ethics guidelines (see section 1.5.3) to ensure that stocks of herbal medicines are obtained from a reputable source of supply.

5.5.3.8 Enquiries/recommendations of herbal medicines

The number of times pharmacists were asked by their patients and customers for advice or information on herbal medicines over the last 7 days was a median of 2.00 (semi-interquartile range = 2.00). The number of times pharmacists recommended and/or sold herbal medicines to their patients and customers over a period of 7 days was a median of 1.00 (semi-interquartile range = 1.00). Both values show that there were outliers that received a larger proportion of enquiries or made a greater number of recommendations on herbal medicines.

Figure 5.5 shows that the majority of enquiries received by pharmacists involved interactions between herbal medicines and conventional medicines.

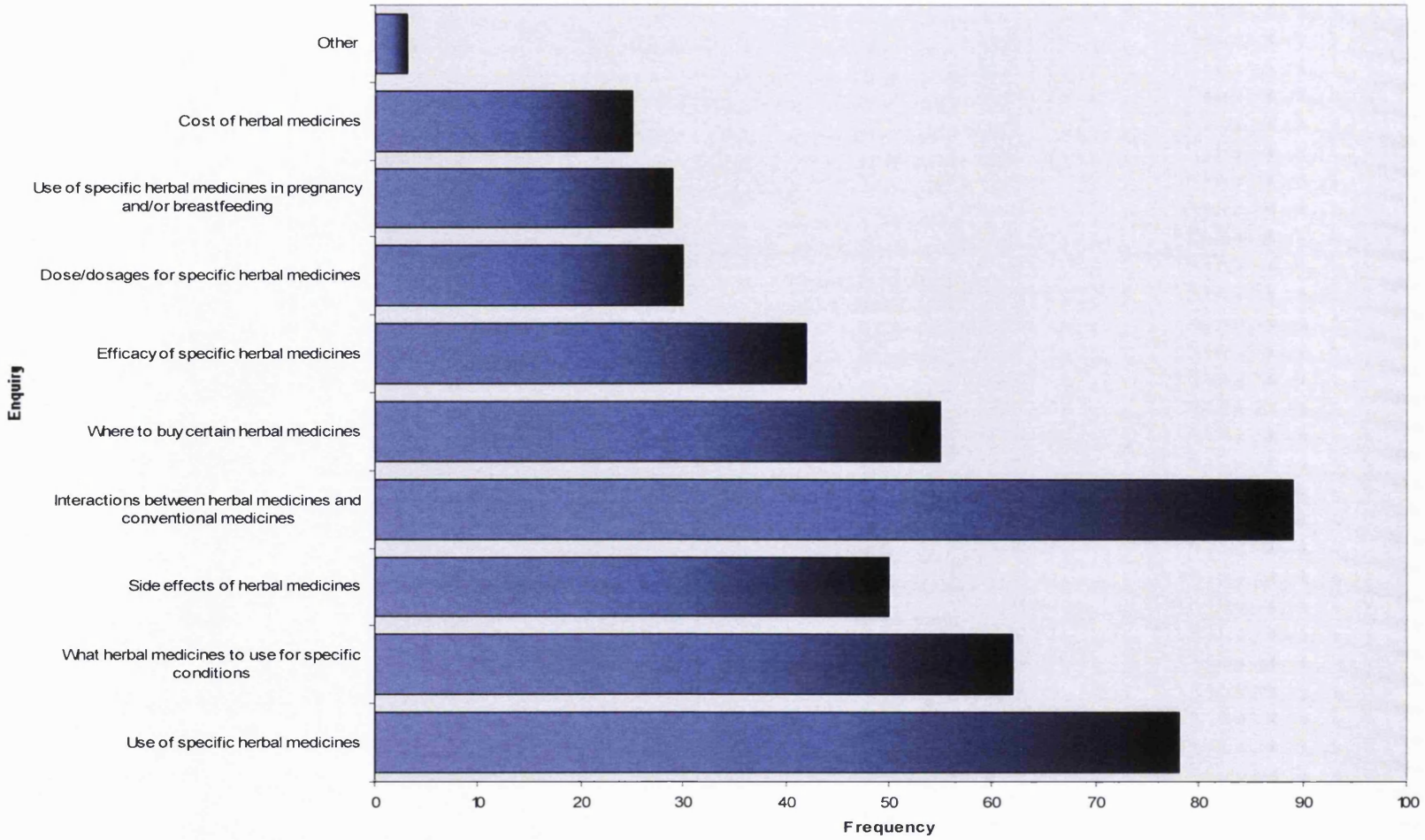


Figure 5.5 Enquiries received by community pharmacists over a period of 7 days

5.5.3.9 Information sources on herbal medicines

Figure 5.6 show that the most popular information sources available and used by community pharmacists were the Martindale, the NPA and the products' manufacturers. Few pharmacists used the RPSGB information department despite having this resource available. These findings are consistent with the focus group data in phase one section 5.4.3.9.

Pharmacists were asked for specific resources that they would like to have available to assist them in advising on herbal medicines. The majority requested for up-to-date herbal reference books or herbal versions of common reference books such as the BNF, Martindale and Datasheet Compendium:

"*A reference source similar to BNF on herbal medicines*" [female respondent 20]

Many pharmacists also stated that they would like access to the internet:

"*Internet access in store*" [female respondent 61]

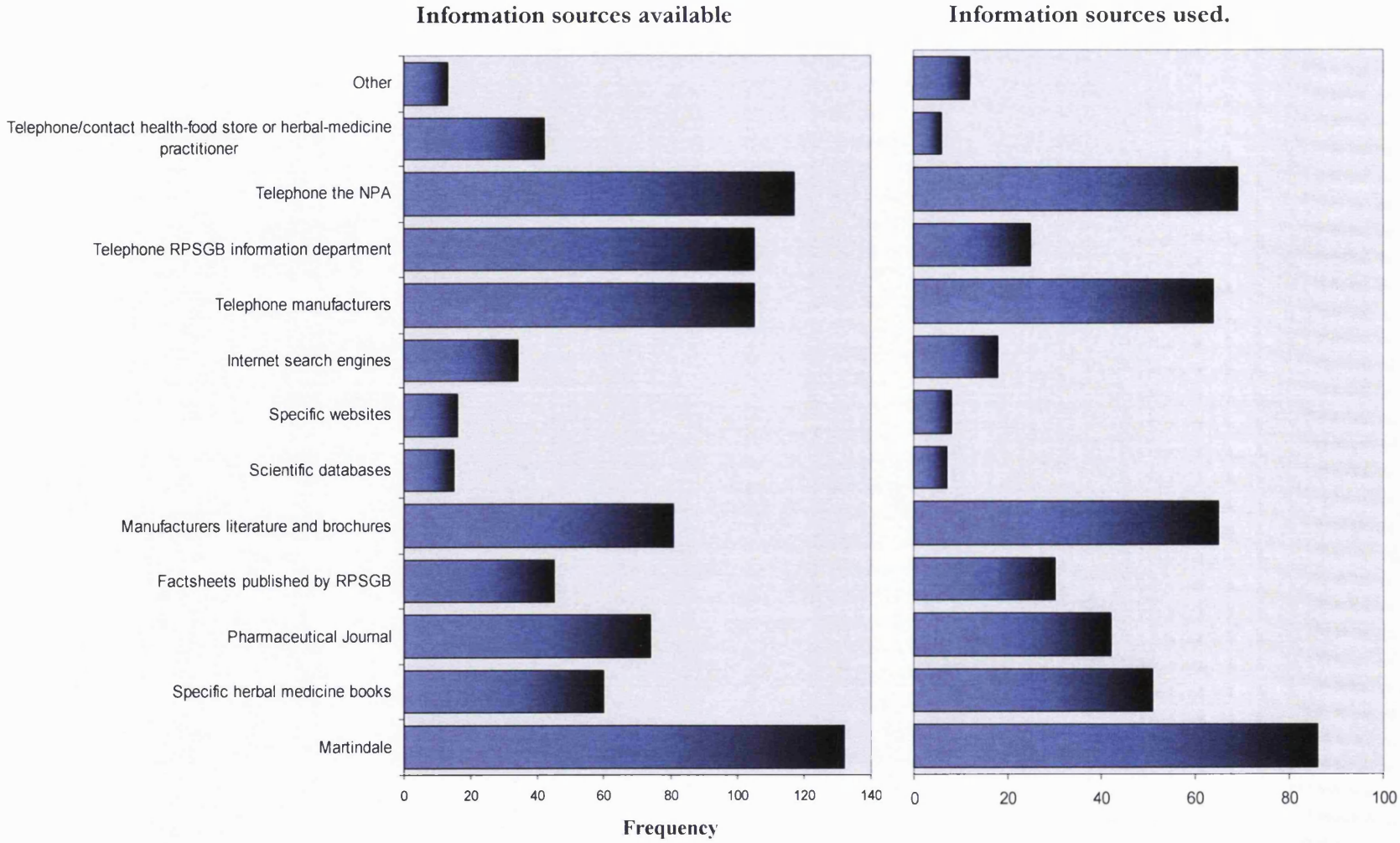


Figure 5.6 Information sources available in the pharmacy and those used by community pharmacists

5.5.3.10 Training in herbal medicines

Since registering as a pharmacist, 104 (62.3%) pharmacists had undertaken training in herbal medicines. Table 5.11 shows that the majority of pharmacists completed distance learning packages and continuing professional development (CPD) activities. CPD activities included reading articles in The Pharmaceutical Journal and books on the subject matter.

Table 5.11 Postgraduate training undertaken in herbal medicines (n = 104) †

Training	Yes/No (%)
Employer-provided training	28/61 (26.9/58.7)
Distance-learning packages	64/31 (61.5/29.8)
Workshops, seminars, local branch lectures	29/59 (27.9/56.7)
Formal postgraduate course	3/78 (2.9/75.0)
Continuing professional development activities	43/45 (41.3/43.3)
Relevant research degree	2/77 (1.9/74.0)
Other (*e.g.* manufacturers course)	4/29 (3.8/27.9)

† Percentages do not total 100 because of missing data

As part of the undergraduate studies 137 (82.0%) of community pharmacists stated that they received some form of teaching in herbal medicines and/or pharmacognosy. Table 5.12 shows that the majority of training received was in the undergraduate core curriculum as a specific stand-alone pharmacognosy/natural products course.

Table 5.12 Undergraduate teaching on herbal medicines, n=137, (%)

Course	Core	Elective
Specific stand-alone pharmacognosy/natural products	99(72.3)	15 (10.9)
Specific stand-alone herbal and/or complementary medicines	16 (11.7)	7 (5.1)
Pharmacognosy/natural products teaching integrated as part of another	51(37.2)	8 (5.8)
Herbal and/or complementary medicines course integrated as part of another	26 (19.0)	7 (5.1)

5.5.3.11 Knowledge in herbal medicines

Table 5.13 show that the majority of pharmacists felt that they were "quite competent for a few herbal medicines".

Table 5.13 Frequency data for pharmacists perceived competence in herbal medicines	
Competent for most herbal medicines	3
Quite competent for most herbal medicines	23
Quite competent for a few herbal medicines	94
Not competent for most herbal medicines	44

The majority of pharmacists, 128 (76.6%), mentioned some form of CPD activity as a tool that they would be willing to use to achieve a satisfactory level of competence in advising patients and the public on the safe and effective use of herbal medicines. In total, 87 (52.1%) pharmacists mentioned distance learning packages such as the CPPE as a specific CPD activity that they would undertake.

5.5.3.12 ADR reporting for herbal medicines

While working as a community pharmacist, 87 (52.1%) stated that they had either identified or received a report from a patient or customer of a suspected ADR associated with a medicine (including herbal and complementary medicines). Of these, 18 community pharmacists stated that the ADR had been associated with a herbal medicine and had occurred in the last 12 months. Data was only available for 15 of the community pharmacists. The total number of reports identified or received in the last 12 months was 36.

In total, 81 reports were claimed to have been submitted by 34 (20.4%) community pharmacists. Of these, 7 involved suspected ADRs associated with the use of herbal medicines, submitted by 4 different pharmacists. Three reports were submitted in the last 12 months by one pharmacist which showed that certain individual pharmacists are more proactive in submitting ADR reports. This data shows that community pharmacists are identifying and receiving more ADR reports associated with herbal medicines than they are

submitting. This in part can be explained by the results in table 5.14 and figure 5.7 which show the criteria used by pharmacists for the submission of a yellow card report for a suspected ADR associated with a herbal medicine.

Table 5.14 Criteria for the submission of a yellow card report for a suspected ADR associated with a herbal medicine (n=167)†	
	Yes/No (%)
The ADR must be serious	83/73 (49.7/43.7)
The ADR must be previously unknown for that herbal medicine	61/95 (36.5/56.9)
I must be certain that the herbal medicine caused the ADR	92/72 (55.1/43.1)
The herbal medicine has to be a licensed product	29/127 (17.4/76.0)
The herbal medicine has to be an unlicensed product	10/139 (6.0/83.2)
† Percentages do not total 100 because of missing data	

In total, 32 (19.2%) pharmacists knew that all five criteria were incorrect. Figure 5.7 shows the distribution of scores for criteria used in the submission of a yellow card report for a suspected ADR associated with a herbal medicine.

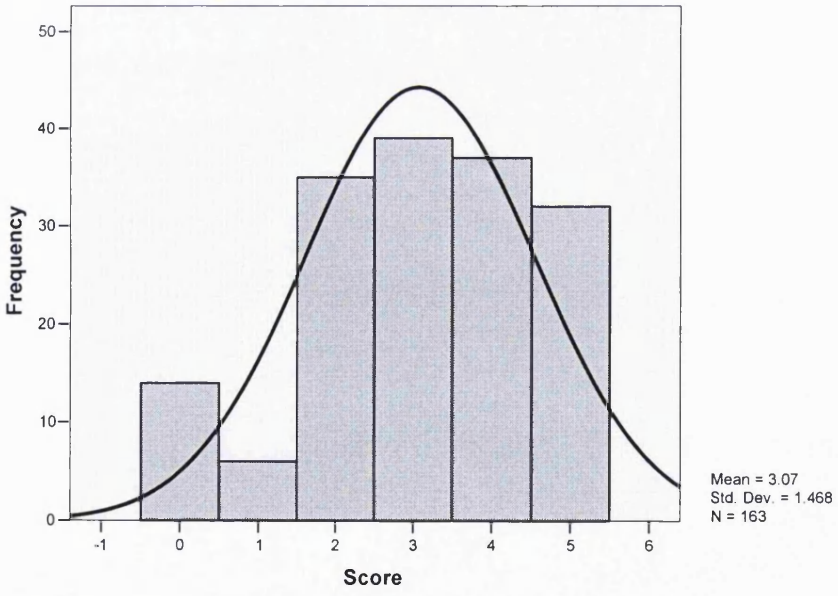


Figure 5.7 Histogram of overall scores for correctly identifying the criteria used for the submission of a yellow card report for a suspected ADR associated with a herbal medicine

5.5.3.13 Views of respondents on issues regarding herbal medicines

Respondents were asked to indicate their level of agreement on a Likert scale for the statements in table 5.15. The scale comprised of five points: 5 = strongly agree, 4 = agree, 3 = neutral, 2 = disagree and 1 = strongly disagree. To help with analysis, codes 5 and 4 were combined into "agree" and codes 1 and 2 were combined into "disagree". Factor analysis was used to identify any underlying concepts or constructs – *i.e.* groups of items that seemed to measure the same thing.

Table 5.15 Respondents views on issues around herbal medicines, n = 167 (%)†			
Statement	Disagree	Neutral	Agree
1. Community pharmacies should not sell any herbal medicines	131 (78.4)	31 (18.6)	4 (2.4)
2. Herbal medicines should only be available from pharmacies	62 (37.1)	51 (30.5)	53 (31.7)
3. Pharmacies should only sell licensed herbal medicines	19 (11.4)	25 (15.0)	118 (70.7)
4. Herbal medicines should be required to have a product licence/marketing authorisation to be placed on the market	8 (4.8)	20 (12.0)	137 (82.0)
5. Herbal medicines should be manufactured to Good Manufacturing Practice standards	0 (0)	1 (0.6)	165 (98.8)
6. Herbal medicines should not be manufactured to the same standards as conventional medicines	143 (85.6)	14 (8.4)	6 (3.6)
7. Licensed herbal medicinal products should be included in the British National Formulary	6 (3.6)	22 (13.2)	139 (83.2)
8. Community pharmacists are in an ideal position to monitor for ADRs associated with herbal medicines	7 (4.2)	17 (10.2)	142 (85.0)
9. Yellow card reports for suspected ADRs should not be submitted for unlicensed herbal medicines	134 (80.2)	24 (17.4)	9 (5.4)
10. Patients/consumers should be able to submit yellow card reports for suspected ADRs associated with herbal medicines	34 (20.4)	29 (17.4)	104 (62.3)
11. I am more likely to submit a yellow card report for a suspected ADR associated with the use of a conventional OTC medicine than for the same suspected ADR associated with the use of a licensed herbal medicine	80 (47.9)	38 (22.8)	48 (28.7)
12. I am more likely to submit a yellow card report for a suspected ADR associated with the use of a conventional OTC medicine than for the same suspected ADR associated with the use of an unlicensed herbal medicine	74 (44.3)	35 (21.0)	58 (34.7)
13. It is part of the pharmacist's role to disseminate information to patients/consumers about herbal safety concerns	7 (4.2)	18 (10.8)	140 (83.8)
14. Staff in health-food stores are best placed to provide advice on herbal medicines	102 (61.1)	50 (29.9)	14 (8.4)
15. Advising on herbal medicines should be part of pharmacists' professional practice	6 (3.6)	40 (24.0)	121 (72.5)
16. I require more training on herbal medicines to be competent in advising patients/customers on herbal medicines	4 (2.4)	8 (4.8)	155 (92.8)
17. Community pharmacists should only sell or advise on herbal medicines if they have undertaken formal training in herbal medicines	35 (21.0)	42 (25.1)	90 (53.9)
18. Training in herbal medicines should be part of the pharmacy undergraduate compulsory curriculum	13 (7.8)	33 (19.8)	121 (72.5)
19. Training in herbal medicines should be part of the pharmacy undergraduate optional curriculum	67 (40.1)	43 (25.7)	55 (32.9)
† Percentages do not total 100 because of missing data			

Table 5.16 shows the correlation matrix of the statements. The determinant of the matrix was 0.06 which is greater than the value of 0.00001, and so ruled out multicollinearity. However, questions 11 and 12 had Kaiser-Meyer-Olkin (KMO) values of 0.318 and 0.289, respectively and were thus, eliminated from analysis. Elimination of these questions produced an overall KMO value of 0.640 which is above the stated minimum value of 0.5. This showed that factor analysis could be used. Also, the Barlett's test of sphericity was significant (Bartlett's Test = 0.000) which showed that the majority of these items were sufficiently related to proceed with factor analysis.

Table 5.16 Survey item correlation matrix

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
1	1.000																		
2	.025	1.000																	
3	.232	.188	1.000																
4	.113	.135	.546	1.000															
5	-.138	.047	.306	.316	1.000														
6	.052	.041	-.109	-.342	-.390	1.000													
7	-.117	.064	.008	.081	.258	-.133	1.000												
8	-.155	.221	.116	.116	.267	-.056	.247	1.000											
9	.262	.053	.099	-.018	-.071	.331	-.269	-.149	1.000										
10	-.079	-.022	.023	.080	.148	-.155	.154	.172	-.044	1.000									
11	.235	-.110	.111	-.116	-.040	.166	-.166	-.126	.334	-.086	1.000								
12	.310	-.061	.163	-.004	.017	.134	-.219	-.187	.400	-.210	.797	1.000							
13	-.255	.019	-.159	-.081	.164	-.135	.202	.159	-.221	.093	-.146	-.222	1.000						
14	.104	-.356	-.066	-.134	-.041	.018	-.153	-.229	-.007	-.011	.288	.244	-.080	1.000					
15	-.365	.008	-.074	.037	.044	-.093	.290	.266	-.130	.128	-.154	-.261	.343	-.353	1.000				
16	.150	.036	.063	.102	.169	-.121	.284	.061	.029	-.024	.137	.152	-.023	-.035	.061	1.000			
17	.285	.128	.242	.164	.083	-.105	-.037	-.018	.081	.021	.220	.250	-.069	.168	-.074	.269	1.000		
18	-.112	.045	-.105	.038	.042	-.075	.265	.115	-.095	.067	-.031	-.066	.185	-.221	.471	.115	-.025	1.000	
19	.110	.021	.103	-.048	.028	.095	-.130	-.043	.090	-.021	.009	.065	-.132	.166	-.313	-.073	-.042	-.540	1.000

Principal Component Analysis (PCA) was used to extract factors (see table 5.17). Kaiser's criterion of retaining factors with eigenvalues greater than one was applied, leaving five factors.

Table 5.17 Total variance explained

	Initial Eigenvalues			Extraction Sums of Squared Loadings		
Component	Total	% of Variance	Cumulative %	Total	% of Variance	Cumulative %
1*	2.973	17.488	17.488	2.973	17.488	17.488
2*	2.313	13.603	31.091	2.313	13.603	31.091
3*	1.585	9.321	40.413	1.585	9.321	40.413
4*	1.437	8.452	48.864	1.437	8.452	48.864
5*	1.138	6.695	55.559	1.138	6.695	55.559
6	.996	5.862	61.421			
7	.904	5.317	66.737			
8	.846	4.975	71.713			
9	.763	4.489	76.201			
10	.698	4.107	80.308			
11	.669	3.936	84.244			
12	.628	3.694	87.938			
13	.498	2.929	90.867			
14	.464	2.731	93.598			
15	.432	2.540	96.138			
16	.368	2.162	98.300			
17	.289	1.700	100.000			

* factors extracted

The five extracted factors were rotated using the varimax method (SPSS, 2003). Varimax was used as it produces more interpretable factors (Field, 2005). The component matrix is displayed in table 5.18. Factors less than 0.4 were omitted. With the exception of statement 10, the matrix displays the relationship between the extracted factors.

Table 5.18 Rotated component matrix					
	Factor				
Statement	1	2	3	4	5
9	-.593				
7	.579				
5	.533		.475		
13	.514				
1	-.490				.486
10					
19		-.828			
18		.820			
15		.617			
4			.835		
3			.741		
6	-.460		-.546		
2				.719	
14				-.682	
8	.454			.553	
16					.794
17					.631

Table 5.19 shows the interpretation of the factors.

Table 5.19 Interpreting the factors	
Factor one: Standards Items related to factor 1 describe pharmacists' views towards improving standards with regards to herbal medicines. For example, products should be produced to a specific quality and pharmacists should be involved in the sales and pharmacovigilance of them.	**Positive** Licensed herbal medicinal products should be included in the British National Formulary Herbal medicines should be manufactured to Good Manufacturing Practice standards It is part of the pharmacist's role to disseminate information to patients/consumers about herbal safety concerns
	Negative Community pharmacies should not sell any herbal medicines Yellow card reports for suspected ADRs should not be submitted for unlicensed herbal medicines
Factor 2: Knowledge and professional practice Items related to factor 2 describe pharmacists' views related to their knowledge and professional practice *i.e.* training should be compulsory rather than optional to adequately prepare pharmacists for advising the public.	**Positive** Training in herbal medicines should be part of the pharmacy undergraduate compulsory curriculum. Advising on herbal medicines should be part of pharmacists' professional practice.
	Negative Training in herbal medicines should be part of the pharmacy undergraduate optional curriculum
Factor 3: Licensing and quality Items relating to factor 3 describe pharmacists' perception towards the licensing and quality of herbal medicines *i.e.* they should be licensed and produced to a certain quality, for them to be sold within a pharmacy.	**Positive** Herbal medicines should be required to have a product licence/marketing authorisation to be placed on the market Pharmacies should only sell licensed herbal medicines
	Negative Herbal medicines should not be manufactured to the same standards as conventional medicines
Factor 4: Restriction of availability Items related to factor 4 describe pharmacists' view to restrict the availability of herbal medicines to pharmacies as they are best placed to offer advice on herbal medicines and monitor suspected ADRs associated with them.	**Positive** Herbal medicines should only be available from pharmacies Community pharmacists are in an ideal position to monitor for ADRs associated with herbal medicines
	Negative Staff in health-food stores are best placed to provide advice on herbal medicines.
Factor 5: Community pharmacists role Only two items related to factor 5 therefore it was excluded from further analysis.	**Positive** Community pharmacists should only sell or advise on herbal medicines if they have undertaken formal training in herbal medicines I require more training on herbal medicines to be competent in advising patients/customers on herbal medicines

The internal reliability of the extracted factors was determined using Cronbach's alpha (see table 5.20). For each item excluded, alpha values were also calculated to ensure the reliability of each item within that factor. An alpha value between 0.7 and 0.9 is considered good - very good, although this was not achieved for most of the factors. However, as the alpha values if the item was deleted, were consistent with the overall alpha value for the factor, this showed reliability of the item within that factor. Also the corrected item-total correlations (excluding item 6) show consistency.

Table 5.20 Reliability coefficients of the extracted factors

	Item	Corrected item-total correlations	α if item deleted
Factor 1 α = 0.53	7	0.35	0.45
	5	0.30	0.49
	13	0.25	0.51
	9	0.30	0.48
	1	0.33	0.46
Factor 2 α = 0.72	18	0.65	0.49
	15	0.47	0.72
	19	0.57	0.64
Factor 3 α = 0.62	4	0.60	0.23
	3	0.44	0.51
	6	0.26	0.69
Factor 4 α = 0.53	2	0.39	0.38
	8	0.27	0.54
	14	0.41	0.33

Scale scores for each factor were calculated and histograms for each factor were plotted (see figure 5.8, 5.9, 5.10 and 5.11). The distribution of scores for factor two (figure 5.9) were bimodal showing that the respondents either agreed or disagreed with the items. Also for all four factors the arithmetic mean was below the mean score for each factor, which shows that the majority of respondents held a positive view towards each factor.

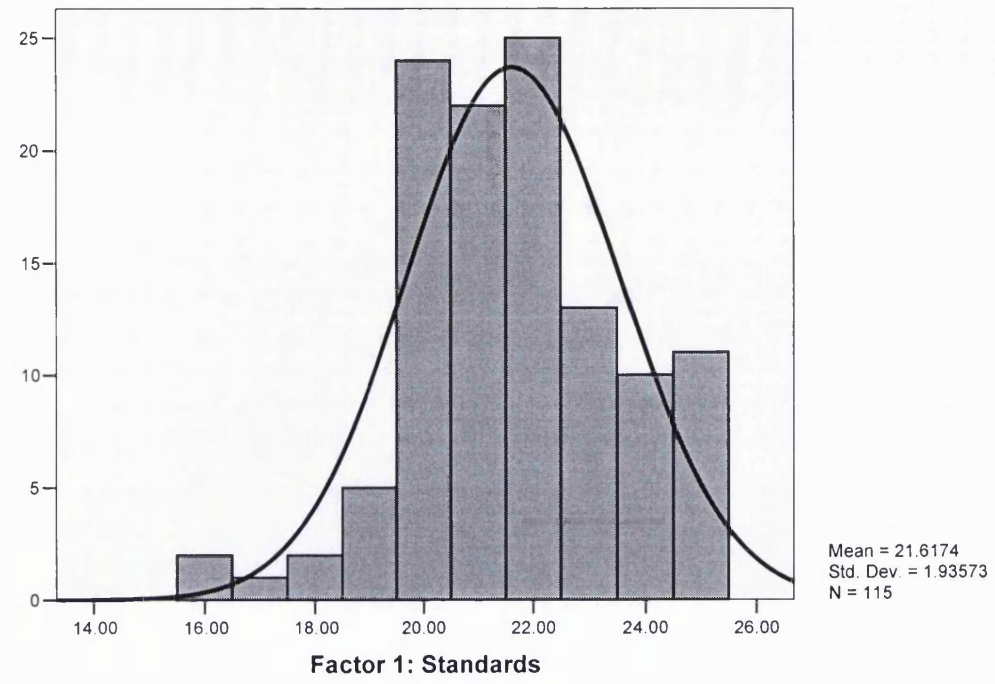


Figure 5.8 Histogram to display distribution of scores for factor one

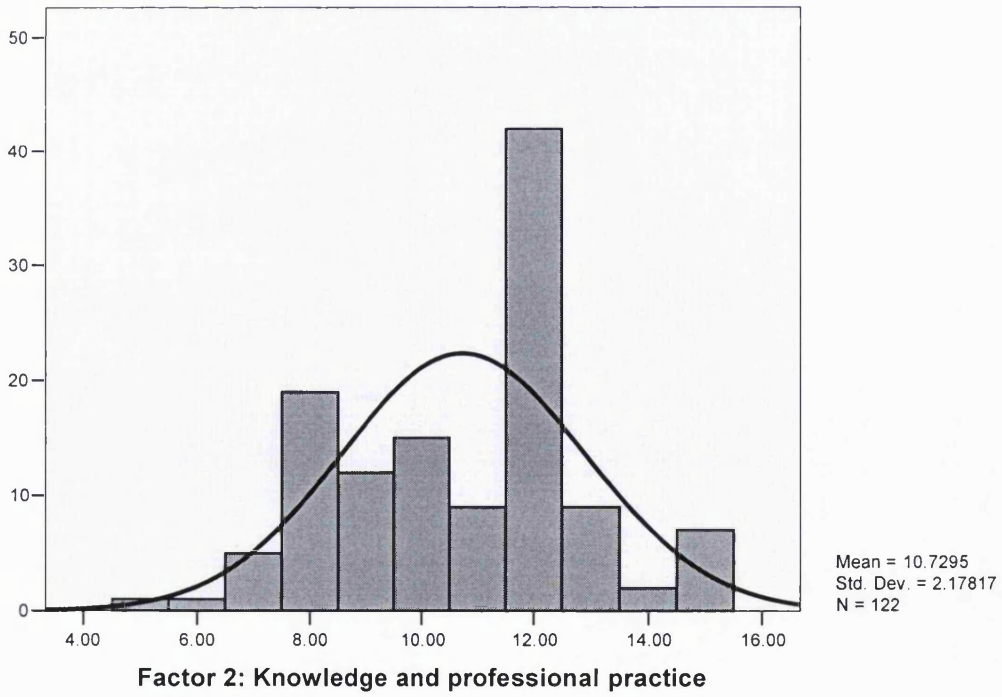


Figure 5.9 Histogram to display distribution of scores for factor two

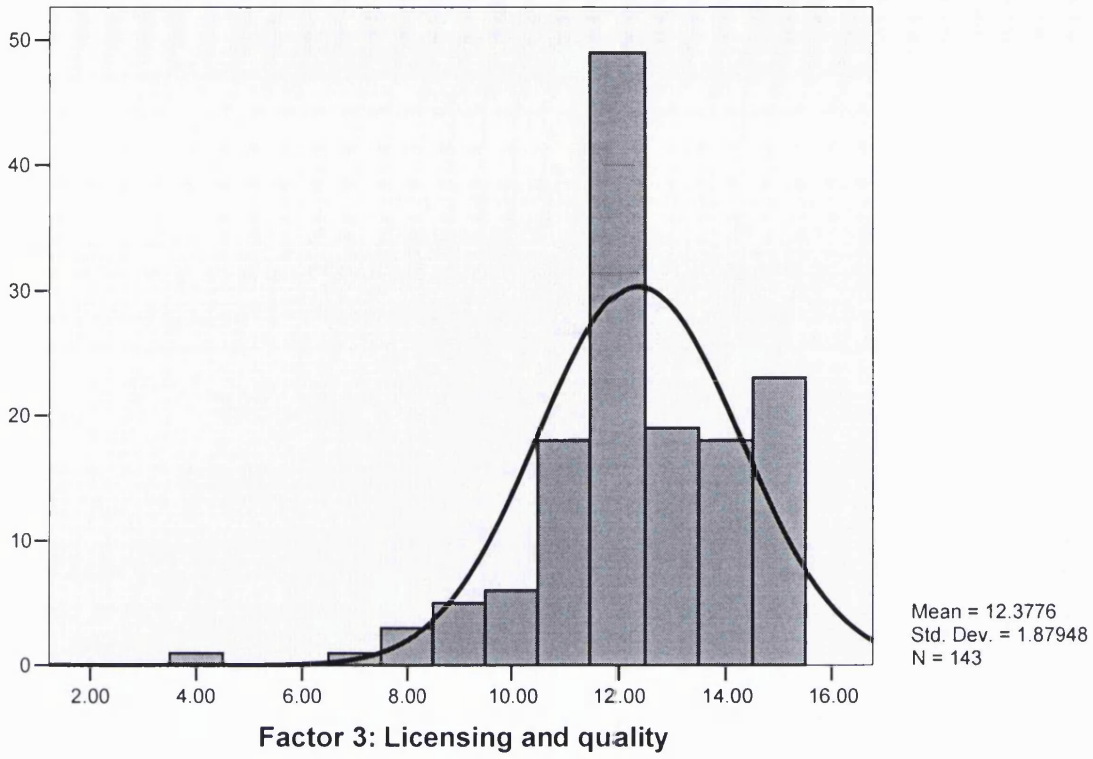


Figure 5.10 Histogram to display distribution of scores for factor three

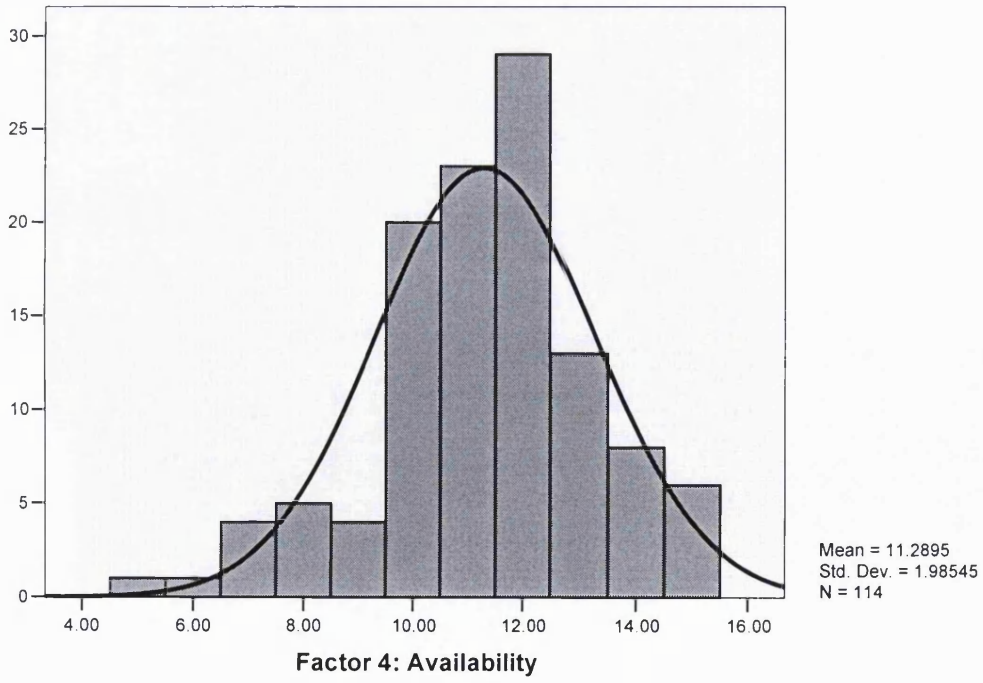


Figure 5.11 Histogram to display distribution of scores for factor four

The relationships between the scores assigned and demographic characteristics of the respondents were explored, by dividing the respondents into high and low scorers according to mean score for each factor. Correlation coefficients are summarised in table 5.21. There was no statistically significant difference between the factors and the respondents demographics (p>0.05; for all).

Table 5.21 Correlations between the factors and respondent demographics (n=167)

	Pearsons correlation coefficient (p value)			
	Factor 1	**Factor 2**	**Factor 3**	**Factor 4**
Gender	3.21 (0.20)	1.19 (0.55)	2.17 (0.34)	1.01 (0.61)
Age group	5.90 (0.21)	6.02 (0.20)	2.09 (0.72)	3.92 (0.42)
Registration year group	3.45 (0.49)	1.58 (0.81)	4.08 (0.40)	3.97 (0.41)

5.6 Overall discussion

The definition for herbal medicines and what products are classified as herbal clearly caused much confusion amongst pharmacists and it is concerning that few pharmacists could correctly define herbal medicines. As outlined in section 1.5.1, herbal medicines essentially include plant juices, gums, essential oils and other directly derived crude plant products. Thus, natural products such as bacteria, fish oils, glucosamine, vitamins and minerals are non-herbal. The European Pharmacopoeia and The Medicines Act 1968 define herbal medicines as those where the plant should be subject to a relatively simple process of drying, fragmenting or crushing (see section 1.5.1). Thus, it does not include semi-synthetic products or chemically defined isolated constituents such as digoxin and aspirin even though they have botanical origins.

It appears that pharmacists used the term conventional and unconventional to differentiate as to whether or not a product was herbal or non-herbal, which was demonstrated by the following quote (section 5.5.3.5):

"*Medicines of plant origin which are not conventional medicines*" [female respondent 222]

Contrary to this, there are conventional medicines that are also classified as herbal *e.g.* senna. The difficulty of utilising the term unconventional for herbal medicines has been raised in The Pharmaceutical Journal (Houghton, 2006). This was also demonstrated in phase I, as many pharmacists viewed senna as a conventional medicine and thus, as a non-herbal medicine for the following reasons:

- it is a licensed preparation
- it is standardised
- it has been available on the market for a number of years
- it's active constituent is known

However, none of these criteria influence whether or not a product is herbal or non-herbal. For example, standardisation refers to where an active constituent is known in a herb and the product is then standardised to contain a specific amount of that constituent. This indicates that the product has undergone some form of quality control and minimises batch-to-batch variation. These misconceptions may also explain as to why pharmacists scored poorly when trying to assign the following so called "conventional" medicines; colpermin capsules, senokot syrup and fybogel sachets as herbal or non-herbal within phase II.

There was also confusion regarding the classification of homeopathic preparations, as in phase I some pharmacists expressed that they were dilute preparations with negligible effect and therefore non-herbal, irrespective of whether or not they contained a herbal ingredient. This was also reflected in phase II as the majority of pharmacists (52.1%) classified homeopathic preparations of dilute plant material as non-herbal. Herbal medicines are complicated as they can span across many therapies including aromatherapy, homeopathy, ayurveda *etc.* However, the concentration of the preparation does not influence whether or not a product is considered herbal or non-herbal, for example, Arnica homeopathic cream is derived from the plant *Arnica Montana,* thus, it is a herbal medicine, irrespective of its concentration.

As seen in phase I, on further deliberation some pharmacists were able to correctly assign products *e.g.* essential oils, which could be attributed to their scientific background. Despite, pharmacists viewing that their training in herbal medicines, through the pharmacognosy component of the undergraduate syllabus, did not adequately fulfil their requirements for

practice at that time, it could be argued that this form of undergraduate training provided a firm grounding in herbal medicines. There has been much debate amongst academics on whether or not undergraduate training should be scientific or practice based (Florence, 2006; Nathan, 2006; Husband 2007). The trends in the course content of UK schools of pharmacy are further investigated under chapter 6.

The majority (86.8%) of pharmacies stocked herbal medicines, which is consistent with previous findings (Barnes and Abbott, 1999). Decisions to stock a product within a pharmacy were predominantly consumer demand based. Thus, it was not unexpected that popular products included Echinacea, St John's wort, Milk thistle, Ginkgo, Fever few and Calendula, as these have received much attention in the press. Most pharmacists reported stocking herbal medicines alongside vitamins, minerals and other dietary supplements, which some felt caused confusion between distinguishing what are herbal medicines. There was a clear difference between pharmacies in terms of whether they stocked mainly licensed or unlicensed products. Some pharmacists (9.0%) also had no idea as to what products their pharmacy stocked, which is concerning as the RPSGB Code of Ethics (2006) states that "pharmacists providing homoeopathic or herbal medicines or other complementary therapies have a professional responsibility to ensure that stocks of homoeopathic or herbal medicines or other complementary therapies are obtained from a reputable source of supply". Where pharmacists had control, products were selected according to the manufacturers' reputation. In principle this would satisfy the ethical obligations set out by the code of ethics, but when taking into consideration that the products available are largely unlicensed, this is debatable. Clearly further work is required on what factors pharmacists consider when classifying a manufacturer to be 'reputable', the lengths taken by pharmacists to ensure the quality of the product and interpretation of the code of ethics.

Both phase I and phase II showed that most pharmacists felt that the pharmacy was the appropriate place to sell herbal medicines and held the opinion that herbal medicines are important to pharmacy as they play an integral part to the patients' overall care, which is encouraging. Some pharmacists (31.7%) even viewed that the sales of herbal medicines should be restricted to pharmacies only. However, many pharmacists expressed a reluctance to recommend herbal medicines due to insufficient information on the product and felt that their

knowledge on herbal medicines was not adequate. Thus, if pharmacists are to take a lead on herbal medicines, they need to undertake further training and require further information.

Previous work by Quinn and Waterman (1997), show that 78% of the 112 community pharmacists surveyed reported that they had received no formal training on herbal medicines. Inversely, this study showed that the majority of pharmacists, (82.0%), had received some form of teaching in herbal medicines as part of their undergraduate course, which is encouraging. This was predominantly as a specific stand-alone pharmacognosy/natural products course. Also most pharmacists felt that training in herbal medicines should be compulsory in the undergraduate curriculum and that postgraduate training should be voluntary and based upon the individuals need. Pharmacists reported in phase I that a CPPE package would provide an ideal method for postgraduate training, but as stated by some pharmacists, herbal medicines form a low percentage of their daily activities and it would not be unexpected that training in herbal medicines is a low priority for pharmacists. However, from phase II, 62.3% of community pharmacists stated that they had undertaken training in herbal medicines since registering as a pharmacist and the majority had done this *via* distance learning packages. The course content for both undergraduate and post-graduate needs to be explored as despite the available training, few pharmacists (15.9%) rated their perceived competence in herbal medicines to be above "quite competent" for a few herbal medicines, also in phase I it was highlighted that counter staff in some cases possessed the same level of knowledge as the pharmacist.

In phase I, most pharmacists stated that not enough information was available on herbal medicines and as a result they had to rely on information supplied by the manufacturers, despite knowing that the information supplied may be biased. Phase II also demonstrated that manufacturers were a popular information source and that few community pharmacists used the RPSGB information department despite having this resource available. Pharmacists also expressed that the lack of information available on herbal medicines was in part responsible for their lack of knowledge and their ability to advise the public appropriately. Thus, most pharmacists held the opinion that there should be tighter control of herbal medicines so that information on the safety, efficacy and quality of the product are available. The majority of pharmacists requested for the development of a 'quick herbal reference book', similar to the BNF, which is consistent with the findings in phase II where the majority of pharmacists,

requested for up-to-date herbal reference books or herbal versions of common reference books.

The majority of pharmacists stated that they were asked for advice by the public on herbal medicines, which is consistent with previous findings (Barnes and Abbot, 1999). However, the level varied between stores and as expressed by one participant it is difficult to assess the volume of work as a number of queries are dealt directly by the counter staff. Phase II identified that the majority of enquiries received by pharmacists involved interactions between herbal medicines and conventional medicines, use of specific medicines and recommendations for specific conditions. Phase I showed that some pharmacists felt that the public viewed pharmacists as a professional in medicines and thus, approached them for advice.

It is encouraging that most of the participants in phase II believed that advising on herbal medicines should be part of their professional practice (72.5%). However, it is clear that most pharmacists require more training to be competent in advising, as in phase II the majority (92.8%) of pharmacists agreed/strongly agreed with the statement "I require more training on herbal medicines to be competent in advising patients/customers on herbal medicines". Also in phase I some participants expressed the opinion that health food shop assistants were currently more able to deal with public enquiries. The question on whether or not community pharmacists are better than health food shop assistants in giving advice on herbal medicines has been previously investigated (see section 1.5.2), but is inconclusive, largely due to flaws in the study method.

Phase I established that most pharmacists were unaware of how herbal medicines were regulated and that few pharmacists considered submitting a yellow card report for a suspected ADR associated with a herbal medicine. Also, it was identified that most pharmacists would either contact the manufacturer or instruct the consumer to stop taking the product to see if their symptoms subsided, if they suspected an ADR associated with a herbal medicine. Those pharmacists that did consider submitting a yellow card report for a suspected ADR associated with a herbal medicine said they would if the reaction was serious, unreported or if they could assign causality, which shows a lack of understanding of the current pharmacovigilance system. These findings were confirmed by phase II as community pharmacists were identified as receiving more ADR reports associated with herbal medicines than they were submitting them

to the MHRA. In addition to these findings, the majority of pharmacists were unable to correctly identify the criteria used for the submission of a yellow card report for a suspected ADR associated with a herbal medicine, which again shows a poor of understanding of the current pharmacovigilance system and the need for further education/training in this area.

Factor analysis was used to explore the respondents view's on issues regarding herbal medicines. Four underlying concepts (factors 1, 2, 3 and 4) were identified relating to:

- Standard of herbal medicines
- Knowledge and professional practice
- Licensing and quality
- Restriction of herbal medicines to pharmacies

The majority of respondents showed a positive response to each factor *e.g.* training in herbal medicines should be compulsory in the undergraduate curriculum and herbal medicines should be licensed (see table 5.19), which again supports the above findings.

5.6.1 Limitations

As outlined in section 3.6.1, there is much debate as to what constitutes an acceptable response rate as recent studies suggest a low response rate is common with questionnaires involving healthcare professionals due to the volume of requests received by them (McAvoy and Kaner, 1996). The questionnaire had been piloted to ensure that the questionnaire took less than 20 minutes to complete and predominantly tick boxes had been utilised to minimise time to complete the questionnaire. Despite these efforts a low response rate (33.6%) was observed in phase II of the study. A number of steps such as reducing the length of the questionnaire and specifically focusing on questions related to the reporting of herbal ADRs or providing an incentive (financial or CPD credits) may have increased the response rate. It is also known that at the time of administration of the questionnaire, the implementation of the new NHS contract was proceeding which had significantly increased the workload of community pharmacists and therefore could have contributed to the poor response rate. Lastly it is possible that community pharmacists are not interested in herbal medicines or they do not perceive them as being important, as mentioned in phase I of the study that herbal medicines

do not form a major part of their workload/day-to-day activities. However, irrespective of the low response rate for phase II, the overall findings from phase II were consistent with phase I.

There are a number of inherent limitations associated with focus groups as outlined under section 3. However, in addition to these it was not ideal that the author had not conducted the focus group discussions. As a result of this it was vital to fully appreciate what conversations took place in the discussions and to accurately reflect the interview process, thus all transcripts were carefully checked for omissions using both the field notes and audio recordings. The audio recordings were repeatedly played and listened to. Key themes emerging were also independently reviewed for consistency. It was apparent that an overwhelming majority of participants shared similar views throughout the discussions. These views were also confirmed by the findings from the quantitative study, which was one of the primary aims of conducting the second arm of the study. In addition to adding validity to the qualitative data, the second arm of the study (Phase II) also eliminated the introduction of bias by the facilitator.

All research should have ethics approval, as it increases the robustness of the study. However, at the time of conducting the study, community pharmacists were considered outwith the NHS as they are independent contractors and therefore outside the remit of the central office for research ethics committee. A letter of confirmation is included in appendix 3. As The School of Pharmacy does not have an in-house ethics panel, The University of London ethics board was contacted to see if they would review the study protocol and documents, however this was declined despite an affiliation with the institute. Thus, a peer review of the study was conducted by an expert in the field. As the focus groups were conducted prior to starting the doctorate training, it is possible that the same hurdles existed and thus ethics approval was not sought. Also it is not known if there was such a drive by researchers to gain ethics approval at that time.

Initially it was planned to conduct subset analysis (pharmacists working in multiples *versus* independents, locums *versus* permanently employed pharmacists) for the quantitative data to identify trends. However, this was not conducted for the following reasons:

- The objective of the study was to overall explore community pharmacists' experiences with and views on herbal medicines

- Data division would reduce the sample size further
- Qualitative data from phase 1 did not identify any differences in opinions between different subgroups of pharmacists
- Pharmacists do not remain static within their field of work

5.7 Overall conclusion

In conclusion, the above study showed that there was a lack of understanding amongst pharmacists regarding the following:

- definition of herbal medicines
- categorisation of products
- licensing requirements
- quality controls
- pharmacovigilance aspects with respect to herbal medicines

Pharmacists do perceive that herbal medicines are an integral part of their professional practice, as herbal medicines play an important part to a patients overall care. If pharmacists are to take a lead they need further undergraduate and postgraduate education and training. Currently there is a lack of reliable information on herbal medicinal products and thus, a reference book similar to the BNF is needed. Thus, the findings from the above studies also provide essential background information for the other chapters presented in this thesis, in particular, to support the rational for the training of pharmacists to enhance herbal ADR reporting levels.

Chapter 6

TRENDS IN THE TEACHING OF PHARMACOGNOSY/NATURAL PRODUCTS, HERBAL MEDICINES AND COMPLEMENTARY/ALTERNATIVE MEDICINES: A CROSS-SECTIONAL SURVEY OF UK SCHOOLS OF PHARMACY

6.1 Background

The teaching of pharmacognosy to pharmacy undergraduates has become more relevant with the increased use of herbal medicines, as community pharmacists are in the best place to advise the public on the safe and effective use of these products (see section 1.6). However, there are concerns that teaching in pharmacognosy is insufficient and has led to a generation of pharmacists that are unschooled in the safe use of plants as medicines. There is also evidence to suggest that community pharmacists are often inadequately trained in herbal medicines (Quinn and Waterman, 1997) especially in relation to their pharmacovigilance (Barnes and Abbot, 1999; Chang *et al.*, 2000).

Academic pharmacists in the UK continue to make calls for increased emphasis on the teaching of pharmacognosy and herbal medicinal products in undergraduate Masters of Pharmacy (MPharm) programmes at UK schools of pharmacy (Houghton and Barnes 2004; Florence, 2006). Even the Lancet has acknowledged this in a recent editorial entitled "Don't forget pharmacognosy" (Lancet, 2006). Further to this, at present pharmacovigilance is not an established academic specialism and current pharmacy curriculum does not cover all aspects of pharmacovigilance, particularly regarding herbal medicines. For example, most UK schools of pharmacy include teaching on spontaneous ADR reporting in their undergraduate pharmacy programmes, but only one school of pharmacy also teaches this subject with respect to herbal medicines (Cox *et al.*, 2004).

6.2 Chapter aim and objectives

The diagram below summarises the aims and objectives in this chapter

Chapter	Aim	Objectives	Method
6	To investigate trends in the teaching of pharmacognosy/ natural products, herbal medicine and complementary/alternative medicine: a cross-sectional survey of UK schools of pharmacy	1. To determine the proportion of 'old' and 'new' schools of pharmacy including teaching of pharmacognosy on their core and elective programmes 2. To determine the inclusion of areas related to pharmacognosy, namely herbal medicines and aspects of complementary and alternative medicines (CAM), in the curriculum 3. To identify the method of delivery and extent of teaching in these areas 4. To explore respondents' views on the teaching of pharmacognosy and related areas	Cross-sectional survey of UK schools of pharmacy Comparative study

6.3 Method

6.3.1 Study design

A cross-sectional survey was conducted involving a postal questionnaire.

6.3.2 Questionnaire

Data were collected using the instrument developed for a previous study conducted in the academic year of 1999/2000 (Barnes, 2001), with some modifications. These included new questions on respondents' views on teaching of pharmacognosy and related subjects and new questions on the content of relevant core and elective programmes.

6.3.3 Study procedure

The sampling frame comprised all 'old' (established more than 5 years ago), 'new' (first cohort of students within last 5 years) and proposed schools of pharmacy in the UK (n = 16, 3 and 7,

respectively). In November 2004, a copy of the questionnaire and a covering letter were posted to academic staff known to be involved with pharmacognosy/related subjects, or to the head of school or other appropriate individuals at the University. In total, 4 follow-up contacts (2 postal, 1 telephone and 1 electronic) were made to non-responders at approximately 4-week intervals. Responses were accepted for 3 months after the final follow-up mailing to allow respondents enough time to gather information on course details and speak to other members of staff. Two processes of data cleaning were used to ensure the accuracy of data entry. First outlying values were searched and corrected according to the original data. Secondly all data was rechecked for consistency after a set interval by the author.

6.3.4 Data analysis

Responses were summarised using standard descriptive statistics. Due to the small sample size, non parametric tests were used to calculate the statistical differences between the two datasets, using SPSS version 13.

6.4 Results

6.4.1 Response rate

From the 26 schools of pharmacy contacted in 2004/2005, responses from 18 (69%) were received (11 'old', 2 'new' and 5 proposed schools of pharmacy) compared to 15 (94%) schools of pharmacy in 1999/2000. Of the 16 'old' schools of pharmacy contacted in 2004/2005, there was no statistically significant difference between the proportions of respondents for 1999/2000 and 2004/2005 (15/16 *versus* 11/16 for 1999/2000 and 2004/2005, respectively; $p = 0.172$; Fisher's exact test; 2-tailed).

6.4.2 Characteristics of respondents

Demographic characteristic data for 2004/2005, comprised position, discipline, sex, qualifications and whether or not the respondent was involved in teaching pharmacognosy and related subjects to undergraduate students as part of the MPharm curriculum. These data are summarised in table 6.1. The majority of the respondents were male (89%), registered

pharmacists in the UK (83%) and were involved in the teaching of pharmacognosy to undergraduate students as part of the MPharm programme (56%). Of the ten respondents involved in the teaching, the median number of years that they have been teaching pharmacognosy at UK schools of pharmacy was 30 (semi-interquartile range 11).

Table 6.1 Demographic details of respondent

		1999/2000† Proportion (n=15)	2004/2005 Proportion (n=18)
Position	Professor	20.0% (3)	27.8% (5)
	Reader	(0)	5.6% (1)
	Principal lecturer	13.3% (2)	16.7% (3)
	Senior lecturer/lecturer	60.0% (9)	33.0% (6)
	Course director	6.7% (1)	5.6% (1)
	Head of department	(0)	5.6% (1)
Discipline	Pharmacognosy	*	44.4% (8)
	Pharmacy practice	*	22.2% (4)
	Pharmacology	*	16.7% (3)
	Pharmaceutics	*	11.1% (2)
	Missing data	*	5.6% (1)
Sex	Male	80.0% (12)	88.9% (16)
	Female	20.0% (3)	11.1% (2)
Qualifications	Registered pharmacist	53.3% (8)	83.3% (15)
	Pharmacy degree	60.0% (9)	72.2% (13)
	Other science degree	46.7% (7)	27.8% (5)
Involved in the teaching of pharmacognosy?	Yes	86.7% (13)	55.6% (10)
	No	13.3% (2)	44.4% (8)

* Not surveyed in 1999/2000 questionnaire
† Data collected by JB (Barnes, 2001)

6.4.3 Characteristic of schools of pharmacy

6.4.3.1 Accreditation status

Of the 18 respondents from 2004/2005, all of the 'old' schools of pharmacy had full accreditation status, both of the 'new' and one of the 'proposed' schools of pharmacy had partial accreditation, and the remaining four did not have accreditation at the time of the study (see figure 6.1).

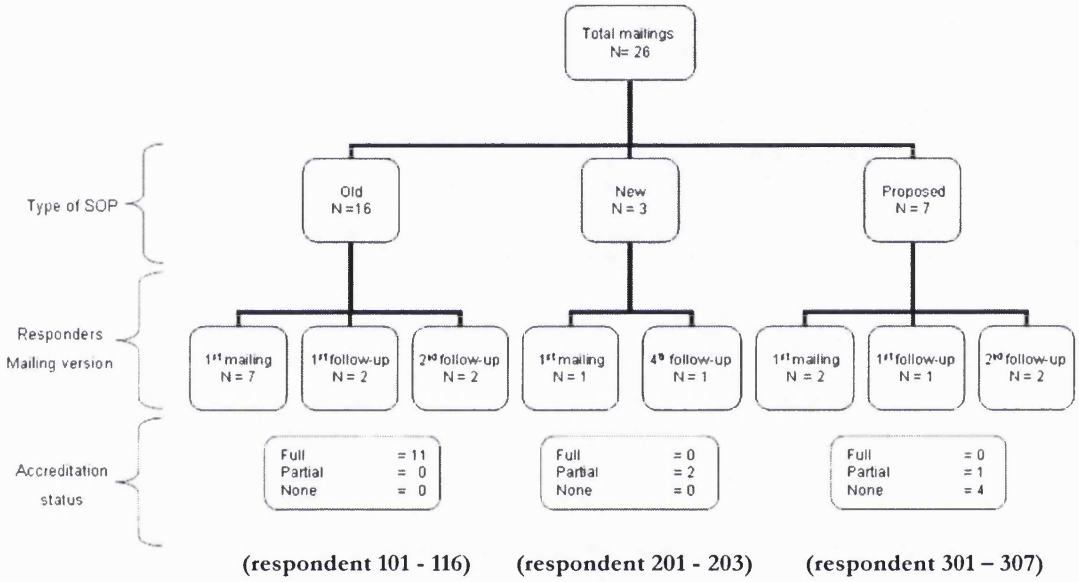


Figure 6.1 Characteristics of the respondent schools of pharmacy

For the four schools with no present accreditation, full accreditation was under consideration by the RPSGB for one of the universities and one was due to be considered in the year 2005. The remaining two universities had no timescale for obtaining full accreditation status, at the time of the study.

Partial accreditation had been obtained by three of the universities. However, full accreditation for one of the universities was being considered by the RPSGB and the other two were planning to obtain full accreditation during the academic years of 2004/2005 and 2008/2009.

6.4.3.2 Student intake

Plans to receive their first intake of MPharm undergraduate students for the four schools with no accreditation varied from 2005/2006 to no timescale at present. For the three schools with partial accreditation, two of the universities had already received their first intake of students and one of the universities was due to receive their first intake in the following academic year.

Of the 11 'old' schools of pharmacy that responded in 2004/2005, the median number of students each year (and semi-inter quartile range) from the first to the fourth year were 135 (30), 135 (17.5), 130 (19) and 120 (22.5) respectively. As can be seen from figure 6.2, there appears to be an overall trend of increased student intake, however, drop-outs and those students repeating the year need to be taken into consideration.

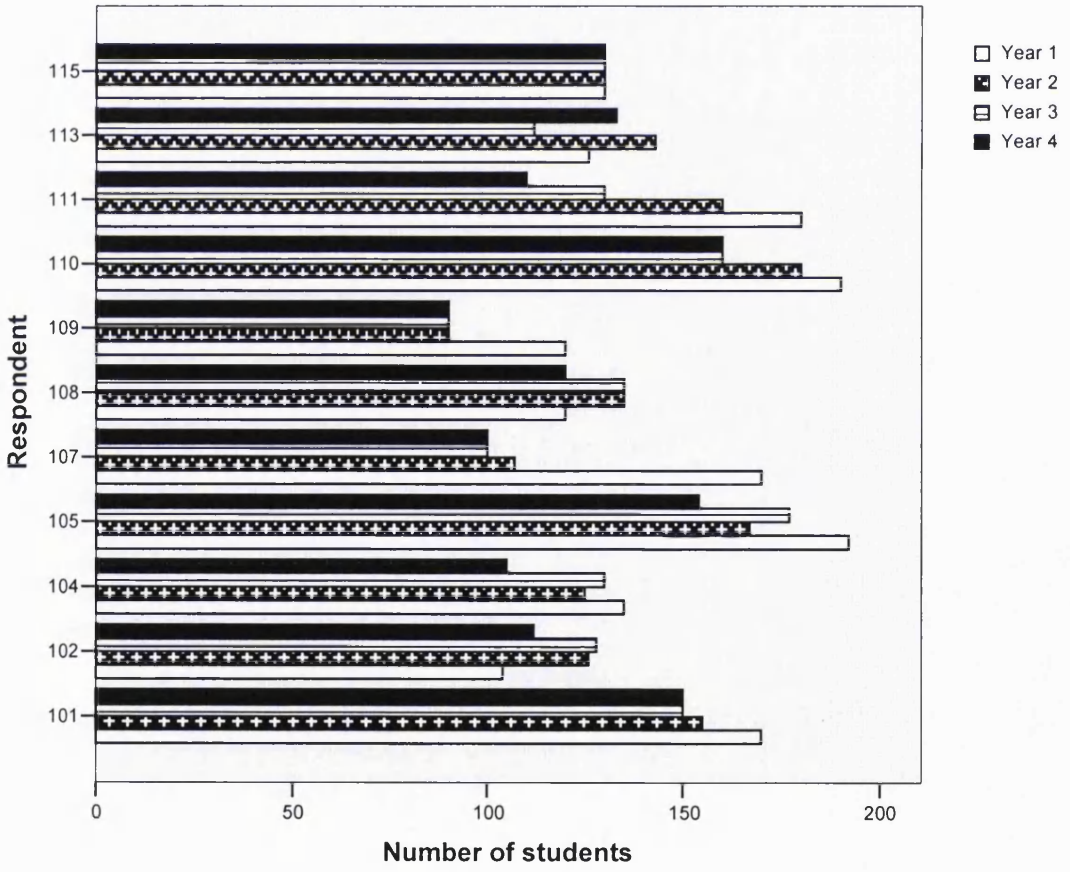


Figure 6.2 Number of students *per* each year group for the 'old' schools of pharmacy during 2004/2005

Data for both 1999/2000 and 2004/2005 were available for 11 'old' schools (as listed in figure 6.3). Table 6.2 shows that there was overall a higher average intake of students for the MPharm degree for 2004/2005 compared with 1999/2000 as the median number (and semi-interquatile range) of students for 1999/2000 and 2004/2005 was 120 (20) and 129 (18.5) respectively.

T able 6.2 Characteristics of schools of pharmacy (n=11)

	1999/2000†		2004/2005	
	Median (QL, QU)	**Range**	**Median (QL, QU)**	**Range**
Student intake	120 (100, 140)	95-156	129 (119, 156)	98-173
Staff teaching pharmacognosy	2 (1, 4.3)	1-6	3 (0, 4)	0-10

QU upper quartile; QL lower quartile
† Data collected by JB (Barnes, 2001)

Figure 6.3 shows that, with the exception of respondent 109 and 113, there was a higher average intake of students in 2004/2005 compared to 1999/2000.

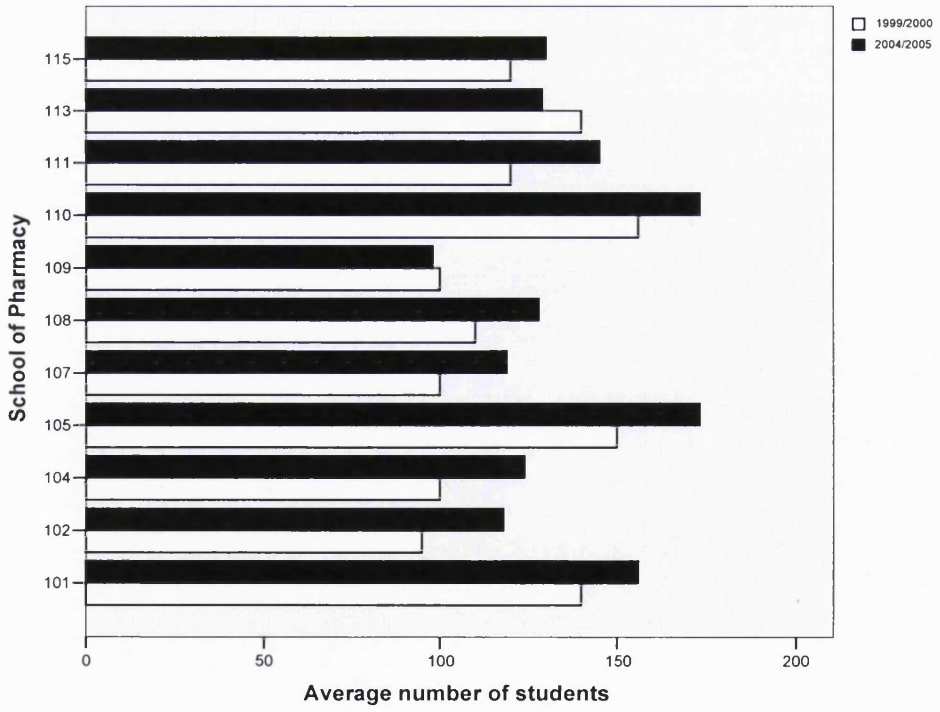


Figure 6.3 Trends in student intake from 1999/2000 to 2004/2005 for the 'old' schools of pharmacy

6.4.3.3 Discrete pharmacognosy/natural products departments

Of the 11 schools of pharmacy that responded to both mailings of the questionnaire, two schools in 1999/2000 reported having a discrete department dedicated to the discipline of pharmacognosy/natural products, compared to six in 2004/2005 (see figure 6.4).

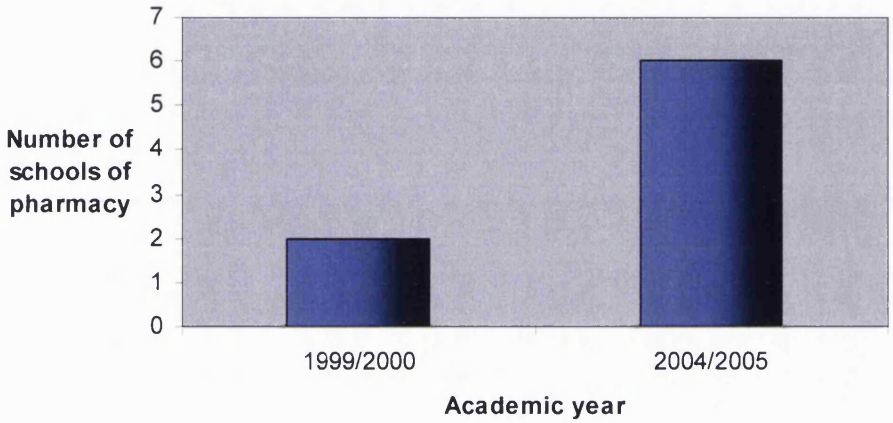


Figure 6.4 Number of schools of pharmacy with discrete pharmacognosy/natural products departments for 1999/2000 and 2004/2005

6.4.3.4 Teaching staff

Despite the increase in the number of schools of pharmacy with a discrete pharmacognosy department there was no discernible increase in the total number of staff involved in the teaching of pharmacognosy and its related subjects on the MPharm programme between 1999/2000 and 2004/2005 (see figure 6.5). A possible explanation for this is that schools without a discrete pharmacognosy department use external lecturers and/or from other departments to teach pharmacognosy and its related subjects.

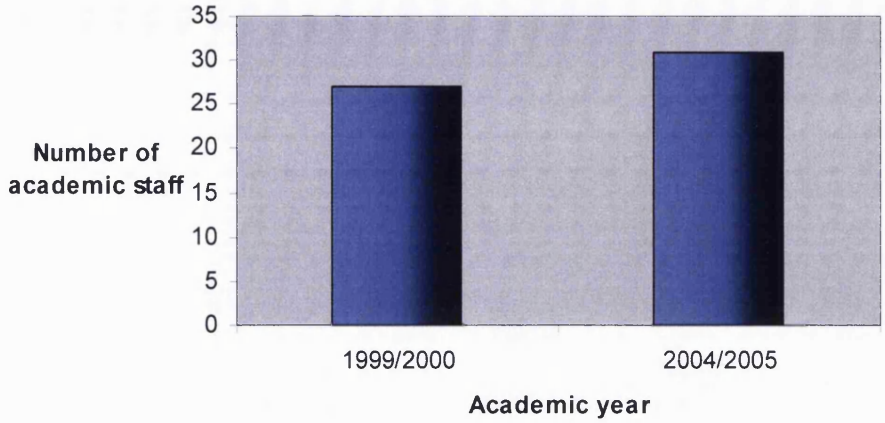


Figure 6.5 Total number of academic staff (full-time equivalents) involved in the teaching of pharmacognosy/natural products for 1999/2000 and 2004/2005

6.4.4 Teaching on the core curriculum

For 2004/2005, of the 13 respondents from the 'old' and 'new' schools, 11 (10 'old' and 1 'new' school of pharmacy) stated that their MPharm programme includes teaching of pharmacognosy and related subjects as part of the core curriculum. There were no statistically significant differences between the proportions for 1999/2000 and 2004/2005 (13/15 *versus* 11/13 for 1999/2000 and 2004/2005, respectively; p= 1.000; Fisher's exact test; 2-tailed).

6.4.4.1 Hours of teaching on the core curriculum

For 1999/2000, for the 13 schools teaching pharmacognosy/related subjects on the core curriculum, the median (lower and upper quartiles; Q_L, Q_U) total number of hours teaching (including self-directed study) and number of contact hours (lectures, tutorials, practical classes and field visits) were 52 hours (38.5, 62.5) and 52 hours (34, 56), respectively (see table 6.3).

For 2004/2005, for the 11 schools teaching pharmacognosy/related subjects on the core curriculum, the median (lower and upper quartiles; Q_L, Q_U) total number of hours teaching (including self-directed study) and number of contact hours (lectures, tutorials, practical classes and field visits) were 64 hours (25, 96) and 50 hours (25, 57), respectively (see table 6.3).

Table 6.3 Hours of core teaching of pharmacognosy and related areas in UK schools of pharmacy				
	1999/2000† (n=13)		2004/2005 (n=11)	
	Median (QL, QU)	Range	Median (QL, QU)	Range
Total teaching	52 (39, 63)	15-195	64 (25, 96)	14-288
Contact	52 (34, 56)	5-69	50 (25, 57)	14-288
Lectures	28 (20, 34)	5-55	28 (16, 36)	12-44
Practicals	21 (10, 24)	0-33	18 (8, 24)	0-252
† Data collected by JB (Barnes, 2001)				

Data for both 1999/2000 and 2004/2005 were available for 10 schools (see table 6.4); there was no statistically significant difference in the total number of hours teaching, number of contact hours, number of lecture hours and number of practical class hours for 2004/2005 compared with 1999/2000 ($p > 0.05$ for all; Wilcoxon Signed Rank Test for two related samples). Figure 6.6 shows that there is no trend in the number of core teaching hours of pharmacognosy and its related subjects within the last five years.

Table 6.4 Hours of core teaching of pharmacognosy and related areas in UK schools of pharmacy (n=10)					
	1999/2000†		2004/2005		*P* value
	Median (QL, QU)	Range	Median (QL, QU)	Range	
Total teaching	55 (34, 68)	15-195	74 (39, 103)	25-288	0.51
Contact	54 (34, 60)	5-69	52 (36, 58)	15-288	0.80
Lectures	24 (15, 35)	5-55	30 (22, 37)	12-44	0.41
Practicals	21 (11, 24)	0-33	18 (10, 24)	0-252	0.79
QU upper quartile; QL lower quartile † Data collected by JB (Barnes, 2001)					

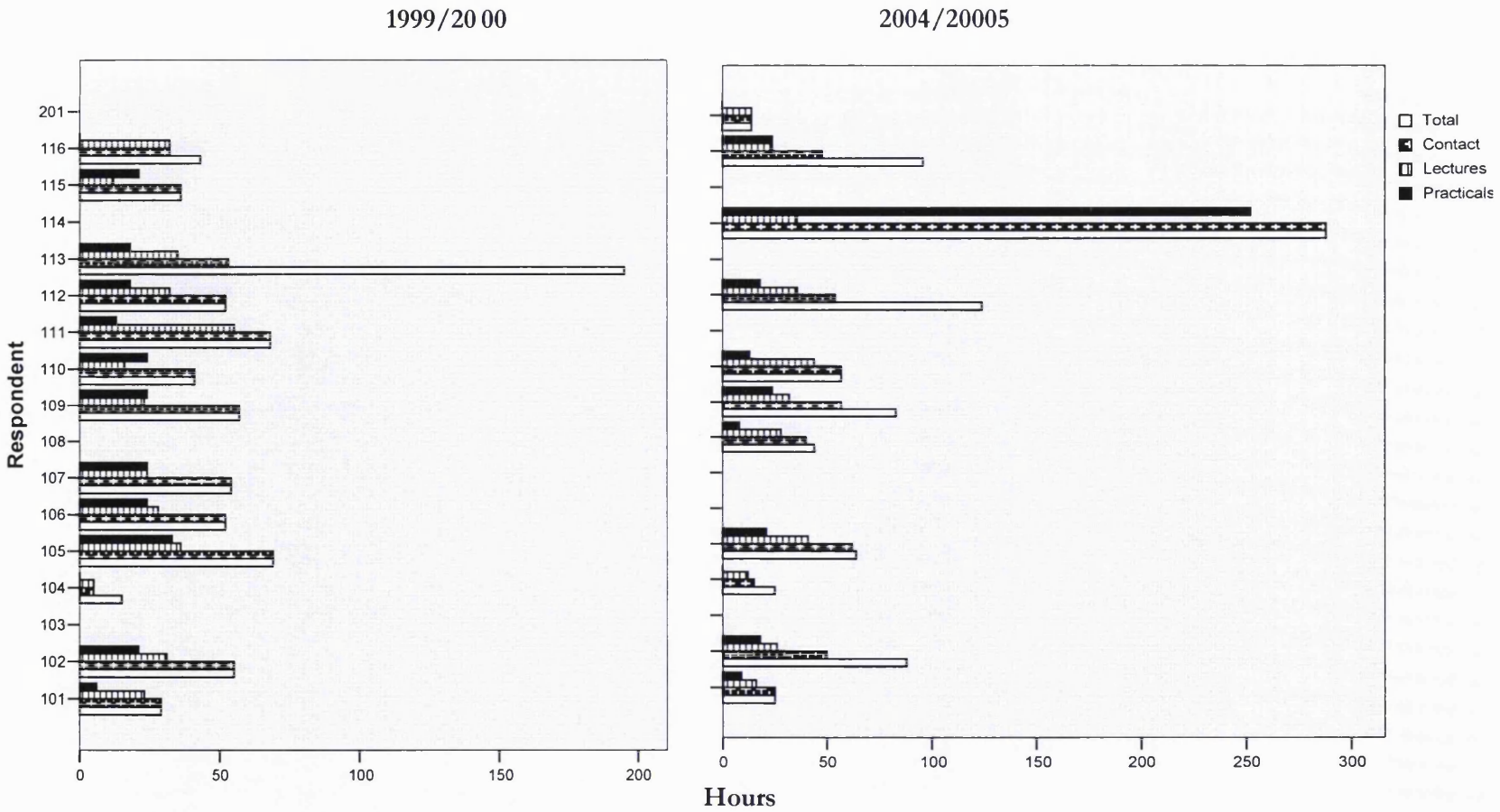


Figure 6.6 Hours of core teaching in pharmacognosy

6.4.4.2 Type of teaching on the core curriculum

Of the 11 'old' schools that responded in 2004/2005, 4 teach pharmacognosy as a discrete course only, 5 as an integrated teaching provision from other disciplines and two as both (see figure 6.7). There was no statistically significant difference between the proportion of schools teaching pharmacognosy as either a discrete or integrated course (6/11 *versus* 7/11; Fisher's exact test; 2-tailed; $p = 0.61$).

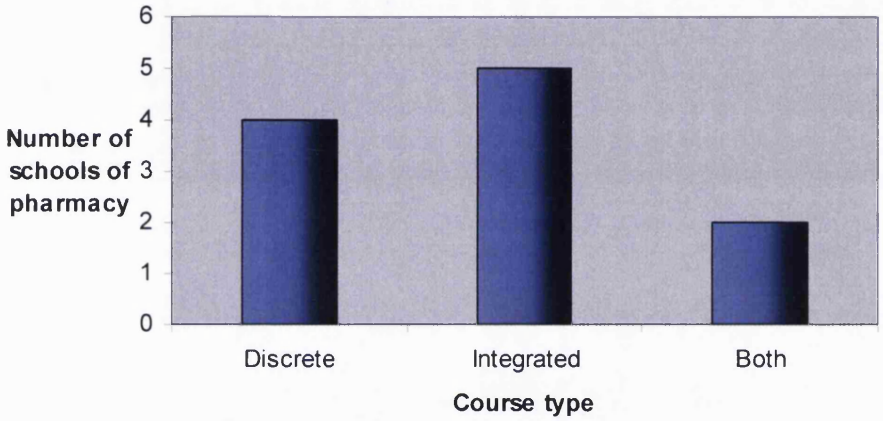


Figure 6.7 Style of teaching of pharmacognosy

Titles of discrete and integrated courses involving the teaching of pharmacognosy given by the respondents are listed in table 6.5.

Table 6.5 Courses on the core curriculum which involve the teaching of pharmacognosy	
Discrete courses	**Integrated courses**
*Sources & development	*Responding to symptoms
*Introduction to pharmacognosy, phytochemistry & special topics	*OTC medicines & therapeutics
Chemistry of medicinal natural products	Nervous, cardivascular, GI, skin, respiratory systems. Drug discovery & infections
Medicinal substances: Structure/function (2nd year) Alternative medicines (3rd year)	Pharmaceutical chemistry, molecular pharmacy, pharmaceutical care & advances in pharmaceutical sciences.
Complementary therapies	Patients, disease & medicines, drug discovery & pharmacy practice
Natural products & medicines from natural products	Chemistry, pharmacy practice, pharmacology & pharmaceutics
	Medicinal chemistry
* Schools of pharmacy where pharmacognosy is taught as part of both a discrete and integrated course	

6.4.4.3 Assessment of core course material

Details on how the core course material on pharmacognosy and related areas is assessed and whether or not it contributes to the overall MPharm degree mark are outlined in table 6.6

Table 6.6 Assessment of core course material				
	Used in assessment		**Contributes to degree**	
	1999/200† (n=13)	**2004/2005 (n=11)**	**1999/2000† (n=13)**	**2004/2005 (n=11)**
Examination	92% (12)	82% (9)	69% (9)	82% (9)
Assessment of course work	77% (10)	82% (9)	62% (8)	64% (7)
Assessment of lab-based practicals	69% (9)	73% (8)	77% (10)	55% (6)
† Data collected by JB (Barnes, 2001)				

Figure 6.8 shows that there has been little change in the assessment methods used at the 10 schools of pharmacy teaching pharmacognosy on the core curriculum between 1999/2000 and 2004/2005.

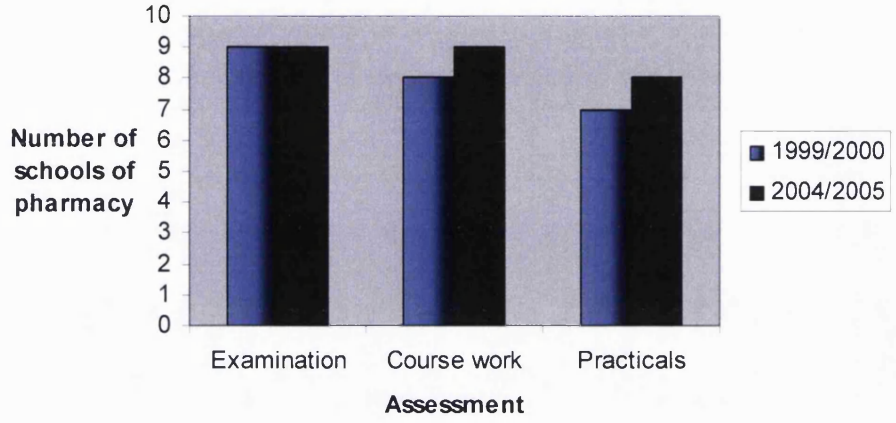


Figure 6.8 Assessment of core course material on pharmacognosy (n=10)

Figure 6.9 shows that there has been a slight decline in the assessment contribution of laboratory-based practicals to the overall MPharm degree mark..

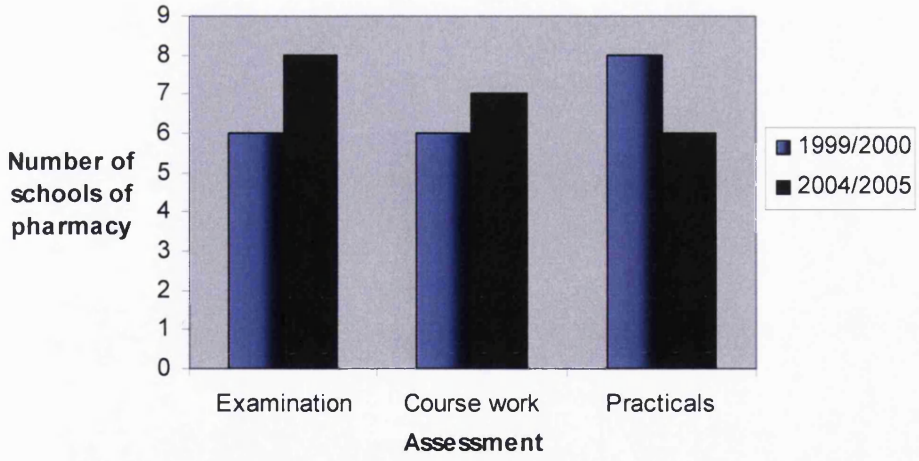


Figure 6.9 Assessment contribution of core course material on pharmacognosy (n=10)

6.4.5 Teaching on the elective curriculum

For 2004/2005, of the 13 respondents from the 'old' and 'new' schools, 7 'old' schools stated that their MPharm programme includes teaching of pharmacognosy and related subjects as part of the options/electives in the MPharm programme. There was no statistically significant difference between the proportions for 1999/2000 and 2004/2005 (8/15 *versus* 7/13 for 1999/2000 and 2004/2005, respectively; $p = 1.000$; Fisher's exact test; 2-tailed).

6.4.5.1 Hours of teaching on the elective curriculum

For 1999/2000, for the 8 schools teaching pharmacognosy/related subjects as part of the electives in the MPharm programme, the median (lower and upper quartiles; Q_L, Q_U) total number of hours teaching (including self-directed study) and number of contact hours (lectures, tutorials, practical classes and field visits) were 57 hours (39, 79) for both (see table 6.7).

For 2004/2005, 6 out of the 7 schools teaching pharmacognosy/related subjects as part of the electives in the MPharm programme provided details of their teaching hours (see figure 6.10). The median (lower and upper quartiles; Q_L, Q_U) total number of hours teaching (including self-directed study) and number of contact hours (lectures, tutorials, practical classes and field visits) were 70 hours (34, 94) and 54 hours (34, 68), respectively (see table 6.7).

Table 6.7 Hours of elective teaching of pharmacognosy and related areas in UK schools of pharmacy

	1999/2000† (n=8)		2004/2005 (n=6)	
	Median (QL, QU)	**Range**	**Median (QL, QU)**	**Range**
Total teaching	57 (39, 79)	10-128	70 (34, 94)	17-96
Contact	57 (39, 79)	10-128	54 (34, 68)	17-90
Lectures	33 (18, 39)	10-66	27 (15, 37)	15-40
Practicals	15 (1, 34)	0-60	3 (0, 30)	0-72

† Data collected by JB (Barnes, 2001)

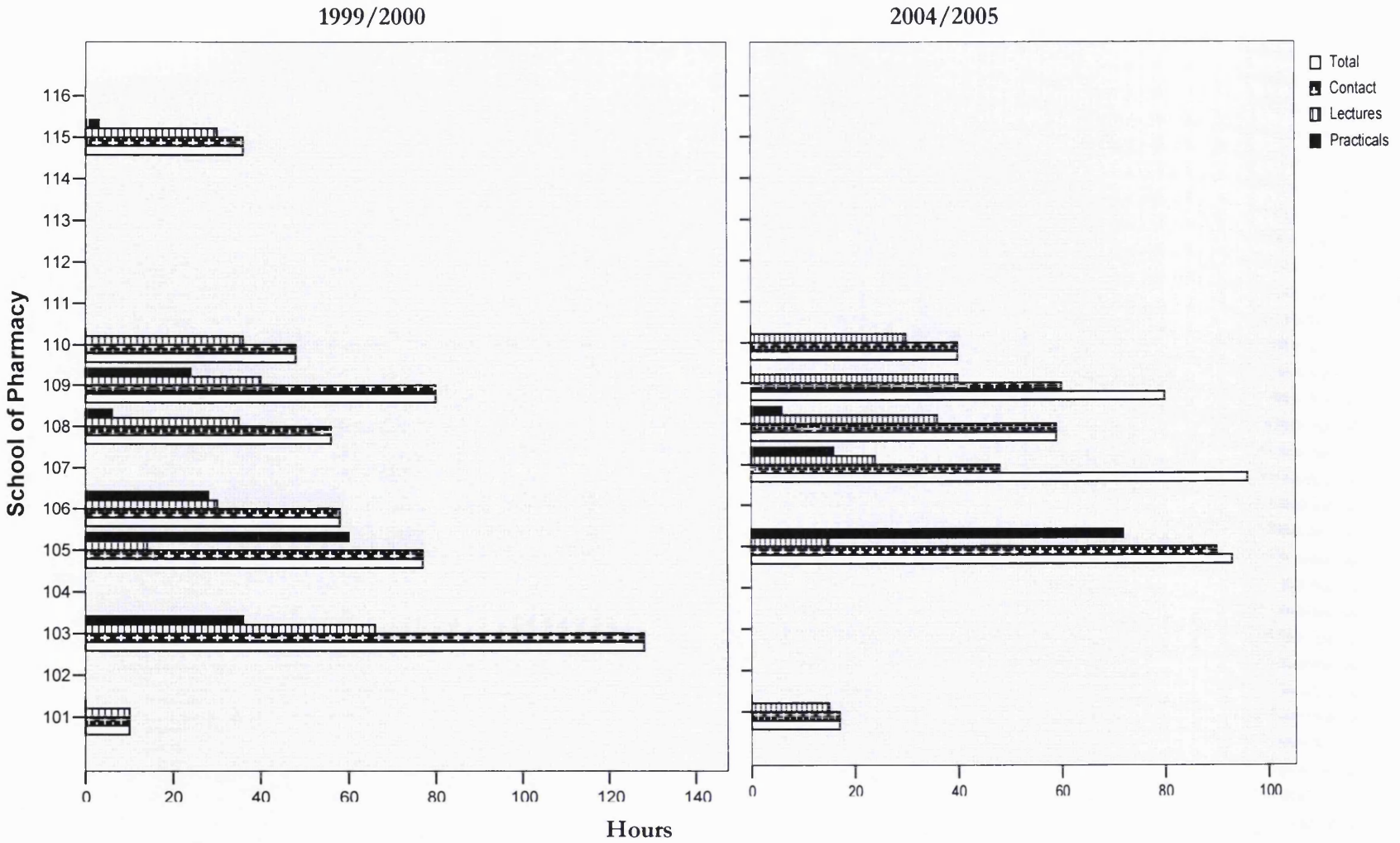


Figure 6.10 Hours of elective teaching in pharmacognosy

Figure 6.10 shows, that overall number of hours of elective teaching in pharmacognosy has slightly increased over the past five years for the five schools where data is available for both years. Data for both 1999/2000 and 2004/2005 were available for 5 schools of pharmacy (see table 6.8 and figure 6.10); there was no statistically significant difference in the total number of hours teaching, number of contact hours, number of lecture hours and number of practical class hours for 2004/2005 compared with 1999/2000 ($p > 0.05$ for all; Wilcoxon Signed Rank Test for two related samples).

Table 6.8 Hours of elective teaching of pharmacognosy and related areas in UK schools of pharmacy (n=5)

	1999/2000†		2004/2005		*p* value
	Median (QL, QU)	**Range**	**Median (QL, QU)**	**Range**	
Total teaching	56 (29, 79)	10-80	59 (29, 87)	17-93	0.47
Contact	56 (29, 79)	10-80	59 (29, 75)	17-90	0.89
Lectures	35 (12, 38)	12-38	30 (15, 38)	15-40	0.71
Practicals	6 (0, 42)	0-60	0 (0, 39)	0-72	0.66

QU upper quartile; QL lower quartile

† Data collected by JB (Barnes, 2001)

6.4.5.2 Type of teaching on the elective curriculum

For 1999/2000, the median (lower and upper quartiles; Q_L, Q_U) number of students taken *per* elective was 24 (20, 32). Range for the minimum and maximum intake of students allowed were 0-24 and 15-70 respectively. In total 10 electives were offered by 8 schools of pharmacy to students (1 in the 2nd year, 3 in the 3rd year and 6 in the 4th year) of which two schools had two electives available in different year groups. For two schools of pharmacy, students had a choice of modules within the elective for pharmacognosy.

For 2004/2005, all 6 schools provided an elective in the final (4th) year, with one school also providing a further elective in the 2nd and 3rd year. Median (lower and upper quartiles; Q_L, Q_U) number of students taken for the options in the 4th year was 24 (12, 30).

6.4.5.3 Assessment of elective course material

Details on how the elective course material on pharmacognosy and related areas is assessed and whether or not it contributes to the overall MPharm degree mark are outlined in table 6.9.

Table 6.9 Assessment of elective course material

	Used in assessment		Contributes to degree	
	1999/00† (n=8)	2004/05 (n=7)	1999/00† (n=8)	2004/05 (n=7)
Examination	100% (8)	71% (5)	88% (7)	71% (5)
Assessment of course work	75% (6)	71% (5)	63% (5)	71% (5)
Assessment of lab-based practicals	50% (4)	14% (1)	63% (5)	14% (1)

† Data collected by JB (Barnes, 2001)

Figure 6.11 shows that there has been little change in the assessment methods used at the 5 schools of pharmacy teaching pharmacognosy on the elective curriculum between 1999/2000 and 2004/2005.

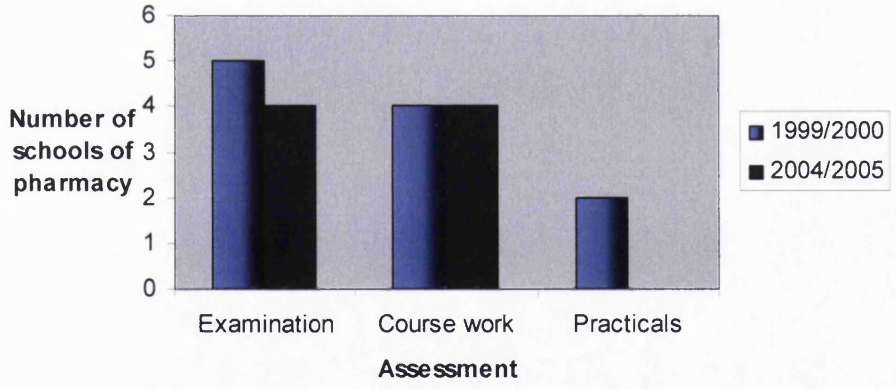


Figure 6.11 Assessment of elective course material on pharmacognosy

Figure 6.12 shows that there has been a decline in the assessment contribution of laboratory-based practicals to the overall MPharm degree mark, though not to significant level..

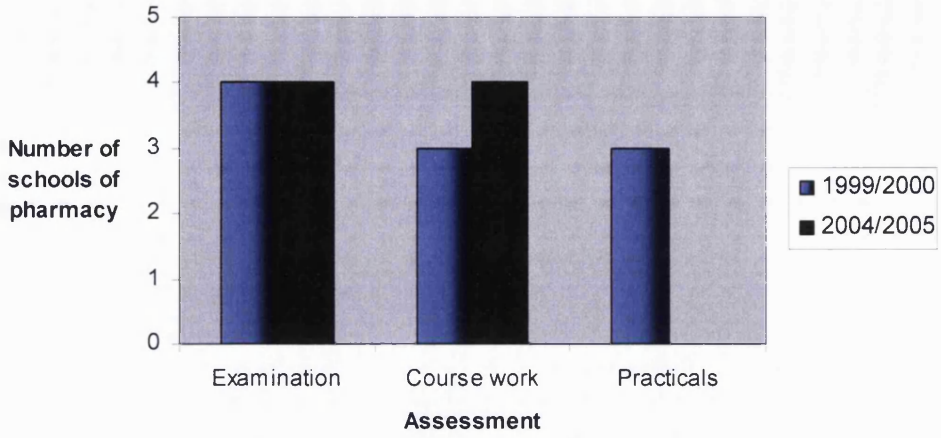


Figure 6.12 Assessment contribution of elective course material on pharmacognosy

6.4.6 Research projects

All of the 11 'old' schools that responded in 2004/2005, allowed students to undertake a research project in pharmacognosy and related areas, compared to 10/15 (67%) in 1999/2000, though this was not statistically significant (p = 0.40; Fisher's exact test; 2-tailed).

Analysis of the number of students who undertook an undergraduate research project and the number of hours allocated for each project for 1999/2000 and 2004/2005 could be undertaken for 7 schools (see figure 6.13). The median (lower and upper quartiles; Q_L, Q_U) number of students undertaking a research project for 1999/2000 and 2004/2005 was 10 (4.5, 11) and 4.5 (2.5, 8.8) respectively. Figure 6.13 also shows that there has been a overall decline in the number of students undertaking a research project in pharmacognosy and its related areas from 1999/2000 to 2004/2005 however, there was no statistically significant difference (p =0.27; Wilcoxon Signed Rank Test for two related samples).

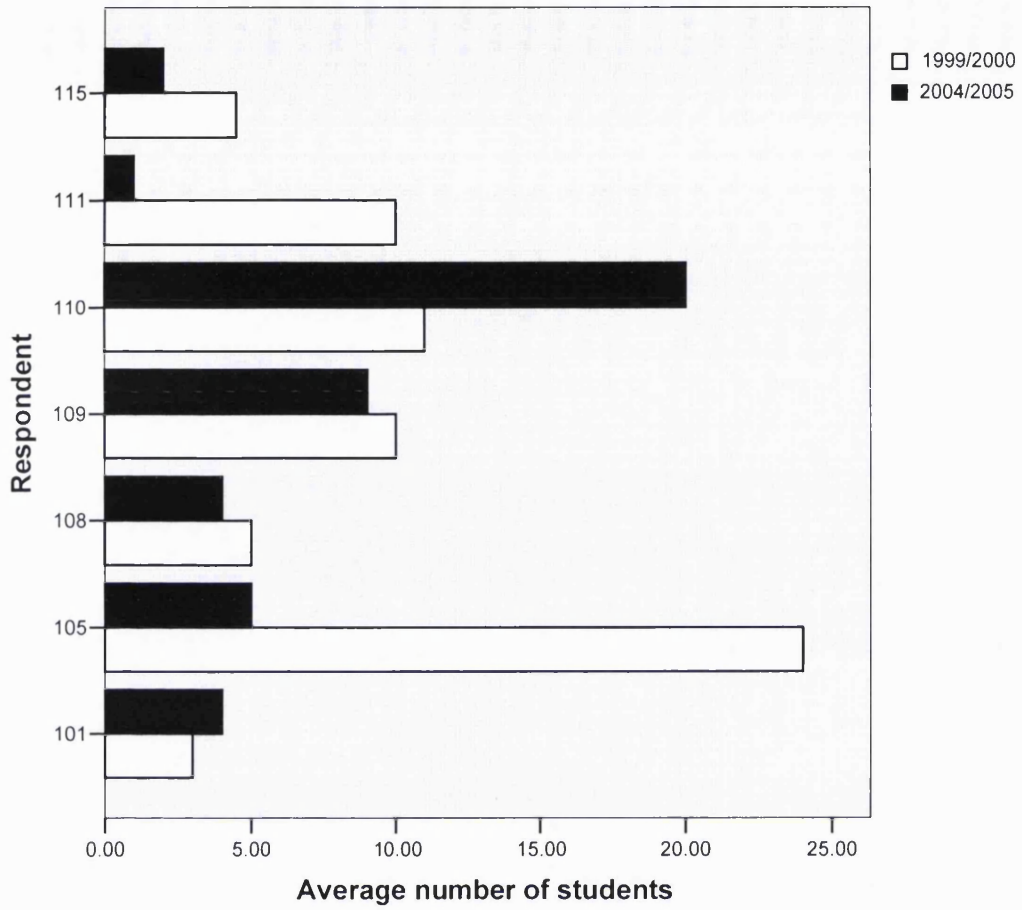


Figure 6.13 Average numbers of students *per* year undertaking a research project in pharmacognosy and its related subjects

The median (lower and upper quartiles; Q_L, Q_U) number of hours required to undertake a research project for 1999/2000 and 2004/2005 was 112 (63, 218) and 210 (193, 400) respectively (statistically significant p =0.03; Wilcoxon Signed Rank Test for two related samples). Figure 6.14 also shows the total number of hours required for each research project has increased over the past five years.

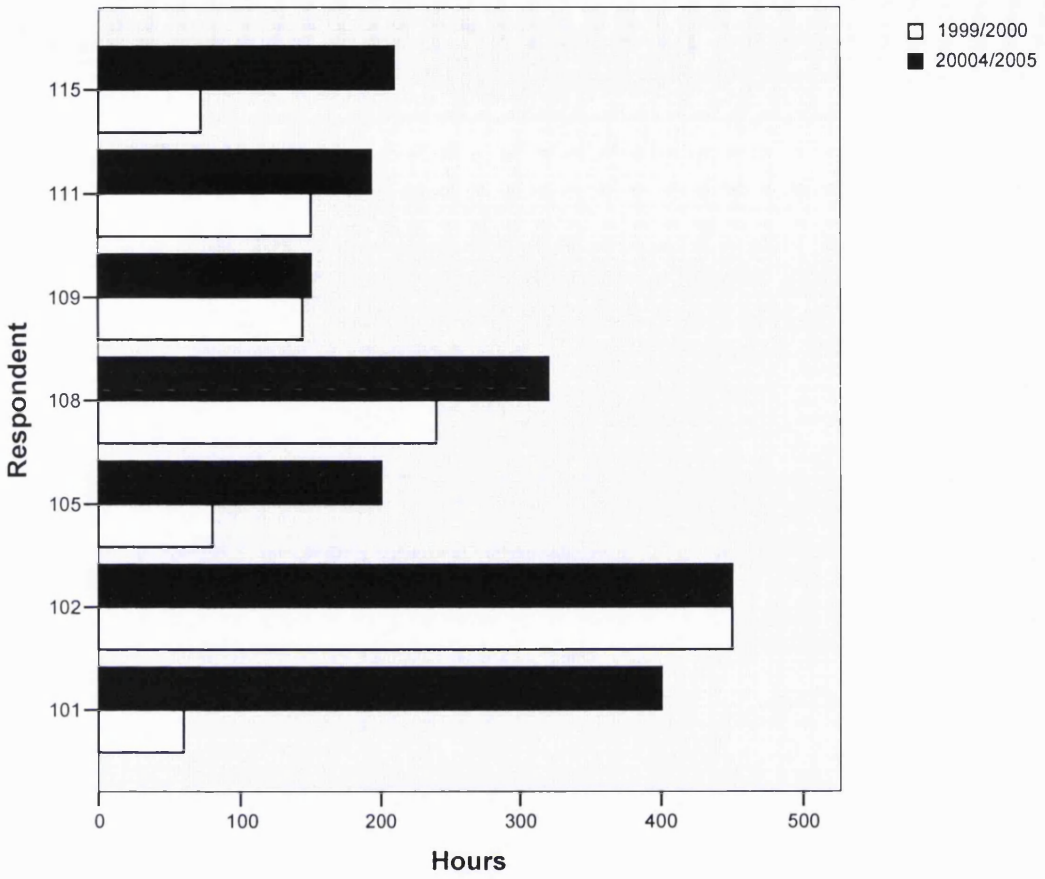


Figure 6.14 Total number of hours required for each research project

6.4.7 Teaching on herbal medicines and CAM

Proposed schools were excluded from this analysis as they had not fully defined their full course details. For both 1999/2000 and 2004/2005 data, only two schools taught all of the CAM subjects listed in table 6.10 on both the core and elective curriculum of the MPharm programme. Respondent 101, in 2004/2005 reported teaching all of the CAM subjects listed in table 6.10 on both the core and elective curriculum of the MPharm programme whereas in 1999/2000 it purely taught these subjects on just the core curriculum. For both 1999/2000 and 2004/2005, the CAM subjects most commonly taught on the core curriculum were essential oils (n=7 and n=9, respectively) and herbal medicines (n=9 and n=8, respectively). The same pattern was also observed for the electives.

Table 6.10 Subjects relevant to pharmacognosy/natural products, herbal medicine and complementary medicine, which are taught on the MPharm curriculum, n (%)

		Core		Option		Taught on either core or option	
		1999/2000† (n=13)	2004/2005 (n=11)	1999/2000† (n=8)	2004/2005 (n=7)	1999/2000† (n=15)	2004/2005 (n=13)
Chinese herbal medicine		5 (38%)	5 (45%)	5 (63%)	4 (57%)	9 (60%)	7 (54%)
Ayurvedic medicine		4 (31%)	3 (27%)	4 (50%)	4 (57%)	7 (47%)	6 (46%)
Homeopathy		5 (38%)	5 (45%)	3 (38%)	3 (43%)	8 (53%)	8 (62%)
Essential oils/aromatherapy		7 (54%)	9 (82%)	5 (63%)	4 (57%)	10 (67%)	11 (85%)
Flower remedies		3 (23%)	4 (36%)	2 (25%)	2 (29%)	4 (27%)	6 (46%)
Anthroposophical medicine		1 (8%)	2 (18%)	4 (50%)	1 (14%)	4 (27%)	3 (23%)
Vitamin/mineral/dietary supplements		4 (31%)	5 (45%)	3 (38%)	2 (29%)	5 (33%)	7 (54%)
Herbal medicines	Safety and toxicity	8 (62%)	8 (73%)	6 (75%)	4 (57%)	12 (80%)	9 (69%)
	Efficacy	7 (54%)	7 (64%)	6 (75%)	4 (57%)	11 (73%)	9 (69%)
	Quality aspects	9 (69%)	5 (45%)	6 (75%)	5 (71%)	13 (87%)	7 (54%)
	Licensing/regulation	7 (54%)	6 (55%)	6 (75%)	3 (43%)	12 (80%)	8 (62%)
	Counselling patients	7 (54%)	5 (45%)	6 (75%)	2 (29%)	12 (80%)	6 (46%)

† Data collected by JB (Barnes, 2001)

6.4.8 Future plans

In 1999/2000, three schools of pharmacy reported proposed changes to the MPharm teaching of pharmacognosy. Respondent 102 reported the introduction of a 3 x 1 hour lecture on natural products in drug discovery which in 2004/2005 was present on the core curriculum. Other proposed changes were the inclusion of CAM sessions (respondent 102), a new 48 hour module in molecular biology and biosynthesis (respondent 107) and the inclusion of complementary therapies (respondent 115).

For 2004/2005, of the 11 'old' schools of pharmacy, 3 had plans to increase and none had plans to reduce the teaching of pharmacognosy/natural products, herbal medicine and CAM during the next five years. Details of the proposed increase in teaching provisions are outlined in table 6.11.

Table 6.11 Details of proposed increase in teaching provision stated in 2004/2000 questionnaire	**Year to be introduced**
'Old' schools of pharmacy:	
3rd year: Drug discovery unit: Peptides from amphibian sources	2005/6
Integration of Phytotherapy into integrated clinical modules	2006/7
Details not available at time of study	
Schools of pharmacy with no accreditation:	
Pharmaceutical chemistry/Drug discovery& development Medicines & professional practice (Final year option)	2006/7 2008/9
Not yet quantified	2007
0.5 full time equivalent teaching post	2008

Of the 3 schools of pharmacy with partial accreditation as of 2004/2005, two had plans to introduce teaching on pharmacognosy as part of the MPharm programme during the next five years, but no details of the teaching planned and its proposed date of introduction were provided. For the schools 4 schools of pharmacy with no accreditation at the time of the study (2004/2005), three of these institutions stated that they had plans to introduce teaching on pharmacognosy as part of the MPharm programme during the next five years. Details of the teaching planned and proposed dates of introduction are outlined in table 6.11.

6.4.9 Respondent views

Responses to statements regarding the teaching of teaching of pharmacognosy and related areas on the MPharm curriculum are summarised in table 6.12.

Table 6.12 Views on teaching of pharmacognosy/natural products and related areas on the MPharm curriculum (n = 18), n (%)†

	Statement	Disagree/ Strongly disagree	Neutral	Agree/ Strongly agree
1	The term *pharmacognosy* is old-fashioned and should not be used by schools/departments of pharmacy to describe teaching and research activities in this area	9 (50%)	5 (28%)	3 (17%)
2	Pharmacognosy/natural products should be included on the indicative syllabus for the MPharm programme	0	1 (6%)	16 (89%)
3	The term *natural products*, rather than *pharmacognosy*, should be used by schools/departments of pharmacy to describe teaching and research activities in this area	8 (44%)	4 (22%)	5 (28%)
4	It is important that schools/departments of pharmacy continue to use the term *pharmacognosy* to describe teaching and research activities in this area	3 (17%)	4 (22%)	10 (56%)
5	Community pharmacists have a professional responsibility to be able to provide reliable, objective information and advice to patients and the public on the safe, effective and appropriate use of herbal medicines	0	1 (6%)	17 (94%)
6	Pharmacognosy should ONLY be offered for study as an option/elective on the MPharm program	16 (89%)	0	1 (6%)
7	Pharmacognosy should NOT be included on the indicative syllabus for the MPharm program	16 (89%)	0	1 (6%)

† Percentages do not total 100 because of missing data

Ideally factor analysis would have been used to validate the structure of the above questions to ensure that they relate to the construct intended to be measured (see section 3.5.1) however, factor analysis was not possible as a sample size of around 300 is required and between 10-15 participants are required *per* variable to ensure its reliability (Bryman and Cramer, 1997).

Table 6.12 shows that there are three clusters of interrelating questions. Questions 2, 6 and 7 can be grouped as these relate to the teaching of pharmacognosy on the MPharm syllabus. Questions 1, 3 and 4 relate to the use of the term pharmacognosy and question 5 relates to the professional responsibility of pharmacists towards providing advice on herbal medicines. Consistency of both the questions and the responses were validated by plotting a histogram for each cluster (see figures 6.15, 6.16, 6.17).

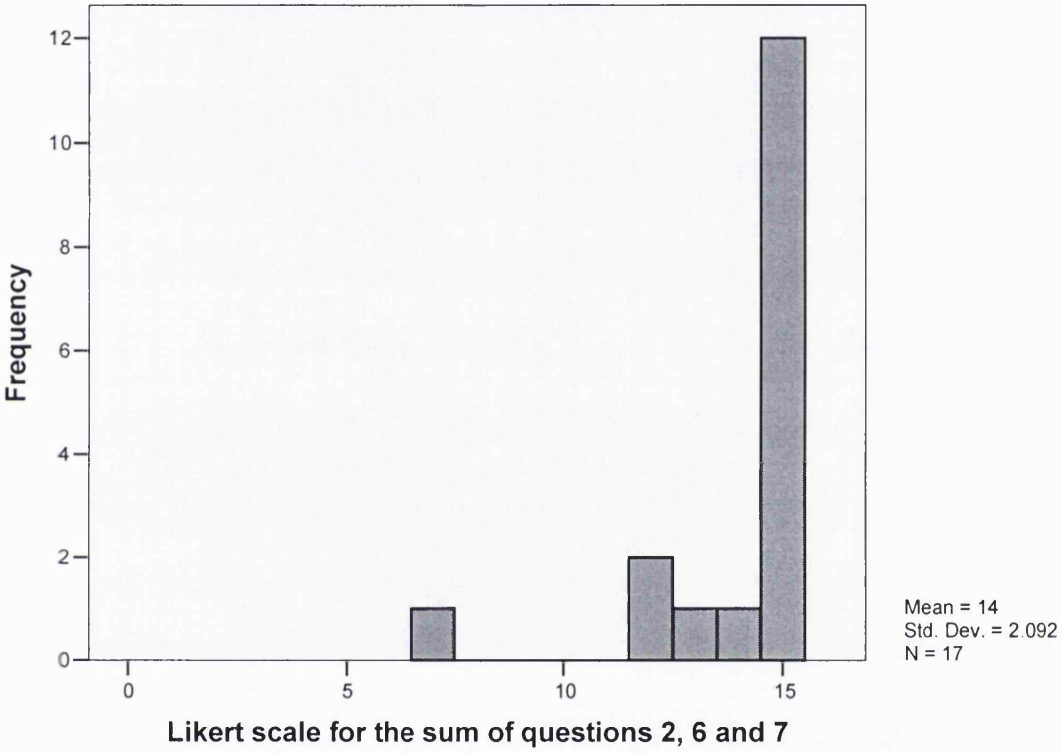


Figure 6.15 Consistency of questions relating to the teaching of pharmacognosy on the MPharm syllabus

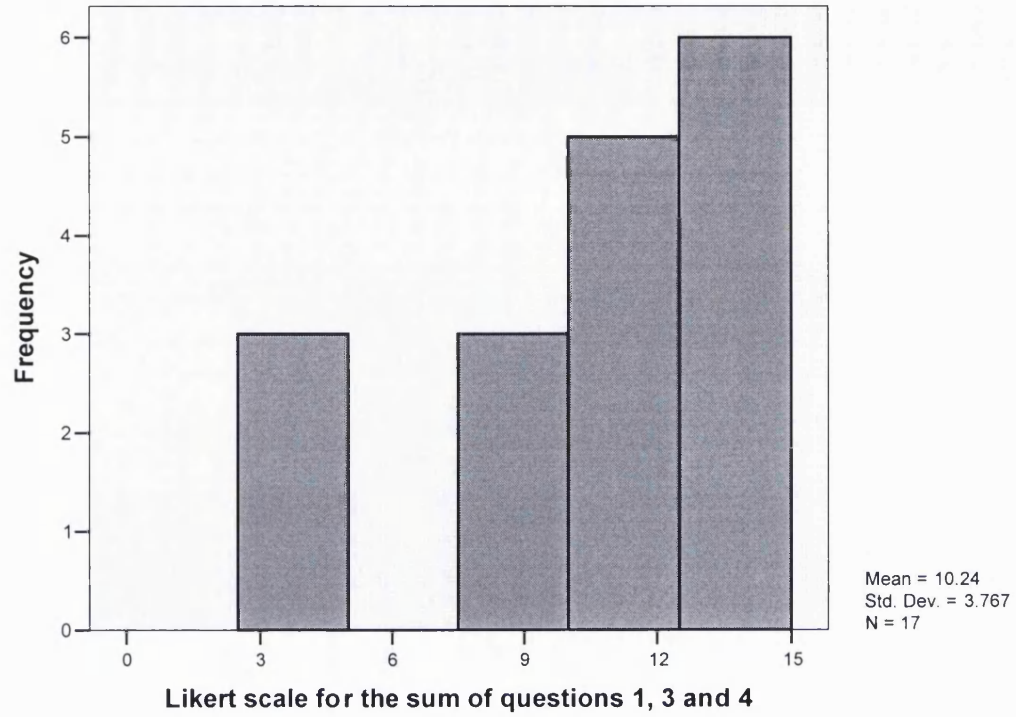


Figure 6.16 Consistency of questions relating to the use of the term pharmacognosy

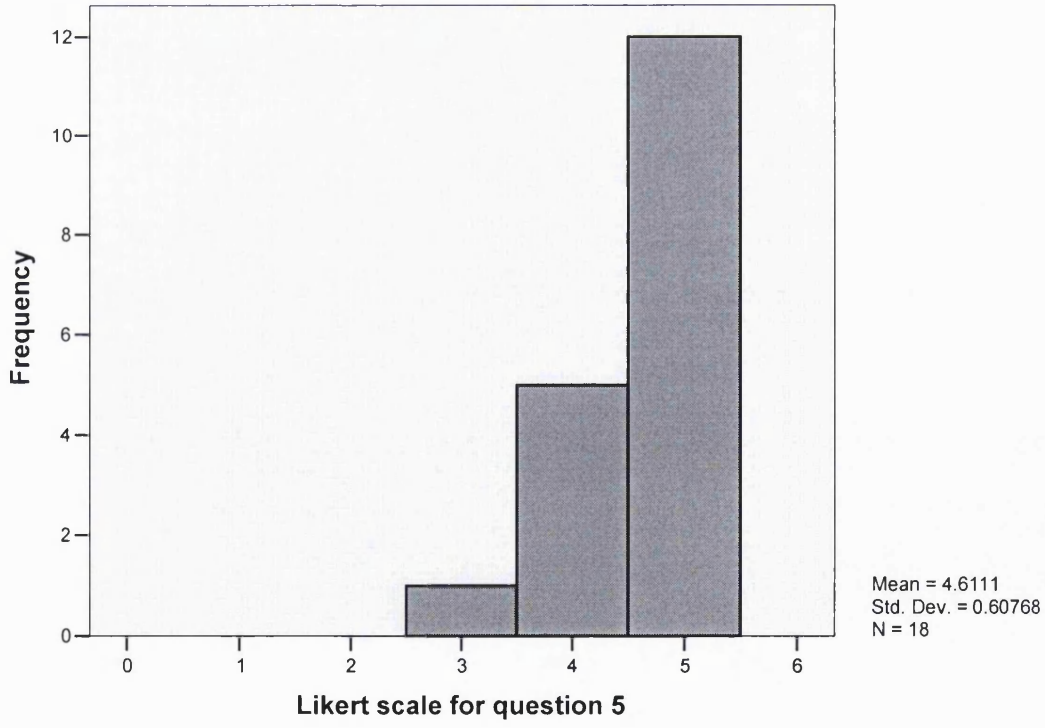


Figure 6.17 Professional responsibility of pharmacists towards providing advice on herbal medicines

Figures 6.15, 6.16 and 6.17, show a high level of consistency of both the questions and responses. Figures 6.15 and 6.17 also show that there was a high level of agreement between respondents towards the inclusion of pharmacognosy as part of the MPharm degree and professional responsibility of pharmacists towards herbal medicines.

Figure 6.18 shows that the majority of the respondents (>90%) felt that the following topics were essential to be taught on the MPharm core curriculum:

- Efficacy
- Safety
- Toxicity
- Pharmacovigilance of herbal medicines
- Natural products in drug discovery
- Natural products chemistry
- Vitamins/minerals and dietary supplements

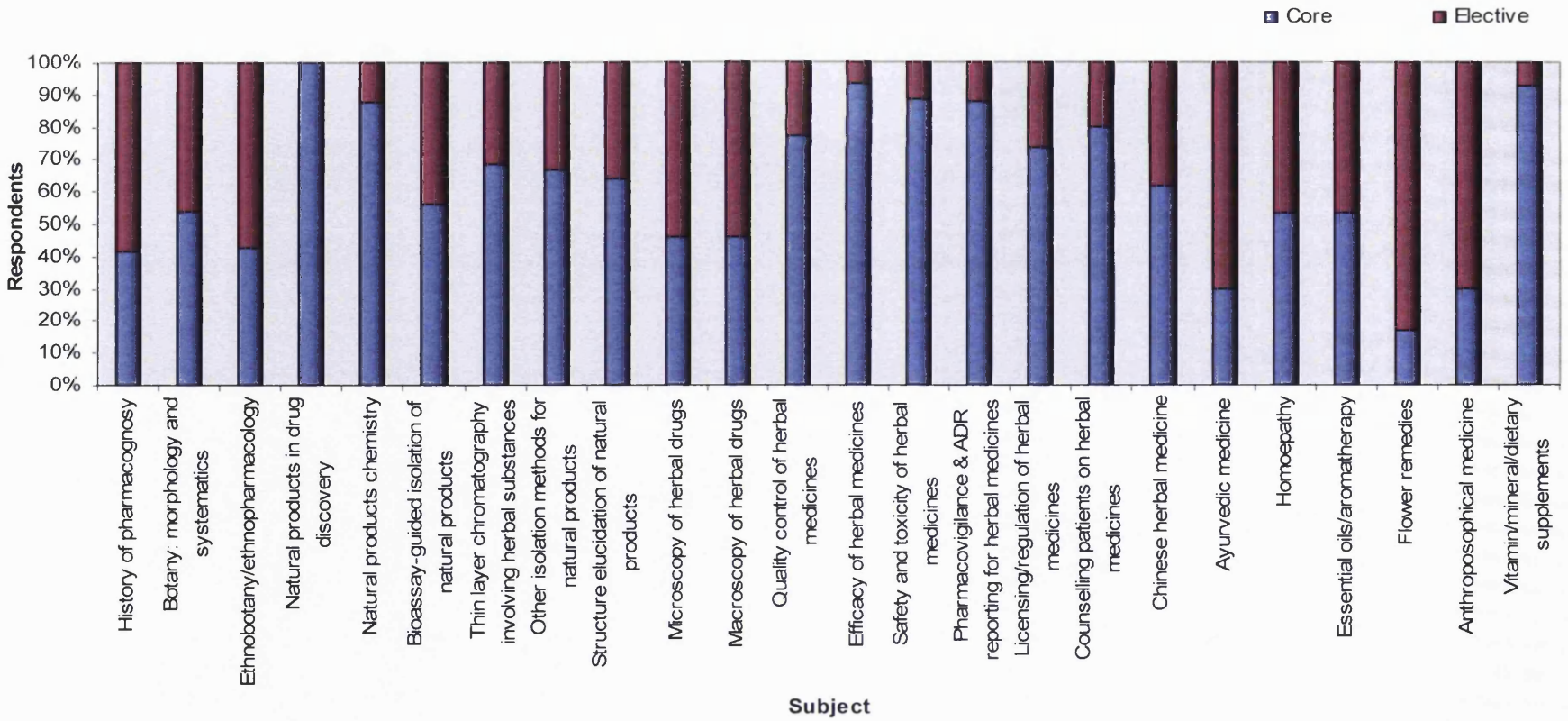


Figure 6.18 Respondent's view on whether or not they thought it was essential that the above subject is taught on the core curriculum of the MPharm or as an option/elective

6.5 Discussion

Over the years natural sources have yielded a rich source of medicinal products and therapeutic lead molecules; galantamine, paclitaxel and senna are a few examples of this (Balunas and Kinghorn, 2005). Natural sources, particularly plants, continue to yield new medicines of importance in pharmacy (Jones *et al.*, 2006). In addition, there is an increasing use of plant-based alternative and complementary medicines, particularly herbal medicines, by the general public (Mintel, 2005). As observed in chapter 5, herbal medicines and related products are widely available for purchase from community pharmacies and pharmacists are a source of information and advice on these products for the consumer.

The Medicines, Ethics and Practice Guide for pharmacists (RPSGB, 2006) states that, if pharmacists are to recommend herbal medicines and other CAMs, they need to have sufficient evidence-based knowledge of them. However, there are concerns that undergraduate teaching in pharmacognosy does not prepare pharmacists adequately for the safe use of plants as medicines and that levels of teaching in this area are diminishing for example, Houghton and Barnes' report on the forum for the International Congress on Natural Products Research (2004) stated that:

"*....there is grave concern at the disappearance of the teaching of those skills and the multidisciplinary mindset of Pharmacognosy in the undergraduate pharmacy syllabus in many countries*"

Under the EU Directive, both theoretical and practical training in pharmacognosy are a prerequisite for the pharmaceutical training of pharmacists (Directive 85/432/EEC). Despite this, the accreditation guidelines for UK pharmacy degree courses, set out by the Royal Pharmaceutical Society of Great Britain, makes no reference to the teaching of pharmacognosy as part of the indicative syllabus (RPSGB, 2005).

However, findings from this study show that within the UK schools of pharmacy, teaching in this area has increased over the past five years, but not to a significant level. Most schools of pharmacy include the teaching of pharmacognosy and related areas on the core curriculum of

their MPharm programme. For those schools that do not teach pharmacognosy on the core curriculum, pharmacognosy was offered as an optional/elective course. The only exception to this was that in 2004/2005, two schools reported that they did not teach pharmacognosy on either the core curriculum or offer an elective in this area however, both schools were one of the non-established courses where the exact syllabus and course content for the four years had not been fully determined, particularly for the final years. As most electives/options for pharmacognosy are offered in the final year it is thus possible that these schools will include some form of optional course in this area. This is also reflected by the following quote by one of the respondents from the non-established courses:

"Curriculum for future years is still under development" Respondent [203]

Thus the above findings imply that the majority of MPharm graduates will have gained some form of training in pharmacognosy and related areas during their degree.

Of the 10 schools of pharmacy where data were available for both 1999/2000 and 2004/2005, there was no change in whether or not they taught pharmacognosy on the core curriculum *i.e.* the 9 schools of pharmacy that reported teaching pharmacognosy on the core curriculum in 1999/2000 also reported teaching pharmacognosy on the core curriculum in 2004/2005. One school that reported teaching pharmacognosy as an optional course in 1999/2000 subsequently discontinued this in 2004/2005. However, their core curriculum content of pharmacognosy was increased substantially over the past five years (see figure 6.6). Therefore, it can be hypothesised that the school recognised the importance of teaching pharmacognosy to all MPharm students. Also, two schools who previously did not offer pharmacognosy as an option in 1999/2000 reported this as an option in 2004/2005. Thus the overall picture is that the number of schools teaching pharmacognosy and related areas has increased for both the core and elective programmes over the past five years.

In terms of the teaching hours in pharmacognosy, there was an overall increase in the total number of core contact hours of teaching from 1999/2000 to 2004/2005 (467 compared to 696; n=10). Most teaching hours were delivered as lectures (56%) in 1999/2000 and as

laboratory-based practicals (56%) in 2004/2005. The increase in the number of hours of practical teaching observed for 2004/2005 is due to one school providing 252 hours worth of practicals (see figure 6.6). The exclusion of this figure would bring the total core teaching hours in line with 1999/2000. The total number of option contact hours of teaching for 1999/2000 and 2004/2005 was 307 and 385 respectively (n=6). Again for both years, formal lectures formed the majority of the total teaching hours. These findings are consistent with the national study to map teaching, learning and assessment in the MPharm curriculum at UK schools of pharmacy, carried out by Aston University (Wilson *et al.*, 2006), which found that the courses have a heavy dependence on formal lectures contributing on average 51% of the taught element of the curriculum.

Methods of assessing students knowledge were similar not only across the two years (1999/2000 and 2004/2005) the study was conducted, but also between core and elective teaching, with most schools using examinations as the main method of assessment followed by coursework. These findings also correlate with the national study conducted by Aston University (Wilson *et al.*, 2006).

The revival in the teaching of pharmacognosy over the past five years is also demonstrated by the increase in the number of schools having a separate pharmacognosy department (two in 1999/2000 compared to six in 2004/2005). Furthermore, there has been an increase in the number of schools allowing students to undertake a research project in pharmacognosy and related areas over the past five years and a significant increase in the number of hours required for the research project in pharmacognosy from those reported in 1999/2000 compared to 2004/2005. The increase in the hours is likely to be due to the RPSGB's accreditation requirement of a "significant research project" as part of the 4 year programme (RPSGB, 2005).

Despite the overall increase in the teaching of pharmacognosy and related areas in the core, elective and research project curriculum since 1999/2000, it is apparent that certain schools are more active in the teaching of pharmacognosy than others as the extent of teaching and content for both core and elective programmes in this area varies between institutions and thus

the knowledge of pharmacists in these disciplines will vary accordingly, depending upon which school they graduate from. In addition, the median number and range of core hours of teaching for 1999/2000 and 2004/2005 was 55 (15-195) and 74 (25-288) respectively. These figures include all forms of teaching throughout the degree course and represent around 2% of the 3 000 hours of directed study of pharmaceutically relevant subjects dictated by the European Directive on pharmaceutical training, which may not be sufficient to adequately prepare pharmacists with regards to the safe use of plants as medicines (Directive 85/432/EEC). Previous work supports this hypothesis as in a survey of 370 pharmacy students, knowledge scores on herbal medicines ranged from 0-92% percent and less than half were able to identify the appropriate use and adverse effects of commonly used herbal products (Mackowiak and Parikh, 2001). Also in chapter 5, it was identified that most community pharmacists felt that their knowledge in herbal medicines was not adequate and required more training to be competent in advising patients/customers on herbal medicines.

This study also shows that most schools of pharmacy include the teaching of CAM related areas such as essential oils, herbal medicines and traditional Chinese herbal medicines in some part (core or elective) of their MPharm programmes for both 1999/2000 and 2004/2005. Some schools also still include the teaching on Ayurvedic, homeopathy, flower remedies, anthroposophical medicine and vitamins/minerals/dietary supplements. This is encouraging as pharmacists will need to be knowledgeable in these areas due the increasing popularity of these treatments (see section 1.5.2). However, there was a decrease in the number of schools teaching various aspects of herbal medicines such as their safety, efficacy, quality, licensing and patient counselling, over the five years. This is unexpected considering the increased popularity of herbal medicines amongst patients and the public (Thomas *et al.*, 2001; Mintel, 2005), coupled with the fact that the importance of herbal medicines has been raised at a global level (WHO, 2004) and pharmacists have been identified as having key roles in ensuring their safe and effective use (see section 1.6). It could be postulated that the decrease in teaching in this area might be due to schools not having staff with expertise in this area or that teaching on the core curriculum is based on research interest rather than the needs of the profession. It is also possible that teaching is restricted due to the limited amount of time available and what is stipulated by the RPSGB's indicative syllabus. Also, as revealed by the

above study a number of courses are integrated and therefore it is possible that aspects such as the counselling of patients on herbal medicines and the pharmacovigilance of herbal medicines are covered by other areas such as pharmacy practice. For example it has been already established that most UK schools of pharmacy include teaching on spontaneous ADR reporting in their undergraduate pharmacy programmes, but only one school of pharmacy teaches this subject with respect to herbal medicines (Cox *et al.*, 2004). This raises the question on whether or not all aspects of herbal medicines (including their pharmacovigilance) should be taught under pharmacognosy, as some aspects of teaching might be lost through the integration with other courses. In support of this, it is also possible that if pharmacognosy and pharmacovigilance are taught side by side, this would emphasise to students the greater necessity to monitor the safety of herbal medicines due to the inherent problems associated with their pharmaceutical quality, safety, regulation, and general lack of information. Ideally herbal medicines should be taught in context to both pharmacognosy and pharmacy practice. For example, under pharmacy practice, practical issues such as herbal interactions with prescription medicines and how to submit a yellow card report could be taught via case scenarios. Whilst under pharmacognosy the inherent problems associated with herbal medicines and their pharmaceutical quality, safety, regulation, lack of information and the need for pharmacovigilance of these products should be covered.

Often pharmacists have highlighted the need for the RPSGB to take a further lead to encourage ADR reporting and have criticised the RPSGB for not doing so (Sweis and Wong, 2000; *Pharm J*, 2000; Cox, 2002). However, the RPSGB Code of Ethics (2006) does mention that pharmacists providing professional practice should ensure that:

> *'They take action to report to the prescriber and relevant authorities, suspected adverse drug reactions where this is likely to assist in the future treatment of the patient, or the future use of the medicine."*

All participants of the 2004/2005 survey were also asked on how strongly they agreed with the statement that community pharmacists have a professional responsibility to be able to provide reliable, objective information and advice to patients and the public on the safe, effective and

appropriate use of herbal medicines and 94% strongly agreed/agreed with this statement. Furthermore, in the 2004/2005 questionnaire there was an additional question on what subjects should be taught on the core curriculum and as part of an elective. The majority of the respondents (>90%) felt that the following topics should be included on the core curriculum:

- Efficacy, safety and toxicity of herbal medicines
- Pharmacovigilance of herbal medicines
- Natural products in drug discovery
- Natural products chemistry

It can be speculated that these answers reflect the respondents own personal view as opposed to the schools. As demonstrated from figure 6.18 there is a vast range of topics that could be covered under the heading of pharmacognosy and different respondents placed different priorities on each of the topics. However, it is essential that some uniformity is achieved amongst different UK schools of pharmacy so that a minimum level of competence in core areas is achieved.

6.5.1 Limitations

Despite the high response rate achieved for both surveys, there are a number of limitations associated with this study. Firstly the two questionnaires contained different questions, for example, certain questions for the 2004/2005 survey were adjusted according to the responses received from 1999/2000 and the 2004/2005 questionnaire probed for further details that were insufficient in the previous questionnaire. The results obtained for the 2004/2005 questionnaire are also not a true reflection of the course content for both the new and proposed schools of pharmacy as the majority have not defined their course for the full four years and in one case

> *"...the university does not yet have a school of pharmacy, though we have plans - currently on hold."* Respondent [303]

There also appears to be confusion as to what is contained as part of the core and elective programme. For example, two schools in 2004/2005 stated that they do not include the teaching of pharmacognosy and related subjects in the core programme of the MPharm degree, however, when requested to state if their course included certain subjects relevant to pharmacognosy, these were reported as being part of the core curriculum. Furthermore, a number of the teaching hours reported for certain subjects did not match total teaching hours reported. This could be due to the fact that a number of the courses are integrated and it is difficult to define them as discrete subjects. This is also reflected by the following respondent's quotes;

> *"Numbers may add up to more than thought to be from previous page since subjects are commonly taught together"* Respondent [109]

> *"It is difficult to assess some of these as our programmes have been 'integrated' since the early 1980's so traditional subjects areas and modes of presentation have long since gone. Natural products chemistry, for example, is not taught as such, but is doubtless there in the bulk of material given under medicinal chemistry. It is hard to disentangle it now"*
>
> Respondent [108]

> *"very difficult to quantify as subject material is very integrated"* Respondent [201]

It is also possible that the term pharmacognosy has increased in scope causing confusion as to what is covered under this term. The term pharmacognosy has been derived from the Greek words "pharmakon" meaning drug and "gnosis" meaning knowledge (ASP, 2005). Pharmacognosy has undergone significant changes and has become focused on drugs of natural origin *i.e.* medicines from plants, animals and minerals. A change of the term to natural products has also been an issue raised by the American Society for Pharmacognosy and is an ongoing debate (ASP, 2005). However, the majority of 2004/2005 respondents strongly disagreed/disagreed that the term *pharmacognosy* is old-fashioned and should not be used by schools/departments of pharmacy to describe teaching and research activities in this area and

strongly agreed/agreed that it is important that schools/departments of pharmacy continue to use the term *pharmacognosy* to describe teaching and research activities in this area.

The accuracy of the core and elective teaching hours could have been confirmed via provision of the course content booklet. This was requested in the covering letter but was only submitted by one of the participants and therefore omitted from the analysis. Attempts to obtain details of the course content from the respective university web pages were also unsuccessful.

6.5.2 Future work

It would be interesting to carry out the same survey again after a set interval, as three of the old schools of pharmacy have indicated that they plan to increase the teaching of pharmacognosy in their curriculum. One school of pharmacy in particular, mentioned that phytotherapy could be included in the future, and a number of the new and proposed schools of pharmacy plan to introduce the teaching of pharmacognosy and related areas to their curriculum. Furthermore, as CAM therapies become more mainstream it would be interesting to see if this drives/influences the undergraduate pharmacy degree courses. As the ability of pharmacists to work in other countries increases particularly within with Europe, it would also be interesting to conduct the same study in other countries, to identify if there is a stronger emphasis in the teaching of pharmacognosy and it's related subjects to pharmacists.

It is evident that pharmacists need to be knowledgeable in herbal medicines. Greater education and training have been identified to increase the quality of ADR reports submitted (Rosebraugh *et al.*, 2003; Bracchi *et al.*, 2005) and to increase the level of reporting (Sweis and Wong, 2000; Green *et al.*, 2001). The use of an educational intervention has been widely tested in areas such as training in protocols of smoking cessation (Sinclair *et al.*,1998; Corelli *et al.*, 2005), but only one study has been carried out in relation to the quality of ADR reporting *via* a 15-minute intervention to medical students (Rosebraugh *et al.*, 2003). Also, in a study by Granas *et al.* (2007) pharmacists receiving 1 day educational intervention were shown to have a more positive attitude to ADR reporting compared to the control group. However, both

studies did not assess if the number of reports received by the national pharmacovigilance centre increased. Preliminary work has been conducted to assess whether or not this subject could be taught "effectively" as part of a pharmacognosy option (Barnes and Aggarwal, 2005). Further work is planned to conduct a randomised controlled study, using the tools developed (where one arm receives the study intervention and the other does not).

6.6 Conclusion

The majority of UK schools of pharmacy include pharmacognosy and its related areas as part of the core curriculum, although the total amount of teaching varies widely between schools (range 14 to 288 hours). The extent of teaching of pharmacognosy and related subjects on the MPharm core curriculum has not shown a statistically significant increase since the academic year 1999/2000 despite continued public interest in plant-based medicines. Some institutions do not teach pharmacognosy and related subjects on the core curriculum at all. There is also strong agreement between institutions that pharmacognosy should be included as part of the indicative syllabus and not only offered for study as an option/elective and that topics covering the efficacy, safety, toxicity and pharmacovigilance of herbal medicines should be included in the MPharm core curriculum. Heads of schools of pharmacy, including new and proposed schools, need to consider whether or not their MPharm programme satisfies the RPSGB requirements and adequately prepares future pharmacists (scientifically and practice-based) to advise on the safe, effective and appropriate use of herbal and complementary medicines.

Chapter 7

THE FEASIBILITY OF EVALUATING A COMMUNITY-PHARMACY BASED METHOD FOR THE PHARMACOVIGILANCE OF AN OVER-THE-COUNTER HERBAL MEDICINE

7.1 Background

Yellow card data cannot be used to estimate the frequency of adverse effects and as there are few clinical trials for most herbal medicines (which only have the statistical power to detect common acute adverse events), there is a need to explore and demonstrate the safety profiles of specific herbal medicines in other ways.

In the UK, the community pharmacist's role in reporting herbal ADRs (MHRA, 1997) and in communicating information to patients about herbal safety concerns has been widely recognised (Breckenridge, 2000) and the MHRA have recently extended the scheme for the involvement of consumers in surveillance of side effects of medicines, but not specifically for herbal medicines (Pharm J, 2003). However, these initiatives relate to passive rather than active monitoring of safety. Furthermore, the role that spontaneous reporting schemes might play in pharmacovigilance in the future has been questioned, in part because there may be more efficient ways of detecting signals of safety concerns (Waller and Evans, 2003).

In summary, it is widely recognised that there is a need for new methods for monitoring the safety of herbal medicines and pharmacists have been identified as having key roles to play (see section 1.6).

7.2 Chapter aim and objectives

The diagram below summarises the aims and objectives in this chapter:

Aim	Objectives	Method
To develop and assess a new method for monitoring the safety of herbal medicines purchased OTC using community pharmacists	1. To conduct a literature search of studies utilising community pharmacies to recruit subjects 2. To develop a paper model for the active surveillance of herbal medicines through community pharmacy 3. To determine if adverse event data for herbal products can be collected systematically from consumers using a community-pharmacy-based method of recruitment 4. To present an evidence-based argument on whether or not this type of study is feasible in the community setting	Literature review and content analysis Paper model Practical model Feasibility

7.3 Literature search

A comprehensive literature search was conducted to identify all studies utilising community pharmacies to recruit subjects as part of an active surveillance method.

7.3.1 Aim and objectives

Aim	Objectives	Method
To conduct a literature search of studies utilising community pharmacies to recruit subjects for the development of the study protocol	1. To carry out a systematic literature search 2. To develop a study protocol (paper model) for the active surveillance of herbal medicines	Literature search and protocol development

7.3.2 Method

7.3.2.1 Search strategy

A full systematic literature search was carried out in September 2003 and then periodically till December 2005. The search strategy involved using MeSH headings and keywords. A 'snowball' approach was used where the bibliographies of relevant identified papers were further searched for relevant citations; these papers were obtained and the process repeated until no further new publications were identified. Databases and combination of terms used for the literature search are outlined in table 7.1

Table 7.1 Search strategy for literature search	
Dates	All years
Electronic Databases	Science direct, Embase, Biosis, Web of Science, RPS e-EPIC, Medline
Terms to achieve all literature retrieval	Community Pharmacy/Pharmacist Herbal medicines/Herb/Plant/Natural product/Complementary/ Alternative/Dietary supplements Safety Monitoring/Pharmacovigilance/Spontaneous reporting/ Adverse drug reaction Consumer/Patients/Public Non-prescribed medicines/over-the-counter (OTC)

7.3.3 Results

7.3.3.1 Types of studies identified

In total, 16 articles were found that related to active surveillance methods used in pharmacy to collect adverse event data. Those that have been conducted mainly involve pharmacy based cohorts for the collection of adverse event data (Bond and Hannaford, 2003). One of the first studies conducted in the UK, was by Borden and Lee (1982), where they attempted to monitor the effect of orally administered antibacterial agents by using pharmacists to recruit patients. However, participation was restricted to treatment centres with pharmacies on site and excluded hospital outpatient clinics and large referral centres, thus the target population might not have been representative. This method also required large input by pharmacists, whereas the objective of the study described in this chapter was to develop a model that required minimal input by healthcare professionals to eliminate selection bias and under-reporting. Furthermore, herbal medicines are often not prescribed within this environment, therefore this method would not have been suitable for our study.

With the increase in technology, a number of studies have been conducted using community pharmacy databases (Beto *et al.*, 1996; Van Grootheest *et al.*, 2003; Faber *et al.*, 2005). This method was largely based on PEM (which is outlined in Section 1.3.3). Here the sample was

generated directly from prescriptions received in the pharmacy instead of collecting data from the prescription pricing authority. This method minimised the time required for the identification of potential research participants. Many computer systems within the UK are not fully integrated with secondary care thus information on non-participants clinical status and other required data fields is limited. Therefore, the representativeness of the sample can not be fully measured (comparison between the participants and non-participants can not be conducted). Furthermore, it is widely known that the use of OTC products are not routinely recorded by pharmacists (Barnes, 2001) on their computer system which renders this method inappropriate for herbal medicines, hence these studies were excluded.

Another post-marketing method used with OTC products included a clinical trial prototype (Van Ganse *et al.*, 2005; Chrubasik *et al.*, 2005). In such studies, patients were selected and randomised to one of two treatment arms, of which one was an OTC medicine. Patients were then followed up in the community setting and were requested to self record any adverse events. These types of studies have found that patient generated data can provide a detailed source of information. However, these studies were specifically aimed to look at the efficacy of a product or how well it was tolerated in comparison to another medicine, whereas the specific objective of this study was to develop a community pharmacy based active surveillance method (and not to develop a randomised controlled clinical trial).

Another approach, based on PEM concepts, was to use community pharmacists to recruit all individuals who purchase a specific medicine (Sinclair *et al.*, 1999; Layton *et al.*, 2002). Consumers, pharmacists and GPs were then followed up for data on adverse events. This methodology has never been explored with OTC herbal medicines and it remained to be established whether or not this system could be effectively applied to herbal medicines, what advantages this system could offer over other traditional methods, how this system could be implemented and whether or not it would present different and/or additional challenges in terms of pharmacist and particularly, consumer recruitment and follow up. These 9 studies are presented in table 7.2.

Table 7.2 Post-marketing studies based in community pharmacy

Area and reference	Pharmacists recruited n (%)	Medicine	Consumer recruitment, follow-up and methods of data collection	Number of consumers recruited/responded
US (Louik and Mitchell, 2005)	2600	Hyoscyamine and dicyclomine	1) Introductory phone call and $5 incentive 2) Introductory phone call with no payment 3) mailed questionnaire with introductory letters and $5 incentive 4) Mailed questionnaire with introductory letters and no payment All received an enrolment questionnaire and a 6-week follow up questionnaire.	Method 1: Approached 784; Responded n (%) Enrolment 230 (29), Follow-up 45 (5.7) Method 2: Approached 950; Responded n (%) Enrolment 187 (20), Follow-up 25 (2.6) Method 3: Approached 609; Responded n (%) Enrolment 109 (18), Follow-up 21 (3.4) Method 4: Approached 624; Responded n (%) Enrolment 78 (13), Follow-up 25 (4)
Grampian, UK (Stewart *et al.*, 2005)	7	Amoxicillin, salbutamol, paracetamol or ibuprofen	Preliminary interview 5-day prospective diary	267 (85.5%) parents agreed to participate of these 106 (40%) returned diary/questionnaire.
Grampian, UK (Sinclair *et al.*, 2005)	64 (68.8)	All medicines for treatment of allergic rhinitis	Pharmacy staff gave recruitment pack to any consumer purchasing a product for allergic rhinitis. After 5 days recruits were sent a postal questionnaire. A follow up questionnaire was also sent at 4 and 8 weeks.	Potential recruits: 412; Recruited/responded: Initial 391, 5 days 324, 4 weeks 240, 8 weeks 222, 26 weeks 208
Norway (Hasford *et al.*, 2004)	62	Diclofenac	Baseline data was collected in the pharmacy. Follow-up was conducted at days 5 and 19 after commencing the study medication.	446 individuals participated in the study, 383 completed questionnaires
Hampshire, UK (Layton *et al.*, 2002)	129 (48.7)	Ibuprofen	1) Pharmacy staff inserted a recruitment pack into a shop bag of individuals purchasing ibuprofen. All research participants received a 7 day, 2 and 6 month follow up questionnaire.	Potential recruits: 7320; Responded/recruited: Initial 473, 7 day 399, 2 mth 333, 6 mth 285

Area and reference	Pharmacists recruited n (%)	Medicine	Consumer recruitment, follow-up and methods of data collection	Number of consumers recruited/responded						
				Method	Potential recruits	Recruited/responded				
						Ini-tial	7 day	2 mth	6 mth	12 mth
Grampian, UK (Sinclair *et al.*, 1999 and 2001)	61 (49.6)	Ibuprofen	1) Pharmacy staff inserted a recruitment pack into a shop bag of individuals purchasing ibuprofen. 2) Pharmacy staff explained the study to customers purchasing ibuprofen, and gave a recruitment pack to complete outside of the pharmacy. 3) Pharmacy staff explained the study to customers purchasing ibuprofen and asked all interested customers to complete recruitment within the pharmacy with the option of completing at home if required. 4) Pharmacy staff explained the study and sought immediate completion of the recruitment documents. Research participants were asked to keep a 7-day diary. 5) Shortened recruitment questionnaire All received a 7 day, 2, 6 and 12 month follow up questionnaire.	1	227	41	39	41	38	35
				2	194	61	54	54	48	46
				3	368	218	173	168	144	138
				4	136	82	50	48	40	38
				5	227	153	127	110	103	92

Area and reference	Pharmacists recruited n (%)	Medicine	Consumer recruitment, follow-up and methods of data collection	Number of consumers recruited/responded
UK (Gibb *et al.*, 2001)	45	Flurbiprofen lozenges	Pharmacist obtained consent and provided study medication. Follow up data was obtained in a structured telephone interview.	7139 eligible research participants were recruited of these 6811 (95.4%) were interviewed.
New Zealand (Gauld *et al.*, 2000)	175 (16)	Diclofenac potassium	Written and verbal information was provided by pharmacy staff. Questionnaire was mailed at 7-days post-purchase. 2nd questionnaire posted 30 days post-purchase.	1240 purchasers were recruited. 990 (79.8%) valid responses were received for the 7 day follow up, of these 556 were sent a 30 day follow up questionnaire of which 480 (86.4%) responded.
Australia (Colebatch *et al.*, 2000)	17	1st time user of any long-term medication	Patients commencing on long-term medication were asked to record adverse events in a diary for 8 months. Three methods of recruitment were used; 1) Community pharmacies by a pharmacist 2) Community pharmacies by a research nurse 3) Clinical pharmacist in teaching hospitals	Method: 1 — Potential recruits: 180 — Recruited/responded: Initial 77, 8 months 91 Method: 2 — Potential recruits: 91 — Recruited/responded: Initial 20 Method: 3 — Potential recruits: 47 — Recruited/responded: Initial 22

7.3.3.2 Critique of the studies identified

7.3.3.2.1 Medication researched

The majority of the above 9 studies have been used in the assessment of reclassified agents. For example, the study by Gibb *et al.* (2001) was used to evaluate the safety of the POM flurbiprofen in an OTC environment to promote its deregulation to P status and the study by Gauld *et al.* (2000) used the recently reclassified (POM to P) medicine diclofenac. Similarly, the Hampshire and Grampian studies used ibuprofen which required the involvement of a community pharmacist or was purchased from the pharmacy counter as a P medicine. As the majority of herbal medicines are sold from community pharmacies (Mintel, 2003) a similar method could be useful for their pharmacovigilance.

7.3.3.2.2 Recruitment method

As outlined in Chapter 3, recruitment plays a pivotal role in the design of a study, as this dictates the response rate and the subsequent validity of the data collected. Willison *et al.* (1995) reported that the recruitment process by pharmacists is also fraught with its bias in that pharmacists would not invite difficult patients into their study. Previous studies involving purchasers of a conventional OTC medicine (ibuprofen) have found that consumer recruitment was highest using a method requiring greater pharmacy input (Sinclair *et al.*, 1999) and a shortened postcard version for consent (Sinclair *et al.*, 2001); however, it could not be assumed that this would have also applied to purchasers of an OTC herbal medicine. Contrary to this, in an extension of the same study to the Hampshire study, feedback from pharmacists felt that the shop-bag method of consumer recruitment was the most appropriate due to other work commitments (Layton *et al.*, 2002). Thus, two methods were proposed to be tested for consumer recruitment (see section 7.4.4.5).

Many studies have excluded proxy purchasers (Sinclair *et al.*, 1999), though such exclusions do introduce another bias as this population forms an important subgroup. The intended consumer in such cases, often tend to be older with multiple problems and on multiple medications therefore they are more likely to experience an adverse event. As all

epidemiological studies require a good representation of the target population, proxy purchasers should be included in the study, provided that the intended user meets all of the other inclusion criteria. Likewise, existing and previous users should be included in the study as they do represent the target population, provided that the total duration of treatment is noted.

7.3.3.2.3 Follow-up method

A number of studies have largely followed up patients by telephone interviews (Willison *et al.*, 1995; Borden and Lee, 1982) or asked patients to call on a toll–free number with any unusual symptoms or changes they experienced since starting their medication. Such methods were not feasible due to financial constraints.

In a study by Bond and Bradley (1996), health diaries were used to monitor the therapeutic outcome following the sale of an OTC "hyperacidity" product. Of the recruited purchasers, only 22% returned completed diaries. Low recruitment rates using diaries were also observed by Sinclair *et al.* (1999) suggesting that research participants preferred a single or periodic questionnaire to a regular diary. In addition, it is difficult to assess what is a suitable amount of time to ask patients to continue to report in a diary as excessive periods would be envisaged to lead to significant attrition rates. In contrary, a study by Colebatch *et al.* (2000) showed that most adverse events occurred by 4 months, thus sufficient time is required for the identification of rare and long-term adverse reactions and those due to chronic use of a medicine. Thus, periodic postal questionnaires were selected for use in this study, in an attempt to maintain high follow-up rates alongside longitudinal data.

7.3.3.2.4 Questionnaire design

As outlined in section 3.6.1, factors such as the use of lay terminology, formatting, style, length and types of questions in a questionnaire can influence response rates and must be taken into consideration.

Difficulties arose in terms of medication changes. These have been shown to be important in measuring treatment outcomes (Paterson *et al.*, 2004) but, from a pharmacovigilance perspective this is essential for the attribution of an adverse event. Consumers are known to use medicines for a variable length of time as dictated by rate of recovery, clinical indication *etc*, thus the questionnaires had to take into consideration those who are starting the medicine for the first time, long-term users, those who might stop taking the medicine, those using the medicine intermittently and as reported by Sinclair *et al.* (1999), those purchasing the medicine for possible future use. Herbal medicines also pose an additional challenge in terms of identifying the preparation the consumer has purchased, as pharmacies often stock more than one preparation and certain herbs are also contained within a number of multivitamin preparations. Furthermore, herbal medicines sold under the exemptions of the Medicines Act must be sold under their botanical name *i.e. Ginkgo biloba* thus adding to the difficulty of identifying the product.

A number of questionnaires containing checklists have been developed to systematically question their patients about symptoms related to their medication (Corso *et al.*, 1992, Jarernsiripornkul *et al.*, 2002). However, these were considered inappropriate for our study as the checklist can be far too comprehensive and could lead to false positive results. Furthermore, as the ADR profile for most herbal medicines is unknown, it was considered best to collect all adverse events/symptoms rather than producing a predefined list, although recording all patients' experiences from their viewpoint can be subjective.

7.4 Study protocol (paper model) for a pharmacy-based pharmacovigilance system

The following section outlines the study protocol (paper model) developed based on findings from previously reported studies. However, it was not implemented in its entirety, due to reasons outlined under section 7.5.

7.4.1 Background

As outlined in section 7.3, the feasibility of using a community-pharmacy-based method to collect adverse event data has been demonstrated for a conventional OTC medicine, ibuprofen, purchased from pharmacies (Sinclair *et al.*, 1999; Layton *et al.*, 2002) but similar methodology has never been applied to OTC herbal medicines. For the following reasons, it could not be assumed that previous findings from studies conducted on OTC conventional, particularly relating to consumer recruitment and data collection, would apply equally to herbal medicines. In contrast to conventional OTC medicines, which hold product licences, most herbal medicines on the UK market are sold as herbal medicines exempt from licensing requirements (see section 1.5.5), or as unlicensed food supplements (Barnes, 2002; Barnes, 2003). Furthermore, the majority of herbal-medicine users do not seek professional advice in selecting herbal products and the perception amongst most users is that they would not consult a pharmacist if they experienced an adverse effect associated with herbal medicine use (Barnes *et al.*, 1998). It is necessary, therefore, to determine whether or not a community-pharmacy-based method for pharmacovigilance can be usefully applied to OTC herbal medicines and whether or not this would present different and/or additional challenges in terms of pharmacist and particularly, consumer recruitment and follow up.

7.4.2 Aim and objective for the development of the study protocol (paper model)

Aim	Objective	Method
To develop and assess the feasibility of a community-pharmacy—based method for pharmacovigilance of herbal medicines purchased OTC	1. Based on the literature review to develop a novel system of active surveillance utilising community pharmacists 2. To execute the paper model for the active surveillance of herbal medicines through community pharmacy	Paper model

The primary aim of this pilot project was to develop and assess the feasibility of a community-pharmacy-based method for pharmacovigilance of herbal medicines purchased OTC, using ginkgo (*Ginkgo biloba*) products, for oral use as a model herbal medicine. The project's secondary aim was to describe the patterns of use and self-reported symptoms occurring during oral use of ginkgo products, purchased from community pharmacies.

7.4.3 Research questions

The specific research questions the study proposed to explore were:

- What is the response rate among community pharmacies in Hertfordshire invited to participate in the study?
- What is the recruitment rate among purchasers of ginkgo identified in participating pharmacies and invited to take part in the study, for each of the two recruitment methods employed?
- Is there a greater consumer recruitment rate achieved through direct involvement of pharmacy staff or through passive involvement by simply providing consumers with study documentation?
- What are the reasons for and patterns of use of ginkgo purchased from pharmacies?
- Can adverse event data for products containing the herbal ingredient ginkgo be collected systematically from consumers using a community-pharmacy-based method of recruitment?

- What is the frequency and types of adverse events that are self-reported by users of ginkgo purchased in pharmacies?
- What are the pharmacists' and participating consumers' views towards this type of study?

7.4.4 Methods

7.4.4.1 Study design

This pilot project was an observational cohort study involving adult purchasers of oral preparations of the herbal medicine ginkgo from participating community pharmacies in Hertfordshire. There was an experimental component to the recruitment phase of the study in that participating pharmacies were planned to be randomised to recruitment method A or B (see section 7.4.4.5 below).

7.4.4.2 Herbal medicinal product selection

Ginkgo was chosen as the "model" herbal medicine for this study as it is a popular herbal medicine (Bent and Ko, 2004; Kelly *et al.*, 2005), widely available in pharmacies and used by consumers for a variety of conditions (such as poor circulation, tinnitus, ageing, Alzheimer's disease), some of which are not necessarily suitable for self-diagnosis and self-treatment (Barnes *et al.*, 2002). In addition, whilst available data suggest that ginkgo preparations are generally well-tolerated when used at recommended doses, isolated reports of spontaneous bleeding in patients taking ginkgo concurrently with aspirin and/or warfarin have raised concerns about potential interactions between ginkgo and antiplatelet and anticoagulant agents (Barnes *et al.*, 2002). However, ginkgo has not to date been the subject of a major safety concern, in contrast to other popular herbal medicines such as St John's wort which has received significant negative publicity among the popular media and was the subject of a 'Dear Doctor/Pharmacist letter (Breckenridge, 2000).

7.4.4.3 Geographical location of study

Hertfordshire was selected as the study area on the basis that it is a relatively small area with a manageable number of pharmacies compared to a larger city such as London, yet it is in the vicinity of London making training and store visits feasible. Also, the opening of the Hertfordshire School of Pharmacy suggested greater pharmacy activity in the area and possible interest in research.

7.4.4.4 Phase 1 - Recruitment of pharmacies

Figure 7.1 depicts the model proposed for the recruitment of pharmacies.

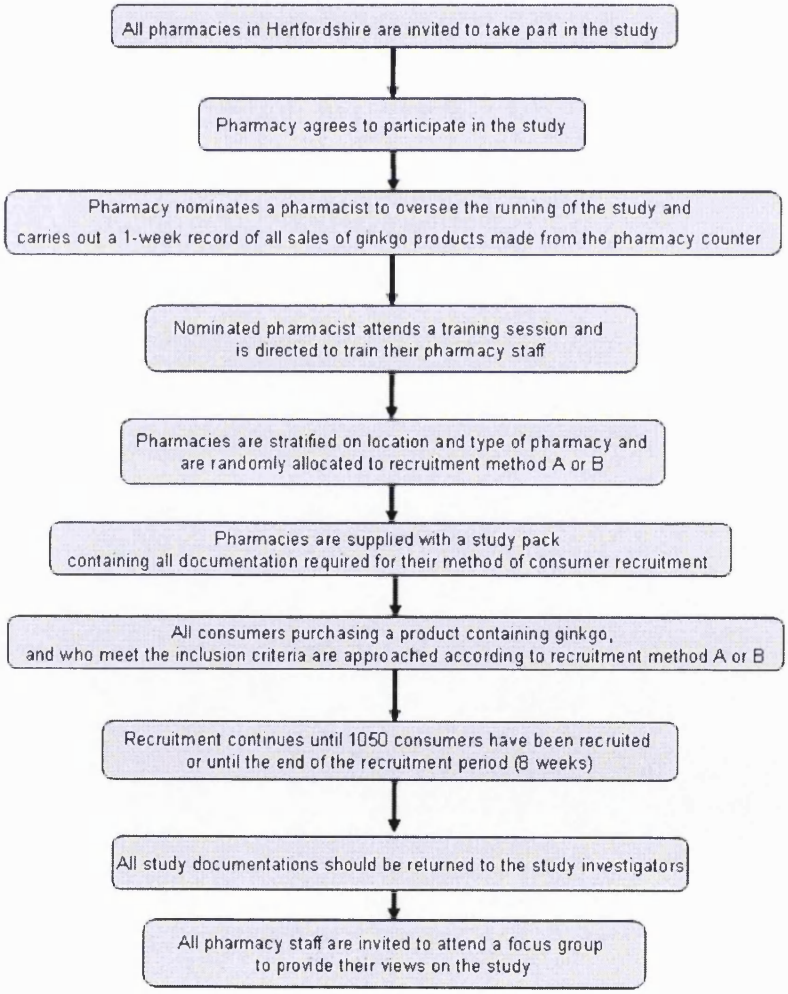


Figure 7.1 Flow chart for consumer recruitment

7.4.4.5 Phase 2 - Recruitment of consumer cohort

Two methods were proposed to be tested for consumer recruitment:

- Method A: Consumers purchasing a ginkgo product are approached directly by pharmacy staff
- Method B: Materials regarding the study (Consumer information sheet, consent form, recruitment questionnaire, and reply-paid envelope) are given to consumers with their ginkgo purchase

A summary of this proposed method is outlined in figure 7.2.

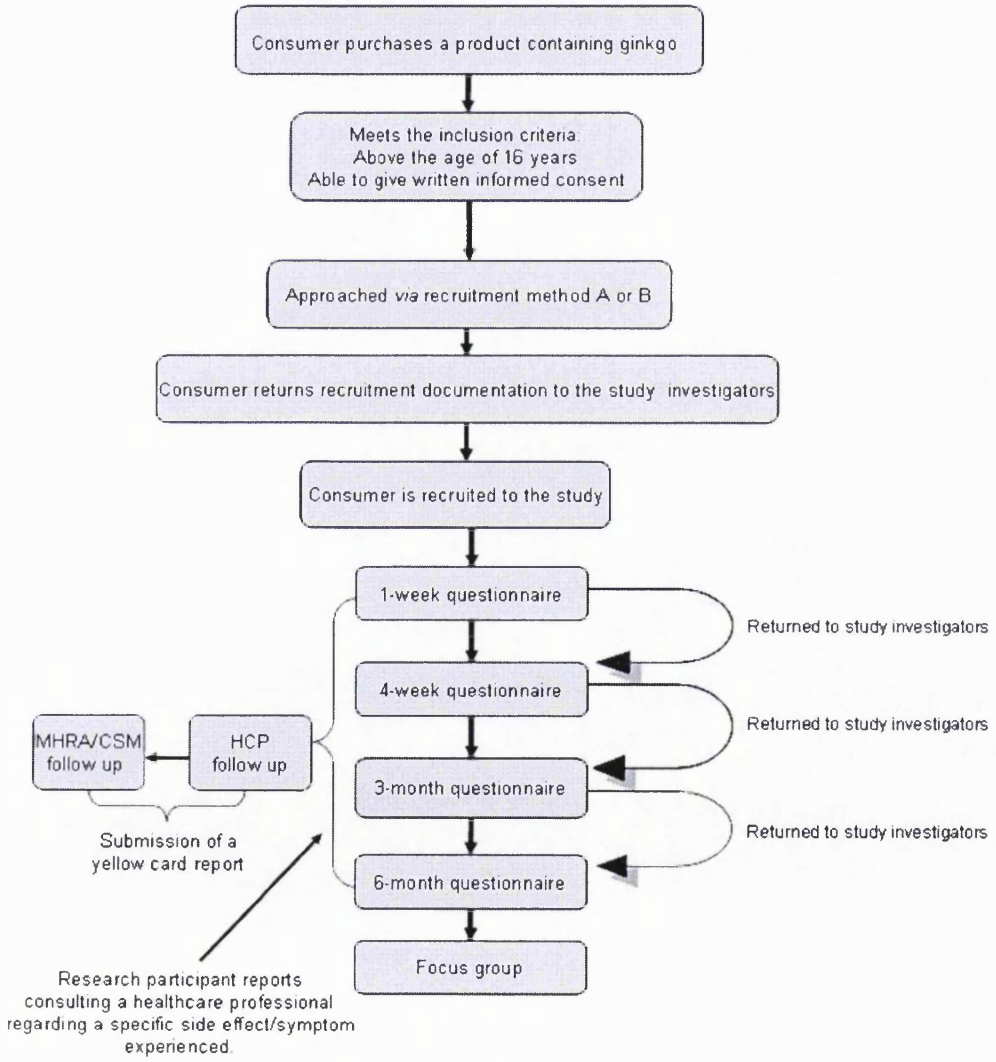


Figure 7.2 Flow chart for consumer follow-up

7.4.4.6 Study documentation

A copy of the study protocol, consumer covering letter, information leaflet, consent form, recruitment questionnaire and week 1 follow-up questionnaire can be found in Appendix 5. The consumer information sheet described the study team, explained the aim and procedures of the study, and advised consumers to consult their GP or pharmacist if their symptoms persisted, if they experienced new symptoms that concerned them (*i.e.* they should behave as they usually would) or if they had any concerns about the ginkgo product they had purchased. To ensure data confidentiality, each consumer recruitment pack was coded with a unique number for each participating pharmacy and for each set of forms, and this number was intended to be used for the participant throughout the study. The consent form included the usual statements regarding data confidentiality, freedom to withdraw from the study at any time *etc.* The recruitment questionnaire requested consumer details (gender, name and address *etc*), information on the ginkgo purchase (product details: name, manufacturer, type of preparation, batch number etc), and where the form was completed. All forms and questionnaires were piloted on seven lay individuals known to the study investigator (most were non-academic staff recruited at the School of Pharmacy), to identify any problems with comprehension and amendments were made in accordance with their comments.

7.4.4.7 Questionnaire design

Follow-up questionnaires were designed to seek information on previous medical history, use of health services for six months before the ginkgo purchase, usage of the ginkgo product purchased as well as any other medication and supplements taken, any symptoms experienced, opinion as to which symptoms (if any) were related to use of ginkgo, and use of health services.

7.4.4.8 Sample size

The project aimed to recruit at least 50 pharmacies (participation rate of 25%); this was considered achievable on the basis that similar previous studies have achieved a participation rate of almost 50% (Sinclair *et al.*, 1999; Layton *et al.*, 2002).

As this was a feasibility study, a sample size calculation was not relevant; the aim was for 21 consumers to be enrolled through each pharmacy, providing a total target sample of 1050 consumers (*i.e.* 50 pharmacies x 21). With a sample of this size, the study would have 95% power to detect a difference of 10% in recruitment between the two methods (*i.e.* 55% *versus* 45% of subjects recruited by different methods; 2-tailed). Although this was not based on the 'cluster' design, the numbers are approximately valid. An approximate sample size calculation based on clustering was carried out as well, but as reliable data on recruitment rates for individual pharmacies are not available in the context of a study involving a herbal medicine, therefore the above approximation was used.

Given resource limitations and the pilot nature of this study, recruitment was limited to once the 1050th participant was enrolled or at the end of 8 weeks from the start of recruitment, whichever was the sooner.

7.4.4.9 Ethics and NHS Research Management and Governance

Ethics approval by Hertfordshire Local Research Ethics Committee and NHS Research Management & Governance approval for the 8 Primary Care Trusts (PCTs) in Hertfordshire (Watford and Three Rivers PCT, North Hertfordshire and Stevenage PCT, Dacorum PCT, Welwyn and Hatfield PCT, South East Hertfordshire PCT, South East Hertfordshire PCT, Hertsmere PCT, Harpenden PCT and Royston, Butingford and Bishops Stortford PCT) were granted in 2005. The total time taken for acceptance from the initial application was 7 months. This delay occurred due to the changes in the ethics approval application process and the necessity for PCT Research Management & Governance approval.

7.5 Practical model of a pharmacy-based pharmacovigilance system

On implementation of the proposed study (paper model) a number of methodological issues were raised and changes were necessary to ensure feasibility (practical model). These are summarised below.

7.5.1 Phase 1 – Recruitment of pharmacies

Recruitment of pharmacies began in May 2005. Addresses for all community pharmacies (n=240) in Hertfordshire were obtained from the RPSGB. In the paper model each pharmacy was planned to be contacted and invited to participate (see figure 7.3) however, for national multiples this would have meant, that for each store wanting to participate in the study, independent authorisation from their head office would have to be gained. Thus, the superintendent pharmacist for each multiple was contacted directly for study clearance (practical model) to aid recruitment of national multiples. For all other pharmacies (independents and small ownerships) the owner/pharmacy manager was sent information about the study and invited to participate. Two follow-ups were carried out to the non-responders at 3-week intervals. As an incentive, all participating pharmacies were offered free entry into a prize draw (one prize of books worth £250 from the Pharmaceutical Press) in recognition of staff time spent in consumer recruitment (independent of the number of consumers recruited). Other initiatives used to recruit pharmacists included inviting all pharmacists in Hertfordshire to a seminar on herbal medicines and placing advertisements about the study on the National Pharmaceutical Association's website and in a newsletter distributed by the Hertfordshire Local Pharmaceutical Committee.

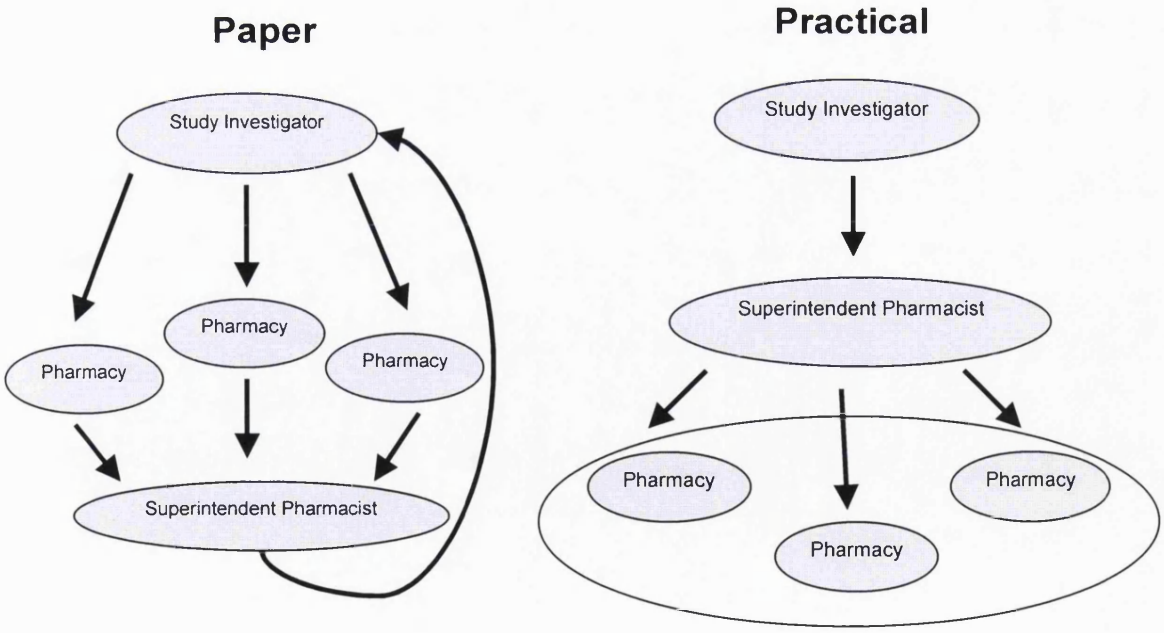


Figure 7.3 Recruitment of pharmacies

Initially it was proposed that each nominated pharmacist would be required to attend a training meeting and to directly train their pharmacy staff, including any locum pharmacists, in the study procedures, however, due to low number of participating pharmacies, each one was directly trained in-store by the study investigator (see figure 7.4). This also ensured that each member of staff was fully trained and that each pharmacy and member of staff received the same level of training.

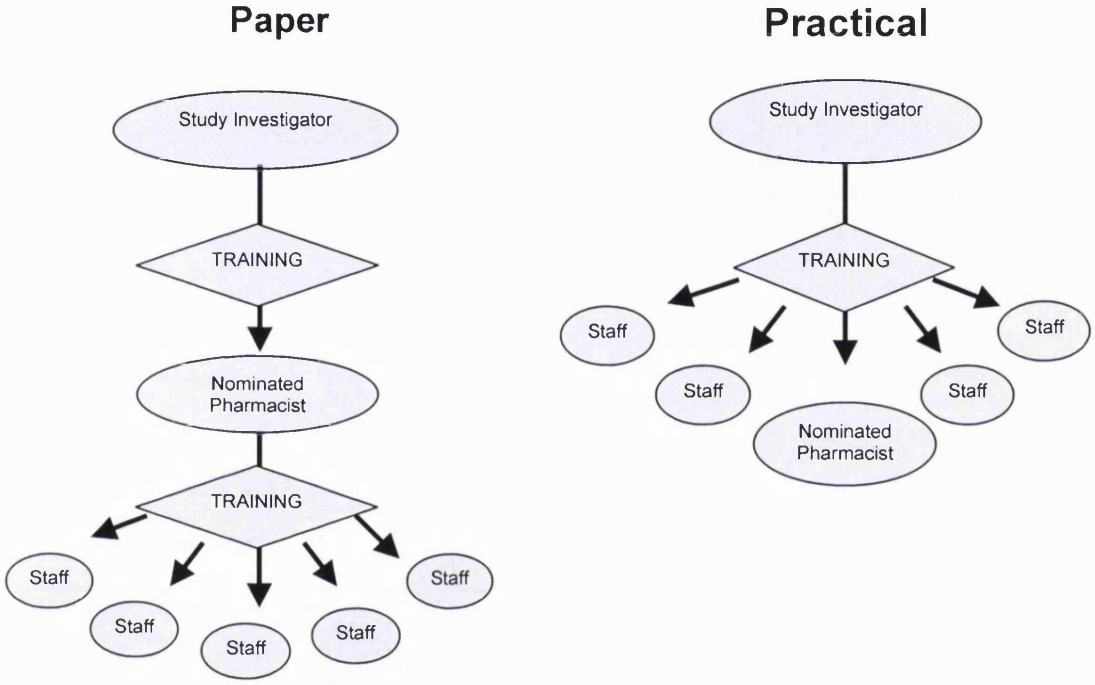


Figure 7.4 Training of pharmacy staff

It was also initially planned that characteristics of participating pharmacies would be used to stratify pharmacies on location of pharmacy (urban, rural) and type of pharmacy (independent, small multiple, large multiple) before being randomly allocated to recruitment method A or B using a computer-generated randomisation list. However as insufficient numbers of pharmacies agreed to participate in the study, stratification on both location and type of pharmacy was not possible. Furthermore, due to the low number of pharmacies participating in the study, it was no longer feasible to randomise pharmacies to two recruitment methods (A and B) thus, participating pharmacies were asked to use either method depending on how much time the consumer had (see figure 7.5). For example, if the consumer had time to discuss the study, to use method A and if the consumer did not have time to discuss the study,

to use method B. A record of the method used and which pack was given was to be kept by each pharmacy, so that research participants recruited *via* each method could be traced using the unique consumer identification number on each consumer recruitment pack.

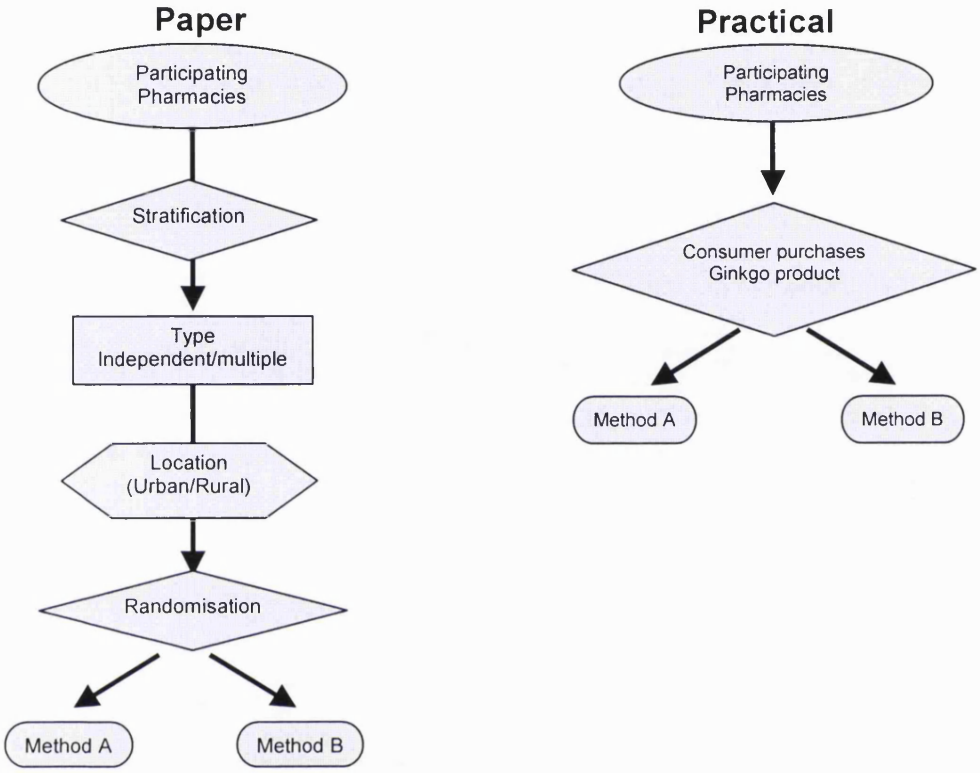


Figure 7.5 Method of consumer recruitment

Further amendments to the paper model included extending the recruitment period from 8 to 12 weeks. This required ethics approval and agreement from the four participating pharmacies, which further delayed the project's progress. Also, due to the impact on timelines the follow-up period was reduced to 3 months.

7.5.2 Data analysis

Checks on data entry for all of the study participants were made by re-entering the data after a set interval and comparing any discrepancies using the original hard copies of data. Data were

stored and analysed using SPSS version 13. Qualitative data on pharmacy staff views on the study were explored using framework approach to analysis (outlined in section 3.7.2).

7.5.3 Results

7.5.3.1 Recruitment of pharmacies

Figure 7.6 outlines the recruitment of pharmacies for the proposed study. In total, 67 pharmacies from a total of 240 (28%) responded to the initial invitation to participate. There was no statistically significant difference in response between multiples and independent pharmacies (26/90 *versus* 41/150 for multiples and independent pharmacies respectively; Pearsons Chi-Square = 0.07; $p = 0.80$). Of the 67 respondents, 5 (7%) agreed to participate, 11 (16%) were excluded (7 did not sell herbal medicines and 4 others did not stock ginkgo products) and 51 (76%) declined the invitation to participate. Of the five pharmacies that agreed to participate only four were trained in the study procedures as one was unable to get study clearance from their head office.

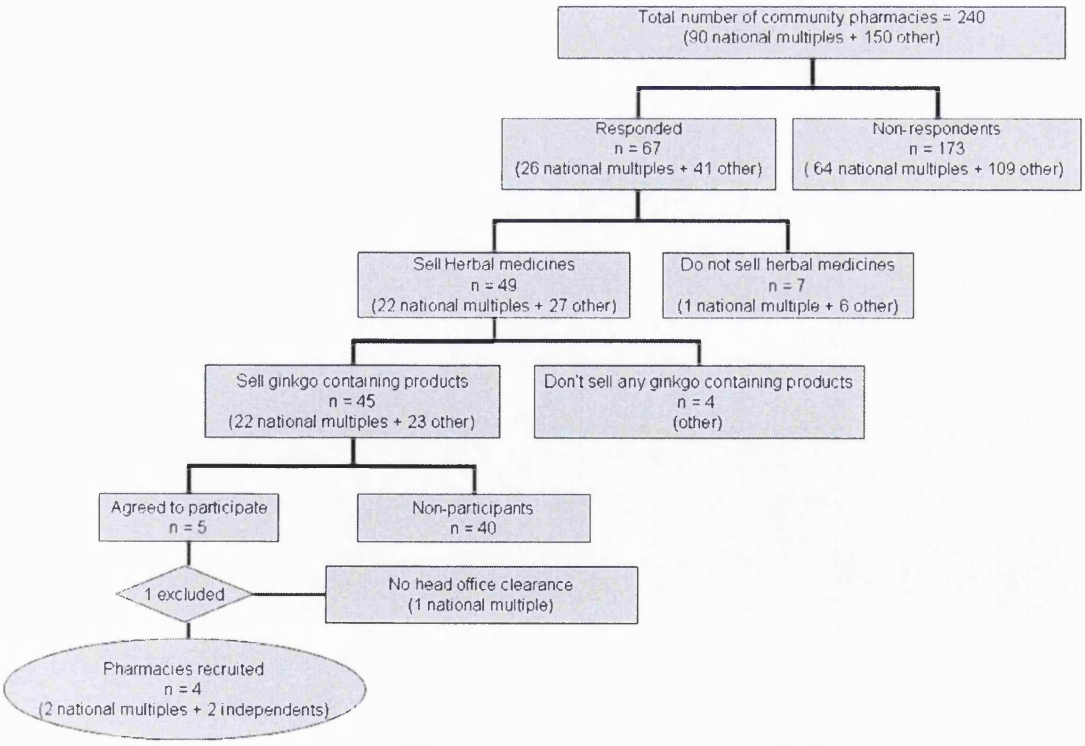


Figure 7.6 Recruitment rate of pharmacies

(Figures do not add up to 100% due to missing data)

7.5.3.2 Products stocked

Figure 7.7 shows the types of ginkgo containing products stocked in the four participating pharmacies and table 7.3 provides further details of the brand name, pharmaceutical formulation and strength. In total 17 products were stocked, of these the majority were single herb products and in tablet formulation, which indicated that there should be sufficient ginkgo sales for participant recruitment.

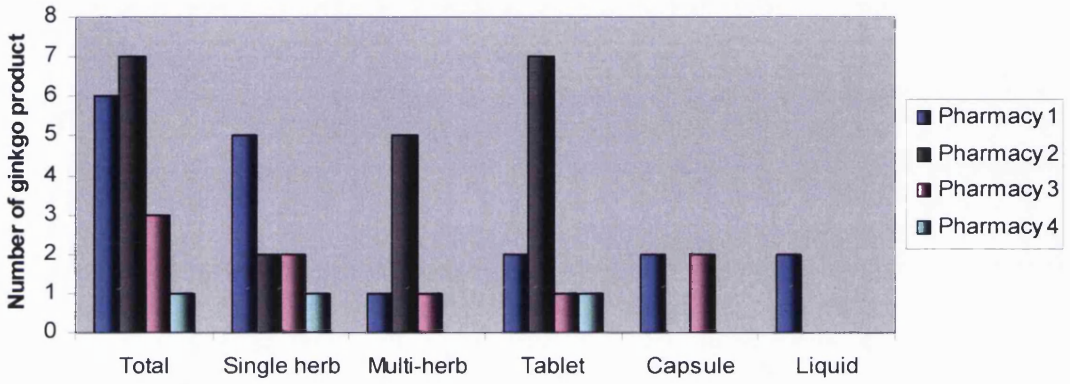


Figure 7.7 Types of ginkgo containing products stocked in participating pharmacies

Table 7.3. Frequency, formulation and strength of ginkgo containing products stocked in the four participating pharmacies

Single herb preparations	**Frequency**	**Form**	**Strength**
Valupak - *Ginkgo biloba*	2	Tablet	120mg
Principle Healthcare - *Ginkgo biloba*	1	Capsule	60mg
Natures Aid - *Ginkgo biloba*	1	Tablet	60mg
Jardines - *Ginkgo biloba*	1	Tablet	64mg
Health Aid - *Ginkgo biloba*	1	Capsule	100mg
A. Vogel - *Ginkgo biloba*	1	Tincture	66% v/v
Bioforce - *Ginkgo biloba*	1	Tincture	66% v/v
Morrisons *Ginkgo biloba*	2	Tablet	60mg
Multiherb preparations			
Red Kooga - Korean Ginseng and Ginkgo	2	Tablet	40mg
Principle Healthcare - Forty plus (Vitamin E, Ginseng, Ginkgo	1	Capsule	10mg
Health Aid Gericaps active	1	Capsule	30mg
Seven Seas Multibionta 50+	1	Tablet	5mg
Whitehall Centrum Performance	1	Tablet	60mg
Sanatogen Vital 50+	1	Tablet	10mg

7.5.3.3 Ginkgo sales data

Figure 7.8 shows that during the 1-week trial period 3 sales were made from two of the pharmacies, and during the 8-week consumer recruitment period 6 ginkgo purchases were made. During the 8-week consumer recruitment all six consumers received a recruitment pack however; no consumers returned the study documents to the study investigators. The consumer recruitment period was therefore extended for a further 4 weeks. Three pharmacies agreed to the extension however, this did not yield any further sales or any research participants and thus, the study had to be terminated. Reasons for the low uptake are discussed below (see section 7.6 below).

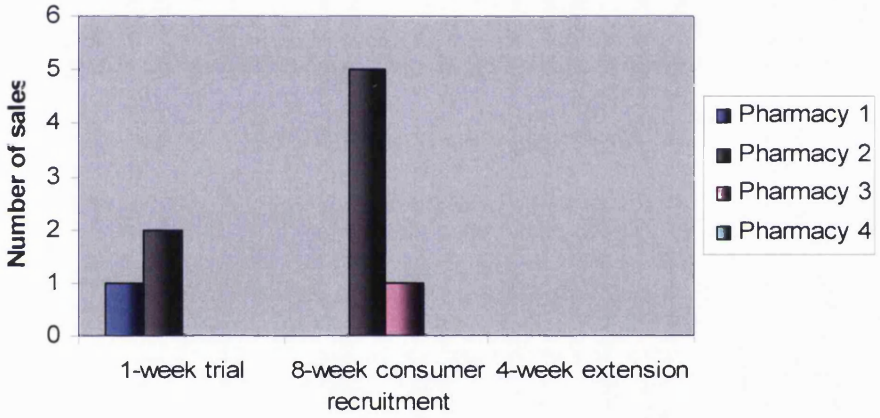


Figure 7.8 Number of sales of ginkgo containing products made from participating pharmacies

Feedback from the four participating pharmacies and superintendent pharmacist of non-participating pharmacies, revealed a number of factors that contributed to the low sales volumes (see table 7.4 and 7.5).

Table 7.4 Feedback from participating pharmacies	
Participating Multiples	
Setting	'The same products are also available through the main supermarket and most customers will purchase these whilst doing their weekly grocery shopping.' [respondent 12] 'Being a pharmacy within a supermarket we have long opening hours and are therefore dependent on locum pharmacists, who may not have adhered to the study procedures.' [respondent 13]
Participating Independents	
Business	'Pharmacy is run completely by locum pharmacists, difficult to train all locums in the study procedures.' [respondent 11]
Location	'Majority of the customers go to the larger multiples in the high street.' [respondent 11] 'Pharmacy itself has very little business therefore unlikely to see large volumes of ginkgo sales.' [respondent 14] 'The pharmacy is not known for stocking a wide range of herbal products, for example, we only stock one ginkgo product. There is also a newly refurbished pharmacy down the road, which most customers tend to go to.' [respondent 14]

T able 7.5 Feedback from superintendent pharmacists of non-participating national multiples	
Workload	'Unfortunately I can not ask my pharmacists to take part in the study as they are all extremely busy at the moment following the introduction of the new pharmacy contract in April. They are all training to provide advanced services as well as getting to grips with the finer details of essential services and this takes priority over everything else.' [respondent 01] 'We feel that the study will place additional demands on our branch teams at a time when they are already under significant pressure and have an additional workload due to the introduction of the new pharmacy contract.' [respondent 02] 'I do not feel that we would be able to devote sufficient time to be able to do justice to your study.' [respondent 03] 'The issue for us is workload and customer impact. The decision on these is made by the Category Manager. As you can imagine, we get lots of requests for our store teams to help with various projects. So, we control this tightly from the centre.' [respondent 05]
Feasibility	'There is also the issue with supermarket pharmacies that very few sales of the products you are studying go through the pharmacy tills.' [respondent 01] 'I have read the brief and do not feel that this type of study would be feasible in the supermarket setting where the herbal remedies are sold from the shop floor rather than the pharmacy. Most of these purchases will be through the checkouts and cashiers will not be suitably trained or have enough time to be involved.' [respondent 04] 'Whilst I appreciate the simplicity of what you are asking, I am not confident that it would happen on a sufficiently consistent basis in store to be meaningful.' [respondent 03]
Priority	'I can't ask our pharmacies to be involved in anything that isn't business critical at the moment.'[respondent 01]
Customer impact	'The issue for us is workload and customer impact. The decision on these is made by the Category Manager. As you can imagine, we get lots of requests for our store teams to help with various projects. So, we control this tightly from the centre.' [respondent 05]

7.6 Discussion

Through traditional surveillance methods, the frequency of an ADR cannot be calculated, whereas active surveillance techniques highlight the total population approached or purchasing a specific product. In addition, baseline characteristics such as the gender of subjects who do not wish to participate can be compared to the research participants, to ascertain the representation of the target population. The proposed active surveillance model is also beneficial when recruiting large numbers of subjects as it does not rely on individual health practitioners and as a result eliminates selection bias. Recall bias is also eliminated as the data collected are prospective rather than retrospective. As the questionnaire requests all symptoms experienced the method has the added advantage of acquiring ADRs that go unreported or are dismissed as not being serious/severe. Furthermore, the reporting of all symptoms is ideal as patients may not be able to discriminate effectively between symptoms which are attributable to either a drug they are taking or due to a pre-existing disease. Several studies have shown that patients can accurately record medication use and changes (Sinclair *et al.*, 1999; Paterson, 2004; Jarernsiripornkul *et al.*, 2002) despite the common belief that the collection of all symptoms from a patient's viewpoint can be subjective, inaccurate and incomplete.

Despite the advantages of active surveillance methods, the implementation of the proposed paper model was unsuccessful. It is widely known that research on herbal medicines presents additional challenges compared to research with conventional medicines however, in addition to the inherent shortfalls associated with research on herbal medicines there were additional steps that could have been implemented to avoid failure of the study i.e. preventable shortfalls. Both the inherent and preventable shortfalls of this study are explored and discussed further.

The availability of ginkgo from non-pharmacy counters may have contributed to the low sales volumes of ginkgo containing products observed in this study, which was outlined by one of the participating pharmacists:

> *"The same products are also available through the main supermarket and most customers will purchase these whilst doing their weekly grocery shopping." [respondent 12]*

This was considered prior to the study however, as the majority of sales of herbal medicines are made from pharmacies and that pharmacists are often asked for advice on these products, the sales of ginkgo products from non-pharmacy counters was thought would not have a major impact on recruitment rates. This also highlights the fact that purchasing a product from a pharmacy store is different to purchasing a product from a pharmacy counter, as unless a product is sold from a pharmacy counter it may not be seen by a pharmacist or a pharmacist may not intervene in the sale. This amounts to little more than purchasing the product from a non-pharmacy outlet such as a supermarket. However, there is the perception that if an item is purchased from a pharmacy that it is safer, even though the pharmacist may not have any control over what products are stocked in the store. Contrary to this, the Medicines, Ethics and Practice guidelines (RPSGB, 2006) state that:

> " *The public is entitled to expect that medicines purchased OTC will be safe, effective and appropriate for the condition to be treated and the intended recipient.*"

The issue of sales at non-pharmacy counters was also true for the studies conducted in Grampian and Hampshire, as ibuprofen is available OTC. However, a high response rate was achieved in both studies. A possible explanation could be that ibuprofen, unlike ginkgo is classified as a P medicine for larger pack sizes and for the higher strength of 400mg, which customers may prefer to purchase over the general sale pack sizes. Also the pharmacy status of medicine ensures that there is some interaction of the purchaser with a healthcare professional. This could have encouraged purchasers to participate in the study as this process allowed the pharmacist to explain the study and invite them to participate or it may have prompted staff to give recruitment packs as each product requires staff to run through a set protocol, whereas with a general sale product the item may not have been identified. As outlined by Gore and Thomas (1995), the restricted availability of products from pharmacies provides for some supervision of use and from a pharmacoepidemiological perspective it allows for the collection of data which is useful for research purposes. This might be the reason why all studies conducted to date have involved pharmacy or prescription only medicines.

In addition, the sales of herbal medicines from other counters raises the question on whether or not consumers that purchase their herbal medicine from the pharmacy counter vary from

those purchasing the product from the main store, which overrides the advantage of the non-population bias associated with active surveillance methods. Thus, the proposed paper model should have incorporated the sales made from all counters within a store or preliminary work should have been conducted to investigate if there is a difference in the two population groups.

Other possible reasons for the low sale volumes of ginkgo containing products include that *Ginkgo biloba* was selected on the basis that it is a popular herbal medicine, based on previous use and prevalence studies, which reported ginkgo as a popular herb (Bent and Ko, 2004; Kelly *et al.*, 2005). There is therefore a need for further proof that ginkgo is widely purchased in the UK, as use of herbal medicines often follow trends, which are largely influenced by the media. Further to this, the identification of products containing ginkgo may have been difficult for pharmacy staff, as a number of preparations available on the market are fortified multivitamins. A number of pharmacies were excluded from the study as they stated that they did not sell herbal medicines or did not stock any ginkgo containing products. However, it is possible that the pharmacist was indeed unaware of stocked products that contained ginkgo. As this was a feasibility study, in hindsight all herbal medicines should have been included, as not only would this have simplified the study and aided pharmacist in identifying products but this would have yielded a greater number of participants and therefore more meaningful data.

It is also possible that pharmacists do not perceive herbal medicines or more specifically the herb selected as topically relevant. Thus, if St John's wort, which has received much media attention, had been the study herb, a higher response rate may have been achieved. With the introduction of the new Directive on Traditional Herbal Medicinal Products it is likely that the importance of herbal medicines in community pharmacy will increase and become more relevant. As this study was planned just prior to the implementation of this Directive, it is possible that there could in future be a higher response rate due to the increased awareness of herbal medicines. Also, as outlined in chapters 5 and 6, community pharmacists need further education and awareness on herbal medicines and pharmacovigilance, which if attained may enhance recruitment levels for such studies.

As well as the low sale volumes, the study also suffered from poor recruitment rates of consumers and community pharmacists. There is much discussion on recruitment rates, which

is outlined in section 3.6.1. In general, it is known that recruitment in follow up studies tends to be low. Sinclair *et al.,* (2001), report other problems associated with recruitment in community pharmacy such as:

- customers find follow-ups potentially threatening
- the doctor-patient relationship differs from that of pharmacist-patient relationships so that customers feel less inclined to accept a pharmacists invitation to participate in a study
- pharmacists do not have exclusively registered populations
- the pharmacist-customer relationship can be commercially sensitive
- community pharmacies often lack privacy
- time constraints

Participation rates of community pharmacists in similar studies vary considerably from 16% (Gauld *et al.*, 2000) to 75% (McCafferty *et al.*, 1996). In the study by Gauld *et al.,* (2000), though pharmacists received compensation for time spent in recruitment, possible reasons for low recruitment suggested by the authors included:

- the high level of commitment over several months
- there were few incentives other than contribution to research and a small financial remuneration.

Other factors identified include: time, staff shortages, and longer working hours as limiting pharmacist's participation (Grewar *et al.*, 1998; Krska *et al.*, 1998; Kennedy *et al.*, 1999; Layton *et al.*, 2002). Furthermore, the invitation to participate was unsolicited in this study. The RPSGB does recommend that at least 10% of pharmacists should be involved in pharmacy practice research (RPSGB, 1997). However, with growing demands on community pharmacists particularly with the introduction of the new pharmacy contract, research is a low priority. This is also demonstrated by the following quote made by one of the respondents:

> *"Unfortunately I cannot ask my pharmacists to take part in the study as they are all extremely busy at the moment following the introduction of the new pharmacy contract in April. They are all*

training to provide advanced services as well as getting to grips with the finer details of essential services and this takes priority over everything else.' [respondent 01]

Factors used to influence response rates are considerable. Monetary incentives are reported to have the highest impact. This study did not test for incentives as these have been shown to have no appreciable effect on questionnaire return in a community pharmacy setting (Grewar *et al.*, 1998). Also, while monetary incentives are reported to have the most impact, they are unfavourably looked upon from an ethical perspective and as this was university funded research, such funds were not available. Although it is not ideal to compare different studies (as each was conducted at different time points with different methods), looking at the studies in table 7.2, only one study offered a monetary incentive to consumers (Nykamp *et al.*, 1994), yet the consumer recruitment rates for the other studies were greater, so this theory may not follow. Two other studies offered a monetary incentive to the pharmacists (Gauld *et al.*, 2000; Layton *et al.*, 2002). In both studies, payment was provided to compensate for time spent on recruitment and remuneration - no incentives were offered for purchasers to participate. However, recruitment rates for the Hampshire area were lower than the Grampian area, where no incentive was offered to community pharmacists (Layton *et al.*, 2002). Another method used for higher pharmacy recruitment rates is *via* the use of a pharmacist network. This method was used in the Grampian studies (see table 7.2) where the same network of pharmacists was used for all of their studies. However, these pharmacists may be particularly well motivated and this could lead to a selection bias which has to be acknowledged. It is also known for study investigators to use personal affiliations and contacts to aid recruitment *e.g.* study investigators have been known to locum at research sites, though this is often not stated in publications. Qualitative methods should have been used to investigate community pharmacists' willingness to participate in the study and what incentives were required. Also working in collaboration with one of the agencies such as the RPSGB, MHRA or DOH would have endorsed/promoted the study and therefore potentially increased the number of pharmacists recruited.

From data published in the British Medical Journal (Bentley, 2005), Hertfordshire Ethics Committee received the lowest number of ethics applications during the timeframe for the study presented in this chapter, thus it could be postulated that pharmacists in Hertfordshire may not be accustomed to participating in research studies. It is possible that if the study was

carried out in a different area e.g. London, a higher response rate may have been achieved. It was proposed to extend the study to another area but, as the study had only received local ethics approval for Hertfordshire, each additional area would require separate ethics and PCT Research Management and Governance approval, which was not possible with the given timelines. Also, there was no guarantee whether an adequate response rate would be achieved.

7.7 Conclusions

Traditionally, pharmacovigilance has focused on prescribed medicines, despite the fact that there is greater need for the pharmacovigilance of OTC medicines and in particular for herbal products (as outlined in section 1.5.9). The study presented in this chapter was the first that aimed to develop and assess the feasibility of a community-pharmacy based study for pharmacovigilance of herbal medicines purchased OTC. However, both the low numbers of participating pharmacies and low sales volumes of the specific herbal medicine to be investigated in this study, contributed to the unsuccessful implementation of the paper model.

Throughout the study the method evolved, to aid recruitment and simplify study procedures (see section 7.5) regardless of these efforts, no additional consumers were recruited to the study. Objective rationalisation of the paper model revealed that a number of baseline assumptions, which had been largely based on previous literature may have been incorrect for this given time, such as:

- ginkgo is a popular herbal medicine
- pharmacy staff would be able to identify products containing a specific herb
- incentives for pharmacists and/or consumers does not increase the response rates significantly

This study identified a number of additional challenges, including obtaining a fair representation of the target population, availability of herbal medicines through non-pharmacy outlets and sales made at other non-pharmacy counters within a pharmacy. Feedback from respondents also highlighted other challenges, such as work pressure, lack of interest and lack of time. Though these might be perceived as being specific to research in herbal

pharmacovigilance, these are generic to pharmacy and research in pharmacy practice. Despite these drawbacks, this study does show that community pharmacy based active surveillance methods have the potential to be used to complement existing surveillance methods though, at this current time, are not feasible for herbal medicines.

Chapter 8

SUMMARY OF FINDINGS, FUTURE WORK AND RECOMMENDATIONS

Herbal medicines are widely used in both developed and developing countries. Most herbal medicines are sold in the UK as 'unlicensed' herbal medicines or food supplements. Under these conditions, manufacturers are not required to consult the regulatory authority (MHRA) before marketing their product. Thus, there are no stringent regulations to prove the safety, efficacy or quality of these products, which makes the necessity for post-marketing surveillance for herbal medicines greater than that required for conventional medicines.

In recent years, herbal medicines have been associated with several safety concerns. For example, St Johns' wort (*Hypericum perforatum*) has been associated with pharmacokinetic interactions leading to therapeutic failure (including unplanned pregnancies), and Kava-kava (*Piper methysticum*) has been associated with cases of hepatic failure. There have also been numerous safety concerns associated with the quality of herbal medicines *e.g.* adulteration with prescription medicines. Thus, it is widely recognised that the need for further vigilance of herbal medicines is required. At present the UK's yellow card ADR reporting system is the main mechanism for the pharmacovigilance of herbal medicines. However, such schemes have inherent limitations, particularly under-reporting of suspected ADRs, which are likely to be even more significant for herbal than for conventional medicines, as outlined below:

- Consumers often perceive herbal medicines as being 'natural' and therefore 'safe', hence they may not associate a suspected ADR with a herbal medicine
- Most herbal medicines are readily available without the need to consult a healthcare professional
- Users are known to be reluctant to inform their GP on the use of these products
- The UK's spontaneous reporting scheme is specifically designed for conventional medicines
- The UK's yellow card for ADR reporting does not request for any specific details or prompt for the reporting of suspected ADRs associated with herbal medicines
- Recognised reporter groups are often unaware that the scheme applies to herbal medicines

Evidence suggests that community pharmacists are in an ideal position to advise, monitor use, identify and report herbal ADRs, which was the main reasoning for the recent inclusion of community pharmacists as official reporters to the UK's yellow card scheme in 1999. Despite

this initiative, numbers of submitted suspected ADR reports associated with herbal medicines remain low. However, the yellow card scheme is at an infancy stage regarding the pharmacovigilance of herbal medicines and there is still great potential to increase reporting in this area. Therefore the focus of the research presented in this thesis was to explore the community pharmacists' role in the pharmacovigilance of herbal medicines and concentrate on the following areas:

- Identify community pharmacists current practices in and awareness of the pharmacovigilance of herbal medicines
- How to improve community pharmacists' ADR reporting of herbal medicines
- Developing methods for enhancing pharmacovigilance of herbal medicines through community pharmacy

In chapter four of this thesis, a cross-sectional survey of associate and official member countries of the WHO-UMC programme showed that the current practices of national pharmacovigilance centres towards reporting ADRs associated with herbal medicines vary. There were also clear differences in the national pharmacovigilance centres' practices between herbal and conventional medicines, despite the WHO's definition on pharmacovigilance making no distinction between the pharmacovigilance of conventional and herbal medicines. Due to limited data on the safety, efficacy and quality of unlicensed products, unlicensed herbal medicines warrant the need for greater post-marketing vigilance compared to licensed herbal medicines; however, even fewer national centres accepted reports for unlicensed herbal medicines compared to licensed herbal medicines, which demonstrates the lack of experience and knowledge of national centres with respect to herbal medicines. Within the UK it was only following a report by Guy's Hospital Toxicology Unit on potentially serious adverse reactions associated with herbal medicines that the scheme was extended to include unlicensed herbal remedies. This report included 9 confirmed cases of heavy metal toxicity, 21 cases of liver toxicity, including two deaths associated with the use of traditional Chinese remedies (Shaw *et al.*, 1997). The question now remains on how many further incidents are required for all national pharmacovigilance centres to include herbal medicines (both unlicensed and licensed) as part of their scheme as, until this is achieved, delays in signal generation are likely to occur. Thus, data collection in other member countries can have an impact on the UK's public health.

Inconsistency in classifying herbal products by national pharmacovigilance centres was identified in chapter 4 and was shown to be independent of the centre's official definition for herbal medicines. It is evident from the different definitions for herbal medicines outlined under table 1.2 as to why differences in interpretation could occur, for example the WHO's (2002) definition adds that:

"*....In some countries, herbal medicines may contain, by tradition, natural organic or inorganic active ingredients that are not of plant origin (e.g. animals and mineral materials).*"

Thus, those national centres using this definition could potentially include by definition mineral and animal products as herbal. These inconsistencies in the classification of products raises concern on the ability to identify signals, as some might be overlooked due to them being incorrectly coded and highlights the need for a globally accepted definition for herbal medicines which is recognised by all national pharmacovigilance centres and all healthcare professionals.

Inconsistencies in the definition and classification of herbal medicines were also demonstrated in chapter 5, as few pharmacists could correctly define herbal medicines or correctly assign specific products as herbal or non-herbal. As a result pharmacists in chapter 7 may not have been able to identify herbal products containing gingko and were therefore incorrectly excluded from the study or for those pharmacies included in the study the pharmacist on duty may have missed potential consumer recruitment opportunities. Although confusion in the identification of products as herbal is detrimental for studies in herbal medicines, in practice this should not impact submission of yellow card reports, as pharmacists should report any suspected ADR if they are unsure whether or not to report, thus the need to specifically identify the product as being herbal is not required and should be a responsibility for the national pharmacovigilance centres.

Within the UK, pharmacists are specifically encouraged to report suspected ADRs associated with herbal medicines, based on the fact that the majority of herbal medicines are purchased from pharmacies and pharmacists are therefore in an ideal position to identify suspected herbal ADRs. Pharmacists were also reported by the majority of national pharmacovigilance centres

in chapter 4 as a specific reporter group encouraged to report suspected ADRs associated with herbal medicines which provides further evidence for their importance in this area. However, Chapter 5 identified that most pharmacists were unaware of how herbal medicines were regulated and that most pharmacists would either contact the manufacturer or instruct the consumer to stop taking the product to see if their symptoms subsided, if they suspected an ADR associated with a herbal medicine rather than reporting it to the MHRA. Those pharmacists that did consider submitting a yellow card report for a suspected ADR associated with a herbal medicine said they would if the reaction was serious, unreported or if they could assign causality, which shows a lack of understanding of the current pharmacovigilance system and the need for further education/training in this area. Thus, it is not surprising that in chapter 5 pharmacists were identified as receiving more ADR reports associated with herbal medicines than they were submitting to the MHRA. Instead of focusing on the idea that community pharmacists in the UK should specifically report suspected ADRs associate with herbal medicines, an emphasis should be placed on making all healthcare professionals aware that the scheme includes licensed and unlicensed herbal medicines and to report all suspected ADRs associated with them.

In chapter 4, it was ascertained that under-reporting of herbal ADRs was not only specific to the UK, as there is a large imbalance in the total number of suspected ADR reports received (since the scheme first began) between conventional and herbal medicines for a number of other national pharmacovigilance centres. However, few national pharmacovigilance centres undertook activities to specifically encourage the reporting of suspected ADRs associated with herbal medicines. The inclusion of additional reporter groups such as CAM and herbal practitioners has already been suggested by the WHO on the basis that they will be exposed to patients specifically utilising these products and therefore may observe associated ADRs. Despite these recommendations, the UK is yet to include these additional reporter groups, which needs to be prioritised. The recent inclusion of patients as recognised reporters, may help to some extent overcome the exclusion of these reporter groups.

Equally importantly to the above, the MHRA needs to increase its public profile and thus it's impact. The MHRA has recently launched a 6 week campaign for community pharmacists to take a lead role in encouraging consumers to report suspected adverse drug reactions and there are also proposals for the inclusion of details of the yellow card scheme in patient information

leaflets (MHRA, 2008b). Whilst these schemes demonstrate a more proactive approach then that held in the past, further promotion of the UK's yellow card scheme and active engagement further with all reporter groups is imperative so that the MHRA becomes a household name similar to the FDA in the USA.

Under the EU Directive, both theoretical and practical training in pharmacognosy are a prerequisite for the pharmaceutical training of pharmacists (Directive 85/432/EEC). Chapter 6 identified that the majority of MPharm graduates will have gained some form of training in pharmacognosy and related areas during their degree. However, it is also concluded in chapter 6 that certain schools of pharmacy were more active in the teaching of pharmacognosy than others, as the extent of teaching and content (core and elective programmes) varied between institutions and thus the knowledge of pharmacists in pharmacognosy and related areas would be expected to vary accordingly, depending upon the school they graduated from.

Post-graduation, pharmacists are given guidance from the Medicines, Ethics and Practice Guide for pharmacists (RPSGB, 2006), which states that, 'if pharmacists are to recommend herbal medicines and other CAMs, they need to have sufficient evidence-based knowledge of them'. Studies conducted in chapter 5 confirmed that most pharmacies sell herbal medicines and that pharmacists are asked for information on these products, highlighting the need for pharmacists to be knowledgeable in this area. However, the median core teaching hours in pharmacognosy and it's related areas reported in chapter 6, represents around 2% of the 3 000 hours of directed study of pharmaceutically relevant subjects dictated by the European Directive on pharmaceutical training, which may not be sufficient to adequately prepare pharmacists with regards to the safe use of plants as medicines (Directive 85/432/EEC). Findings from chapter 5 support this, as although most pharmacists reported receiving training in herbal medicines through their undergraduate core curriculum as a specific stand-alone pharmacognosy/natural products course, they felt that it did not adequately fulfil their requirements for practice and therefore required more training to be competent in advising patients/customers on herbal medicines. There has been much debate amongst academics on whether or not undergraduate training should be scientific- or practice-based (Florence, 2006; Nathan, 2006; Husband 2007). Thus, heads of schools of pharmacy, including new and proposed schools, need to consider whether or not their MPharm programme adequately prepares future pharmacists to advise on the safe, effective and appropriate use of herbal and

complementary medicines. In addition, the accreditation guidelines for UK pharmacy degree courses set out by the Royal Pharmaceutical Society of Great Britain, should provide guidance on the key requirements for the teaching of pharmacognosy as part of the indicative syllabus (RPSGB, 2005) so that there is more consistency amongst schools of pharmacy.

In the study conducted in chapter 6, lecturers in the field of pharmacognosy and its related areas were requested to identify subject areas that should be taught in the pharmacy undergraduate degree. The majority of the respondents (>90%) felt that the following topics should be included on the core curriculum:

- Efficacy, safety and toxicity of herbal medicines
- Pharmacovigilance of herbal medicines

Despite this, the number of schools teaching various aspects of herbal medicines such as their safety, efficacy, quality, licensing and patient counselling, decreased between 2000 and 2005. Reasons behind this need further investigation; however it can be hypothesised that these areas may have been taught under the umbrella of pharmacy practice. Although it is possible that some aspects of teaching might be lost through the integration with other courses, herbal medicines should ideally be taught in context with pharmacognosy and pharmacy practice. For example, under pharmacy practice, practical issues such as herbal interactions with prescription medicines and how to submit a yellow card report for a suspected herbal ADR could be taught *via* case scenarios, whilst under pharmacognosy, the inherent problems associated with herbal medicines and their pharmaceutical quality, safety, regulation, lack of information and the need for pharmacovigilance of these products could be covered. The accreditation guidelines for the UK pharmacy degree course set out by the RPSGB, could be amended to implement such changes.

It is the view of the author that the use of terms such as 'conventional', 'complementary', 'alternative', 'traditional', 'folk remedies' should be removed from scientific disciplines as they are non-distinctive and non-scientific. The removal of these terms would also aid in resolving a number of misconceptions held by both healthcare professionals and the public. For example, studies conducted in chapter 5 identified that pharmacists commonly used the term 'conventional' and 'unconventional' to differentiate whether or not a product was herbal or non-herbal, despite the fact that herbal medicines could be either 'conventional' or 'unconventional' based on individual perception. These different classifications are also

detrimental to pharmacovigilance, as previous work has confirmed that consumers are less likely to report suspected ADRs associated with an 'unconventional' medicine than a 'conventional' medicine as they are perceived as being 'safe' (Barnes *et al.*, 1998).

Studies conducted in chapter 5 also identified a gap in the postgraduate training of pharmacists, as most respondents reported undertaking further training in herbal medicines since registering, yet few rated their perceived competence in herbal medicines to be above 'quite competent' for a few herbal medicines'. It was also highlighted that respondents felt that counter staff in some cases possessed the same level of knowledge as the pharmacist. Also, some pharmacists believed that health food shop assistants were more able to deal with enquiries on herbal medicines. This raises the question as to whether or not pharmacists are more qualified/better resourced than assistants in health food shop in giving advice on herbal medicines. However, pharmacist should be experts in medicines and thus advising on herbal medicines should be part of their professional practice. As pharmacists take on additional roles such as supplementary and independent prescribing, it is important that pharmacists do not disregard these existing roles as these opportunities might be lost to other healthcare professionals such herbal practitioners and health food shop assistants.

With respect to ADR forms submitted, successful assessment is dependent on the quality of the filling of the report. It is not only the failure to report correct information, but also missing information that reduces the quality of the report. Data extraction of the national pharmacovigilance centres ADR reporting forms and accompanying guidelines in chapter 4 revealed deficiencies in the UK's yellow card for both herbal and conventional medicines. Regarding results pertaining to herbal medicines, few ADR reporting forms (including the UKs) specifically mentioned the term herbal medicine and the following data items were found to be absent from the UK's yellow card:

- Manufacturer of the herbal medicinal product
- Active ingredients in the product
- Common/generic name of the herb
- Type of preparation/extract
- Species, genus and plant part used in the preparation

These findings support the idea that the UK's yellow card does not lend itself particularly well to the reporting of suspected ADRs associated with herbal medicines (see section 1.5.9). For example, with the current yellow card, if a report on Valerian were to be submitted by a healthcare professional, it would be unknown which species (*e.g. Valeriana officinalis, Valeriana sambucifolia, Valeriana wallichi etc*) was implicated. It is well know that the constituents can vary significantly between species, and even between which plant part was used in the preparation (Barnes, 2002; Schilter *et al.*, 2003; Liang *et al.*, 2004). Therefore, essential information such as this would be missing from current yellow card reports. At present the MHRA follows up all herbal reports individually to ascertain such details, but this in itself is associated with several problems, such as recall bias. If the yellow card report was to prompt reporters for these further details or to specifically mention the term herbal medicines, it is plausible that this may stimulate ADR reporting for herbal medicines and enhance the quality of the reports submitted; however this remains to be established.

The need for modification of ADR reporting forms were also recognised by national pharmacovigilance centres (56% of respondents agreed/strongly agreed) and the above data items were identified as essential/desirable for the assessment of herbal ADR reports. It is likely that space limitations prohibit the inclusion of these details in the current ADR reporting form. Despite several countries having separate ADR reporting forms specifically for herbal medicines this is not desirable, as multiple forms would over-burden reporters and over complicate the existing system. It would not be ideal to radically change the current UK's yellow ADR reporting form as healthcare professionals are familiar with the current format or to substantially increase the length of the form as it is widely known that lengthy questionnaires can deter responses. Space on the current form could however, be saved by combining the suspected drug and the concomitant medicines sections by simply listing all of the current medicines consumed and then putting an asterisk beside the suspected medicine.

Work on improving the current ADR reporting form is in progress by the MHRA. For example the yellow card reporting forms have been simplified and the online system updated. The online system provides a dropdown choice for suspected drug and adverse reaction (MHRA, 2008a). The system could be further enhanced by automatically recognising a report for a herbal product and then posing the additional data items outlined above. There are also proposals *via* the ICH E2B guideline to harmonise data fields for ADR reporting however, this

will only apply to Japan, the USA and member states in Europe and at present is not present in the Directive.

Despite the above initiatives, under-reporting will always remain an inherent problem with spontaneous reporting and it has been suggested that there might be more effective methods for the post-marketing surveillance of medicines. Active surveillance is beneficial when recruiting a large numbers of subjects as it does not rely on individual healthcare practitioners and as a result eliminates selection bias. In addition, the data collected are prospective rather than retrospective, which eliminates recall bias. The method also collects all potential adverse events as the questionnaire requests all symptoms experienced, thus ADRs that would otherwise go unreported or are dismissed as not being serious/severe would be collected. Furthermore, the reporting of all symptoms is ideal as patients may not be able to discriminate effectively between symptoms which are attributable to either a drug they are taking or due to a pre-existing disease. This is particularly useful for herbal medicines as consumers may not associate a causal link between the ADR and the herb, due to the common belief that they are 'natural' and therefore 'safe'. As most herbal medicines are available without the consultation of a healthcare professional and consumers are reluctant to inform their healthcare provider on the use of these products, active surveillance provides a method to obtain information directly from the consumers. Equally importantly, the target population is known and so the frequency of an event can be calculated unlike traditional surveillance methods. Thus the final study conducted as part of this thesis (chapter 7), explored the feasibility of an active surveillance method for herbal medicines. Previous studies conducted to date have only involved pharmacy or prescription only conventional medicines. This was the first study that aimed to develop and assess the feasibility of a community-pharmacy based study for pharmacovigilance of herbal medicines purchased OTC. However, the study was unsuccessful due to a number of reasons as outlined already in section 7. 6. Despite the failure of the study, the benefits of active surveillance in addition to the current system are clear and further work should be encouraged in this area with the correct infrastructure. Future studies investigating the side effect profile of herbal medicines should include all points of sale (pharmacy counter, other shop counter and health food shops) and all herbal medicines to ensure that the sample size is not constrained. Incentives need to be established for the population groups *e.g.* pharmacists and the consumers. These not only include financial incentives but also augmentation of a greater sense of professional/ethical responsibilities (healthcare

professionals) and moral responsibilities (consumers). Such an approach may also increase the level of ADR reporting *via* the existing yellow card scheme. In addition, it is evident from each of the individual studies that in order to achieve a high response rate the survey instrument must be relatively simple to complete. Endorsement and support *via* a professional body (*e.g.* MHRA, RPSGB) may increase response rate due to a greater perceived importance. As previously mentioned, there needs to be greater awareness for and importance attributed to herbal medicines amongst healthcare professionals and this will only be achieved through greater education for healthcare professionals and collaborative working between organisations such as the Schools of Pharmacy, RPSGB, MHRA and the WHO.

There is hope that with the implementation of the new EU Directive on Traditional Herbal Medicinal Products (Directive 2004/24/EC) by October 2011 that the loop hole in the regulatory system by which unlicensed traditional herbal products are marketed will be eliminated by providing a regulatory framework whereby products are licensed. However, the Directive is not as stringent as the regulation for 'conventional' medicines. For example, the new Directive relies on bibliographic evidence for efficacy rather than demonstrating clinical efficacy. The bibliographic evidence must comprise of 30 years use in total, of which at least 15 years should be of use within the EU, as reliability of information outside the EU is difficult verify this may compromise the products efficacy. From a quality perspective, as the constituents for the majority of herbal medicines is unknown the characterisation, standardisation and hence the quality of the preparation is debateable. In addition, the majority of herbal medicines are sold as food supplements thus, as long as this two tier system exists there is no incentive for the manufacturers to licence their herbal products *via* the new scheme. In essence the new Directive enables herbal products to make medicinal claims, for pharmaceutical quality to be monitored and to some extent allow pharmacists to make decisions based on evidence–based efficacy. However, if the product is still not considered to be under the classification of a medicinal product it is subject to other legislation *e.g.* food or cosmetics (MHRA, 2007). There are also proposals for the extension of the scheme to other categories of medicinal products eg ayurvedic medicines. However, since the launch of the scheme only 8 products have been licensed, thus before such a proposal can be considered the uptake and success of the current scheme in safeguarding public health needs to be established. It is possible that with the implementation of the new EU Directive on traditional herbal medicinal products by 2011, increasingly more importance will be placed on the

pharmacovigilance of herbal medicines, leading to more professional and political impetus to implement the above recommendations and overcome the shortfalls as identified.

Overall, findings collected from this thesis surmise to the following recommendations:

Chapter	Aim	Recommendations
4	To explore the current activities of national pharmacovigilance centres with regard to spontaneous ADR reporting for herbal medicines	1. There should be more consistency between national pharmacovigilance centres. 2. All national pharmacovigilance centres should accept suspected ADR reports for herbal medicines. 3. There should be a globally accepted definition for herbal medicines which is recognised by all national pharmacovigilance centres and all healthcare professionals. 4. CAM and herbal practitioners should be officially included as recognised reporters. 5. Reporter groups should report everything. 6. National pharmacovigilance centres should work in harmonisation with each other to prevent any delays in signal detection. 7. The MHRA needs to increase its public profile and thus it's impact.
4	To make recommendations for a modified UK's yellow card to effectively collect data on suspected ADRs associated with herbal medicines	8. The UK's yellow card should be modified to prompt for and capture more pertinent information required for herbal medicines.
5	To explore community pharmacists' experiences with and views on herbal medicines, using qualitative and quantitative techniques	9. Pharmacists do not need to specifically identify if a product is herbal or non-herbal, as they should be reporting any suspected ADRs where they are unsure on whether or not to report. 10. The MHRA should place a greater emphasis on making all healthcare professionals aware that the scheme includes licensed and unlicensed herbal medicines and to report all suspected ADRs associated with them. 11. Community pharmacists need to be knowledgeable in herbal medicines to meet local needs. 12. Pharmacists should be experts in medicines and thus advising on herbal medicines should be part of their professional practice. 13. Non-scientific terms such as conventional medicines, traditional medicines should be removed from scientific disciplines.

Chapter	Aim	Recommendations
6	To investigate trends in the teaching of pharmacognosy/ natural products, herbal medicine and complementary/alternative medicine: a cross-sectional survey of UK schools of pharmacy	14. The accreditation guidelines for UK pharmacy degree courses set out by the Royal Pharmaceutical Society of Great Britain, should provide guidance on the key requirements for the teaching of pharmacognosy as part of the indicative syllabus (RPSGB, 2005) so that there is more consistency amongst schools of pharmacy. 15. Heads of schools of pharmacy, including new and proposed schools, need to consider whether or not their MPharm programme adequately prepares future pharmacists to advise on the safe, effective and appropriate use of herbal and complementary medicines. 16. Herbal medicines should be taught in context with both pharmacy practice and pharmacognosy.
7	To develop and assess a new method for monitoring the safety of herbal medicines purchased OTC using community pharmacists	17. Community pharmacy based active surveillance methods could be used to complement existing surveillance methods in the UK such as the yellow card scheme for ADR reporting. Further work in this area should be encouraged with the correct infrastructure. 18. Future studies investigating the side effect profile of herbal medicines should include all points of sale (pharmacy counter, other shop counter and health food shops), all herbal medicines and to establish incentives required for each of the population groups *e.g.* pharmacists and the consumers, to ensure that the sample size is not constrained. 19. There needs to be greater awareness for and importance attributed to herbal medicines amongst healthcare professionals and this will only be achieved through greater education for healthcare professionals and collaborative working between organisations such as the Schools of Pharmacy, RPSGB, MHRA and the WHO. 20. A greater emphasis on research needs to be placed by organisations such as the RPSGB.

References

Asch, D.A., Jedrziewski, M.K., Christakis N.A., 1997. Response rates to mail surveys published in medical journals: Journal of Clinical Epidemiology, 50 (10), 1129-1136

ASP, 2005. The case for a name change. The American Society of Pharmacognosy Newsletter, 40 (4), 6

Balunas, M.J., Kinghorn, A.D., 2005. Drug discovery from medicinal plants: Life Sciences, 78 (5), 431-441

Barbour, R.S. and Kitzenger, J., 1999. Developing focus group research: politics, theory and practice, SAGE publications (London, U.K.)

Barnes, J. and Abbot, N.C., 1999. Experiences with complementary remedies: a survey of community pharmacists: The Pharmaceutical Journal, 263, R37

Barnes, J. and Aggarwal, A.M., 2005. An assessment of undergraduate pharmacy students' knowledge of spontaneous reporting for suspected ADRs associated with herbal medicinal products. International Society of Pharmacovigilance 2004. Abstract published in Drug Safety, 28 (10), 943.

Barnes, J., Anderson, L.A., Phillipson, J.D., 2002. Herbal medicines. A guide for healthcare professionals, Pharmaceutical Press (London, U.K.)

Barnes, J., Mills, S.Y., Abbot, N.C., Willoughby, M., Ernst, E., 1998. Different standards for reporting ADRs to herbal remedies and conventional OTC medicines: face-to-face interviews with 515 users of herbal remedies: British Journal of Clinical Pharmacology, 45, 496-500

Barnes, J. 2002. Introduction to herbal medicinal products: The Pharmaceutical Journal, 268, 804-806

Barnes, J., 2003. Pharmacovigilance of herbal medicines. A UK perspective: Drug Safety; 26 (12), 829-851

Barnes, J., 2001. Phd Thesis: An examination of the role of the pharmacist in the safe, effective and appropriate use of complementary medicines. The School of Pharmacy, University of London

Barnett, V., 1991. Sample survey principles and methods: pub lished by Hodder Arnold (London, U. K.)

Bateman, D.N., Sanders, G.L.S., Rawlins, M.D., 1992. Attitudes to adverse drug reaction reporting in the Northern Region: British Journal of Clinical Pharmacology, 34, 421-426

Belton, K.J., 1997. The European Pharmacovigilance Research Group. Attitude survey of adverse drug-reaction reporting by health care professionals across the European Union: European Journal of Clinical Pharmacology, 52 (6), 423-7

Bent, S. and Ko, R., 2004. Commonly used herbal medicines in the United States: a review: The American Journal of Medicine, 116, 478-485

Bentley, C., 2005. Academic medicines: who is it for? British Medical Journal, 330, 361

Beto, J.A., Listecki, R.E., Meyer, D.A., Budhy, R.J., Bansal, V.K., 1996. Use of pharmacy computer prescription database to access hypertensive patients for mailed survey research: The Annals of Pharmacotherapy, 30, 351-355

Bond, C. and Hannaford, P., 2003. Issues related to monitoring the safety of over-the-counter (OTC) medicines: Drug Safety, 26 (15), 1065-1074

Bond, C.M. and Bradley, C., 1996. Over-the-counter drugs. The interface between the community pharmacist and patients: British Medical Journal, 312, 758-760

Borden, E.K. and Lee, J.G., 1982. A methodologic study of post-marketing drug evaluation using a pharmacy-based approach: Journal of Chronic Disease, 35, 803-816

Bouldin, A.S., Smith, M.C., Garnera, D.D., Szeinbacha, S. L., Frate, D.A., Croom, E.M., 1999. Pharmacy and herbal medicine in the US: Social Science & Medicine, 49, 279-289

Bowling, A., 1997. Research methods in health: investigating health and health services: Bowling, A. (ed.), Open University Press (Buckingham, UK)

Bracchi, R., Houghton, J., Woods, F., 2005. A distance-learning programme in pharmacovigilance linked to educational credits is associated with improved reporting of suspected adverse drug reactions *via* the U.K. yellow card scheme: British Journal of Clinical Pharmacology, 60 (2), 221-3

Breckenridge, A., Woods, K., Raine, J., 2005. Monitoring the safety of licensed medicines. Drug Discovery, 4, 541

Breckenridge, A., 2000. Message from Professor A Breckenridge, Chairman, Committee on Safety of Medicines: 29 February 2000

Brown, C.M., Barner, J.C., Shah, S., 2005. Community pharmacists' actions when patients use complementary and alternative therapies with medications: Journal of the American Pharmacists Association, 45 (1), 41-47,

Brown, J.B. and Sas, G., 1994. Focus groups in family practice research: an example study of family physicians' approach to wife abuse: Family Practice Research Journal, 14, 19-28

Bryman, A. and Cramer, D., 1997. Quantitative data analysis with SPSS for Windows: Routledge, (Padstow, U.K.)

Bryman, A., 2001. Social research methods. Oxford university Press (Oxford, U.K.)

Castel, J.M., Figueras, A., Pedrós, C., Laporte, J., Capellà, D., 2003. Stimulating adverse drug reaction reporting: Drug Safety, 26 (14), 1049-1055

Chang, Z.G., Kennedy, D.T., Holdford, D.A., Small, R.E., 2000. Pharmacists' knowledge and attitudes toward herbal medicine: Annals of Pharmacotherapy, 34, 710-5

Chetley, W., 1990. The thalidomide disaster. World health and the pharmaceutical industry. Zed Books (London, U.K.), 21-22

Chrubasik, S., Kunzel, O., Thanner, J., Conradt, C., Black A., 2005. A 1-year follow-up after a pilot study with Doloteffin® for low back pain: Phytomedicine, 12, 1-9

Clarkson, A., Ingleby, E., Choonara, I., Bryan, P., Arlett, P., 2001. A novel scheme for the reporting of adverse drug reactions: Archives of Childhood Diseases, 84 (4), 337-9

Clarkson, A. and Choonara, I., 2002. Surveillance for fatal suspected adverse drug reactions in the U.K. Archives of Disease in Children, 87, 462-7

Clinical Trials Government. Information on Clinical Trails and Human Research Studies. www.clinicaltrials.gov.ct/info accessed 12/01/2007.

Colebatch, K.A., Marley, J., Doecke, C., Miles, H.B., Gilbert A., 2000. Evaluation of a patient report monitoring system: Pharmacoepidemiology and Drug Safety 9, 491-499

Corelli, R.L., Kroon, L.A., Chung, E.P., Sakamoto, L.M., Gunderson, B., Fenlon, C.M., 2005. Statewide evaluation of a tobacco cessation curriculum for pharmacy students: Preventative Medicine, 40 (6), 888-895

Corso, D.M., Pucino, F., DeLeo, J.M., Calis, K.A., Gallelli, J.F., 1992. Development of a questionnaire for detecting potential adverse drug reactions: The Annals of Pharmacotherapy, 26, 890-896

Cox, A., Marriott, J., Wilson, K., 2004. Adverse drug reaction teaching in UK undergraduate medical and pharmacy programmes: Journal of Clinical Pharmacy and Therapeutics, 29, 31-5

Cox, A., 2002. Embracing ADR reporting could improve pharmacists' standing: The Pharmaceutical Journal, 269, 14

Crombie, I., 1984. Inherent limitations of the yellow card system for the detection of unsuspected adverse drug reactions: Human Toxicology, 3(4), 261-9

D'arcy, P., 1991. Adverse drug reaction reporting - pharmacists should have a bigger role in the UK: International Journal of Pharmacy Practice, 3-4

Davis, S. and Coulson, R., 1999. Community pharmacist reporting of suspected ADRs: (1) The first year of the yellow card demonstration scheme: The Pharmaceutical Journal, 263, 786-788

De Smet, P. A.G.M., 2002. Herbal remedies: The New England Journal of Medicine, 347, 2046-2056

De Smet, P. A. G. M., 2007. Clinical risk management of herb–drug interactions: British Journal of Clinical Pharmacology, 63 (3), 258–267

Deurden, M., 2002. Yellow cards: reporting adverse drug reaction: Prescriber, 79-93

Directive 65/65/EEC of 26 January 1965 on the approximation of provisions laid down by law, regulation or administrative action relating to medicinal products (1965). Official Journal of the European Communities, Office for Official Publications of the European Communities, Luxembourg, 022, 3-12

Directive 85/432/EEC. Official Journal of the European Union, Office for Official Publications of the European Communities. CONSLEG 1985L0432 – EN - 31.07.2001 - 001.001-1

Directive 2001/83/EC amended by directives 2002/63/EC, 2004/24/EC and 2004/EC Official Journal of the European Union, Office for Official Publications of the European Communities, Luxembourg

Directive 2004/24/EC as amends Directive 2001/83/EC as regards Traditional Herbal Medicinal Products, Official Journal of the European Union, 30.04.2004, Office for Official Publications of the European Communities, Luxembourg

Edwards, P., Roberts, I., Clarke, M., DiGuiseppi, C., Pratap, S., Wentz, R., 2002. Increasing response rates to postal questionnaires: systematic review: British Medical Journal, 324, 1183-1191

Egberts, T.C.G., Smulders, M., de Koning, F.H.P., 1996. Can adverse drug reactions be detected earlier? A comparison of reports by patients and professionals: British Medical Journal, 313, 530-1

Ernst, E., 2000. Herbal medicines: Where is the evidence? British Medical Journal, 321 (7258), 395-396

Evans, S.J.W., Waller, P.C., Davis, S., 2001. Use of proportional reporting ratios (PPRs) for signal generation from spontaneous adverse drug reaction reports: Pharmacoepidemiology and Drug Safety, 10, 483-6

Faber, A., de Jong-van Berg, L., Netjes, K., Kalverdijk, L., Minderaa, R., Tobi, H., 2005. Recruitment of parents and physicians of stimulant-using children *via* community pharmacies is successful: Journal of Clinical Epidemiology, 58, 1072-1073

Farah, M.H., Edwards, R., Lindquist, M., 2000. International monitoring of adverse health effects associated with herbal medicines: Pharmacoepidemiology and Drug Safety, 9, 105-112

Farah, M.H., Olsson, S., Bate, J., Lindquist, M., Edwards, R., Simmonds, M.S.J., Leon, C., de Boer, H.J., Thulin, M., 2006. Botanical nomenclature in pharmacovigilance and a recommendation for standardization: Drug Safety, 29 (11), 1023-1029

Field, A., 2005. Discovering statistics using SPSS 2nd ed. SAGE Publications Ltd (London, U.K.)

Florence, A., 2006. Baby clothes, sandwiches and T-shirts spoil pharmacy's professional image: The Pharmaceutical Journal, 277, 516-517

Gauld, N.J., Shaw, J.P., Emmerton, L.M., Pethica, B.D., 2000. Surveillance of a recently switched non-prescription medicine (Diclofenac) using pharmacy-based approach: Pharmacoepidemiology and Drug Safety, 9, 207-214

Gibb, I.A., Miller, K., Veltri, J.C., Page, B.A., Charlesworth, P.A., Kellett, N., 2001. Using community pharmacies to evaluate the safety of a prescription only medicine in an OTC environment: a unique method in Europe: The International Journal of Pharmacy Practice, 9 (suppl), R10

Gibson, L., 2005. Adverse reaction reports may be vulnerable to manipulation: British Medical Journal, 330, 1287

Gilroy, C., Steiner, J., Byers, T., Shapiro, H., Georgian, W., 2003. Echinacea and truth in labelling: Archives of Internal Medicine., 163, 699 –704

Giveon, S., M., Liberman, N., Klang, S., Kahan, E., 2004. Are people who use "natural drugs" aware of their potentially harmful side effects and reporting to family physician? Patient Education and Counselling, 53, 5–11

Glisson, J.K., Rogers, H.E., Noble, S.L., 2002. Comparison of recommendation made by pharmacists and health food store employees in a depressed patient. Pharmacotherapy, 22 (10), 1346

Glisson, J.K., Rogers, H.E., Abourashed, E.A., Ogletree, R., Hufford, C.D., Khan, I., 2003. Clinic at the health food store? Employee recommendations and product analysis. Pharmacotherapy; 23 (1), 64-72

Gore, M.R. and Thomas, J., 1995. Nonpresrciption informational services and alternative stores: Implications for a third class of drug: Journal of Social and Administrative Pharmacy, 12, 86-89

Granas, A. G., Buajordet, M., Stenberg-Nilsen, H., Harg, P., Horn, A.M., 2007. Pharmacists' attitudes towards the reporting of suspected adverse drug reactions in Norway: Pharmacoepidemiology and Drug Safety, 16, 429–434

Grayson, D., 2004. Some myths and legends in quantitative psychology. Understanding Statistics, 3 (1), 101-134

Green, C.F., Mottram, D.R., Raval, D., Proudlove, C., Randall, C., 1999a. Community pharmacists' attitudes to adverse drug reaction reporting: The International Journal of Pharmacy Practice, 7, 92-99

Green, C.F., Mottram, D.R., Brown, A.M., Rowe, P.H., 1999b. Attitudes of hospital pharmacists to adverse drug reactions and the "yellow card" scheme: a qualitative study: The International Journal of Pharmacy Practice, 7, 247-255

Green, C.F., Mottram, D.R., Rowe, P.H., Pirmohamed, M., 2001. Attitudes and knowledge of hospital pharmacists to adverse drug reporting. British Journal of Clinical Pharmacology, 51, 81-86

Grewar, J., Matthews, J., McMahon, A.D., MacDonald, T.M., 1998. Capturing data on over-the-counter medicines in community pharmacies: a methodological study: The Pharmaceutical Journal, 259, 736-739

Griffin, J.P., 1986. Survey of the spontaneous adverse drug reaction reporting schemes in fifteen countries: British Journal of Clinical Pharmacology, 22, Suppl 1: 83S-100S

Gulian, C., Barnes, J., Francis, S., 2002. Types and preferred sources of information concerning herbal medicinal products: face-to-face interviews with users of herbal medicinal products: International Journal of Pharmacy Practice, 10, suppl: R33

Hallas, J., 2001. Pharmacoepidemiology – current opportunities and challenges: Norwegian Journal of Epidemiology, 11 (1), 7-12

Harman, R., 2004. Why the international harmonisation process is increasingly important: The Pharmaceutical Journal, 273, 22-226

Hasford, J., Moore, N., Hoye K., 2004. Safety and usage pattern of low-dose diclofenac when used as an over-the-counter medication: results of an observational cohort study in a community-based pharmacy setting: International Journal of Clinical Pharmacology and Therapeutics, 42 (8), 415-422

Healy, B., Burgess, C., Siebers, R., Beasley, R., Weatherall, M., Holt, S., 2002. Do natural health food stores require regulation? The New Zealand Medical Journal, 115 (1161), 1-5

Henderson, L., Yue, Q.Y., Bergquist, C., Gerden, B., Arlett, P., 2002. St John's wort (Hypericum perforatum): drug interactions and clinical outcomes: British Journal of Clinical Pharmacology, 54, 349-356

Houghton, J., Woods, F., Davis, S., Coulson, R., Routledge, P. A., 1999. Attitudes of community pharmacists & general practitioners in Wales: The Pharmaceutical Journal, 263, 788-791

Houghton, P. J. and Barnes J., 2004. Pharmacognosy in the curriculum: a critical need that still needs to be met: The Pharmaceutical Journal, 273, 325

Hougton, P. J., 2006. Herbal medicine must be treated differently from CAM: The Pharmaceutical Journal, 277, 221

House of Lords Select Committee on Science and Technology, Session 1999-2000, 6th report. Complementary and alternative medicine. The Stationary Office, 2000, (London, U.K.)

Howell, S.C., Quine, S., Talley, N.J., 2003. Ethics review and use of reminder letters in postal surveys: are current practices compromising an evidence-based approach? The Medical Journal Australia, 178, 43

Hughs, M.L., Whittlesea, C.M.C., Luscombe, D.K., 2002. Review of national spontaneous reporting schemes: Adverse Drug Reactions and Toxicology Review, 21 (4), 231-241

Humpel, N., Jones, S. C., 2006. Gaining insight into the what, why and where of complementary and alternative medicine use by cancer patients and survivors: European Journal of Cancer Care, 15 (4), 362-368

Husband A., 2007. A solid foundation in science and practice is a must for the NHS's future. The Pharmaceutical Journal, 278, 104

International Conference on Harmonisation [online] www.ich.org [Accessed 2006 Sept 01]

Jarernsiripornkul, N., Krska, J., Capps, P.A.G., Richards, R.M.E., Lee, A., 2002. Patient reporting of potential adverse drug reactions: a methodological study: British Journal of Clinical Pharmacology, 53, 318-25

Jones, W.P., Chin, Y.W., Kinghorn, A.D., 2006. The role of pharmacognosy in modern medicine and pharmacy: Current Drug Targets, 7 (3), 247-264

Jutte, R., Riley, D., 2005. A review of the use of low potencies in homeopathy. Complementary Therapies in Medicine, 13 (4), 291-6

Kayne, S., 2006. Problems in the pharmacovigilance of herbal medicines in the UK highlighted: The Pharmaceutical Journal, 276, 543-545

Kelly, J.P., Kaufman, D.W., Kelley, K., Rosenberg, L., Anderson, T.E., Mitchell, A.A., 2005. Recent trends in use of herbal and other natural products: Archives in Internal Medicine, 165, 281-286

Kennedy, E.J., Krska, J., John, D.N., Hansford, D., 1999. Effect of incentives on recruitment and response rate in a community-based pharmacy practice study. International Journal of Pharmacy Practice, 7, 80-85

Krska, J., Kennedy, E.J., Hansford, D., John, D.N., 1998. Pharmacists' opinions on their involvement in a community pharmacy based practice research study: The Pharmaceutical Journal, 261, R54

Lancet, 2006. Don't forget pharmacognosy: The Lancet, 368, 260

Layton, D., Sinclair, H.K., Bond, C.M., Hannaford, P.C., Shakir, S.A.W., 2002. Pharmacovigilance of over-the -counter products based in community pharmacy: methodological issues from pilot work conducted in Hampshire and Grampian, UK. Pharmacoepidemiology and Drug Safety, 11, 503-513

Lessler and Kalsbeek, W.D., 1992. Nonsampling error in surveys. John Wiley and Sons Inc New York, USA)

Liang, Y., Xieb, P., Chanc, K., 2004. Quality control of herbal medicines: Journal of Chromatography B, 812, 53–70

Liu, J.P., Manheimer, E., Yang, M., 2005. Herbal medicines for treating HIV infection and AIDS: Cochrane Database of Systematic Reviews (3): Art. No. CD003937.

Louik, C. and Mitchell, A.A., 2005. Post-marketing surveillance using pharmacy-based cohorts: results of a pilot study. Pharmacoepidemiology and Drug Safety, 14, 289-295

Mackowiak, E.D. and Parikh, A., 2001. Herbal product education in United States pharmacy schools: core or elective program? American Journal of Pharmaceutical Education, 65, 1-6

Major E., 2002. The yellow card scheme & the role of pharmacists as reporters: The Pharmaceutical Journal, 269, 25-26

Martindale: The Complete Drug Reference, 1961. The Pharmaceutical Press (London, U.K.)

McAvoy, B.R. and Kaner, E.F.S., 1996. General practice postal surveys: a questionnaire too far? British Medical Journal, 313, 732-734

McBride, W.G., 1961. Thalidomide and congenital abnormalities: The Lancet, 2, 1358

McCafferty, S., Rogers, P.J., Wood, S.M., 1996. Influences on community pharmacists' recommendation of non-prescription H2-antagonists: The Pharmaceutical Journal, 256, 593-596

Medicines Act, 1968. The Stationery Office Ltd. (London, U.K.)

Medicines Control Agency, 2002. Safety of herbal medicinal products. (London, U.K.)

Meyboom, R.H.B., Egberts, A.C.G., Edwards, I.R., Hekster, Y.A., de Koning, F.H.P., Gribnau, F.W.J., 1997. Principles of signal detection in pharmacovigilance: Drug Safety, 16 (6), 355-365

MHRA, 1997. Extension of the Yellow Card scheme to pharmacists: Current Problems in Pharmacovigilance, 23, 3

MHRA, 1998. HIV ADR Reporting Scheme - The first seven months: HIV ADR Reporting Scheme News, 1

MHRA[online] www.mhra.gov.uk [Accessed March 07]

MHRA/CSM., 1999. A new reporting initiative for paediatric adverse drug reactions in the Trent region: Current Problems in Pharmacovigilance, 25, 1-4

MHRA/CSM., 2003. Kava kava and hepatotoxicity: Current Problems in Pharmacovigilance, 29, 8

MHRA/CSM, 2004. Black cohosh and hepatotoxicity and Interaction between warfarin and cranberry juice new advice: Current problems in Pharmacovigilance, 30, 10

MHRA/CHM, 2008a. New addition to the yellow scheme – the online reporting form: Drug Safety Update, 1 (9), 6

MHRA/CHM, 2008b. Promotion of the scheme in community pharmacies: Drug Safety Update, 1 (11), 6

Mills, E., Ernst, E., Singh, R., Ross, C., Wilson, K., 2003. Health food store recommendations: implications for breast cancer patients: Breast Cancer Research, 5 (6), R170-R174

Mills, S., 2007. Monitoring herbal safety: Current debate and resources. Symposium report: Pharmacovigilance of Herbal Medicines: Current state and future direction, London, 24–26 April 2006. Phytomedicine (Article in press, accessed ScienceDirect 2007)

Mintel International Group Limited, 2003. Complementary medicines, UK. Market Intelligence. London Mintel International Group Limited.

Mintel International Group Limited, 2005. Complementary Medicines, – UK. Market Intelligence. London Mintel International Group Ltd.

Montastruc. J., Sommet, A., Lacroix, I., Olivier, P., Durrieu, G., Damase-Michel, C., Lapeyre-Mestre, M., Bagheri, H., 2006. Pharmacovigilance for evaluating adverse drug reactions: value, organisation and methods: Joint Bone Spine, 73, 629–632

Morgan, D.L., 1988. Focus groups as qualitative research. SAGE Publications (London, U.K.)

Nathan, A., 2006. Pharmacy education in the UK needs an overhaul. The Pharmaceutical Journal, 277, 747

Nykamp, D., Barnett, C.W., Hooper, C., 1994. Risk of adverse drug events related to ibuprofen use in a community sample: Journal of Pharmacy Technology, 10, 110-114

Paterson, C., Symons, L., Britten, N., Bargh, J., 2004. Developing the medication change questionnaire: Journal of Clinical Pharmacy and Therapeutics, 29, 339-349

Paterson, C., 2004. 'Take small steps to go a long way' consumer involvement in research into complementary and alternative therapies: Complementary Therapies in Nursing and Midwifery, 10, 150-161

The Pharmaceutical Journal, 1987. Hospital pharmacy scheme increases yellow card reports: The Pharmaceutical Journal, 97

The Pharmaceutical Journal, 1997. Slow start to community pharmacist yellow card reporting: The Pharmaceutical Journal, 259, 10

The Pharmaceutical Journal, 1998. Increased involvement of community pharmacists in ADR reporting: The Pharmaceutical Journal, 1998, 260, 47

The Pharmaceutical Journal, 1999. The current state of pharmacovigilance: The Pharmaceutical Journal, 262, 136-137

The Pharmaceutical Journal, 2000. ADR publicity urged on Society: The Pharmaceutical Journal, 264, 393

The Pharmaceutical Journal, 2003. Patients able to report ADRs *via* NHS Direct. The Pharmaceutical Journal, 270, 608

The Pharmaceutical Journal , 2006. Prescribing will increase importance of ADR reporting: The Pharmaceutical Journal, 276, 588

Phytonet www.escop.com/phytonet.htm [accessed 2006 Sept 01]

Pope., C., Ziebland, S., Mays, N., 2000. Analysing qualitative data: British Medical Journal, 320, 114-116

Porche, D.,, 1999. Thalidomide: The Past, Present, and Future: Journal of the Association of Nurses in AIDS Care, 10 (2), 82-84

Quinn, C., G., Waterman, P., A., 1997. Comparison of the teaching of herbal medicine in the United Kingdom and Europe: University of Strathclyde

Rabbur, R.S.M. and Emmerton, L., 2005. An introduction to adverse drug reaction reporting systems in different countries, International Journal of Pharmacy Practice, 13, 91-100

Rawlins, M.D. and Jeffreys, D.B., 1993. United Kingdon Product Licence Applications including new active substances, 1987-89: their fate after appeals: British Journal of Clinical Pharmacology, 35, 599-602

Rawlins, M.D., 1995. Pharmacovigilance: paradise lost, regained or postponed? Journal of the Royal College of Physicians of London, 29(1), 41-9

Roberts, P., Booth, T., Wolfson, D., 1993. The community pharmacist and adverse drug reaction monitoring: (1) a historical & geographical perspective: The Pharmaceutical Journal, 875-878

Rosebraugh, C.J., 2003. Improving the quality of adverse drug reaction reporting by 4th year medical students: Pharmacoepidemiology and Drug Safety, 12, 97-101

Routledge, P., 1998. 150 years of pharmacovigilance: The Lancet, 351, 1200-01

RPSGB, 2006. Royal Pharmaceutical Society of Great Britain: Medicines, ethics and practice - A guide for pharmacists: July 2006 30, (London, U.K.)

RPSGB, 1997. A new age for pharmacy practice research: promoting evidence-based practice in pharmacy. Report of the pharmacy practice R & D task force. Royal Pharmaceutical Society of Great Britain.

RPSGB. Website: www.rpsgb.org/members/education/underg.htm . Accessed 14 April 2005

Rutter, P.M., Brown, D., Jones, I.F., 1998. Pharmacy research: the place of work measurement: International Journal of Pharmacy Practice, 6, 46-58

Sacristan, J.A., Gomez, J.C., Badia, X., Kind, P., 2001. Global index of safety (GIS): A new instrument to assess drug safety: Journal of Clinical Epidemiology, 54, 1120-5

Schilter, B., Andersson, C., Anton, R., Constable, A., Kleiner, J., O'Brien, J., Renwick, A.G., Korver, O., Smit, F., Walker. R., 2003. Guidance for the safety assessment of botanicals and botanical preparations for use in food and food supplements: Food and Chemical Toxicology, 41, 1625–1649

Shakir, S.A.W., 2002. PEM in the UK. In: Mann RD, Andrews EB, editors. Pharmacovigilance, Wiley (Chicester, U.K.), 333-344

Shaw, D., Leon, C., Kolev, S. , Murray, V., 1997. Traditional remedies and food supplements: a 5-year toxicological study (1991-1995): Drug Safety, 17 (5), 342-56

Sinclair, H. K., Bond, C.M., Lennox, A.S., Silcock, J., Winfield, A.J., Donnan, P.T., 1998. Training pharmacists and pharmacy assistants in the stage-of-change model of smoking cessation: a randomised controlled trial in Scotland: Tobacco Control, 7, 253-261

Sinclair, H. K., Bond, C., Largue, G., Price, D., Hannaford, P. C., 2005. Community pharmacy provision of allergic rhinitis treatments: a longitudinal study of patient reported outcome. International Journal of Pharmacy Practice, 13, 249-256

Sinclair, H. K., Bond, C. M., Hannaford, P. C., 2001. Long term follow-up studies of users of nonprescription medicines purchased from community pharmacies: Drug Safety, 24 (12), 929-938

Sinclair, H. K., Bond, C. M., Hannaford, P. C., 1999. Pharmacovigilance of over-the-counter products based in community pharmacy: a feasible option: Pharmacoepidemiology and Drug Safety, 8, 479-491

Smith, F., 2002. Research methods in pharmacy practice. Pharmaceutical Press (London, U.K.)

Stahl, M. I., Edwards, R., Bowring, G., Kiuru, A., Lindquist, M., 2003. Assessing the impact of drug safety signals from the WHO database presented in 'signal'. Results from a questionnaire of national pharmacovigilance centres: Drug Safety, 26 (10), 721-727

Stewart, D., Helms, P., McCaig, D., Bond, C., McLay, J., 2005. Monitoring adverse drug reactions in children using community pharmacies: a pilot study. British Journal of Clinical Pharmacology, 59 (6), 677-683

Strom, B. L. 1994. What is pharmacoepidemiology? In Pharmacoepidemiology 2nd edition, Strom, B. L. (ed), published by John Wiley & Sons (Chichester, U.K.), 3

Sweis, D. and Wong, I. C. K., 2000. A survey on factors that could affect adverse drug reaction reporting according to hospital pharmacists in Great Britain: Drug Safety, 23 (2), 165-172

The Medicines for Human Use (Kava-Kava) (Prohibition) Order 2002 (SI 2002/3170). The Stationery Office (London, U.K.)

Thomas, K. J., Nicholl, J. P., Coleman, P., 2001. Use & expenditure on complementary medicine in England: a population based survey. Complementary Therapies in Medicine, 9, 2-11

Van Ganse, E., Jones, J. K., Moore, N., Le Parc, J. M., Wall, R., Schneid, H., 2005. A large simple clinical trial prototype for assessment of OTC drug effects using patient-reported data: Pharmacoepidemiology and Drug Safety, 14, 249-255

Van Grootheest, A. C., Puijenbroek, E., de Jong-van den Berg, L., 2002a. Contribution of pharmacists to the reporting of adverse drug reactions: Pharmacoepidemiology & Drug Safety 2002a, 11, 205-210

Van Grootheest, A., Mes, K., de Jong-van den Berg, L., 2002b. Attitudes of community pharmacists in the Netherlands towards adverse drug reaction reporting: International Journal of Pharmacy Practice, 10, 267-272

Van Grootheest, A. C., Groote, J. K., de Jong-van den Berg, L. T. W., 2003. Intensive monitoring of new drugs based on first prescription signals from pharmacists: a pilot study: Pharmacoepidemiology and Drug Safety, 12, 475-481

Van Puijenbroek, E.P., Hepburn, P.A., Herd, T.M., Van Grootheest, A.C., 2007. Post Launch Monitoring of food products: What can be learned from pharmacovigilance: Regulatory Toxicology and Pharmacology, 47, 213-220

Vickers, A. J., Rees, R. W., Robin, A., 1998. Advice given by health food shops: is it clinically safe? Journal of the Royal College of Physicians of London, 32 (5), 426-428

Waller, P. C., Coulson, R. A., Wood, S. M., 1996. Regulatory pharmacovigilance in the United Kingdom: current principles and practice: Pharmacoepidemiology and Drug Safety., 5 (6), 363-75

Waller, P. C., Evans, S. J. W., 2003. A model for the future conduct of pharmacovigilance: Pharmacoepidemiology and Drug Safety, 12; 17-29

Weinberger, M., Ferguson, J. A., Westmoreland, G., Mamlin, L. A., Segar, D. S., Eckert, G. J., Greene, J. Y., Martin, D. K., Tierney, W. M., 1998. Can raters consistently evaluate the content of focus groups? Social Science Medicine, 46 (7), 929-933

WHO-UMC, 2004. Yellow cards and green forms. Uppsala Report, 27, 10-11

Wiholm, B., Olsson, S., Moore, N., Waller, P., 2000. Spontaneous reporting systems outside the US. In Pharmacoepidemiology, 3rd edition, Strom, B. L. (ed), published by John Wiley & Sons, (Chichester, U.K.), 175

Willison, D. J., Gaebel, K. A., Borden, E. K., Levine M. A. H., Poston, J. W., Goldsmith, C. H., Wong, B., 1995. Experience in the development of a postmarketing surveillance network: The Pharmacy Medication Monitoring Program: The Annals of Pharmacotherapy, 29, 1208-1213

Wilson, K., Langley, C., Jesson, J., Hatfield, K., 2006. Mapping teaching, learning and assessment in the MPharm in UK schools of Pharmacy. The Pharmaceutical Journal, 277, 369-372

Wingfield, J., Walmsley, J., Norman, C., 2002. What do Boots pharmacists know about yellow card reporting of adverse drug reactions? The Pharmaceutical Journal, 269, 109-110

Wirth, J. H., Hudgins, C. J., Paice, J. A., 2005. Use of Herbal Therapies to Relieve Pain: A Review of Efficacy and Adverse Effects: Pain Management Nursing, 6 (4), 145-167

Wolfson, D., Booth, T., Roberts, P., 1993. The community pharmacist and adverse drug reaction monitoring: (2) an examination of the potential role in the United Kingdom: The Pharmaceutical Journal, 251, 21-24

Wong, I., (1999). Pharmacovigilance resources in the United Kingdom: The Pharmaceutical Journal 263: 7059

World Health Organisation [online] www.who-umc.org [Accessed March 07]

World Health Organisation, 2004. Guidelines on Safety Monitoring and Pharmacovigilance of Herbal Medicines. World Health Organisation (Geneva, Switzerland)

World Health Organisation, 2002a. The importance of pharmacovigilance: Safety monitoring of medicinal products. World Health Organisation

World Health Organisation, 2002b. Legal status of traditional medicine and complementary/alternative medicine: a worldwide. World Health Organisation

APPENDIX I
ADR REPORTING FORMS

In Confidence

YellowCard

MHRA

SUSPECTED ADVERSE DRUG REACTIONS

If you are suspicious that an adverse reaction may be related to a drug or combination of drugs please complete this Yellow Card. For reporting advice please see over. Do not be put off reporting because some details are not known.

PATIENT DETAILS Patient Initials:_____ Sex: M / F Weight if known (kg):_____

Age (at time of reaction):_____ Identification number (Your Practice / Hospital Ref.)*:_____

SUSPECTED DRUG(S)

Give brand name of drug and batch number if known	Route	Dosage	Date started	Date stopped	Prescribed for

SUSPECTED REACTION(S)

Please describe the reaction(s) and any treatment given:

Outcome

Recovered ☐
Recovering ☐
Continuing ☐
Other ☐

Date reaction(s) started:_____ Date reaction(s) stopped:_____

Do you consider the reactions to be serious? Yes / No

If yes, please indicate why the reaction is considered to be serious (please tick all that apply):

Patient died due to reaction ☐
Life threatening ☐
Congenital abnormality ☐
Involved or prolonged inpatient hospitalisation ☐
Involved persistent or significant disability or incapacity ☐
Medically significant; please give details:_____

OTHER DRUGS (including self-medication & herbal remedies)

Did the patient take any other drugs in the last 3 months prior to the reaction? Yes / No

If yes, please give the following information if known:

Drug (Brand, if known)	Route	Dosage	Date started	Date stopped	Prescribed for

Additional relevant information e.g. medical history, test results, known allergies, rechallange (if performed), suspect drug interactions. For congenital abnormalities please state all other drugs taken during pregnancy and the last menstrual period.

REPORTER DETAILS

Name and Professional Address:_____

_____

_____

Post code:_____ Tel No:_____

Speciality:_____

Signature:_____ Date:_____

CLINICIAN (if not the reporter)

Name and Professional Address:_____

_____

_____ Post code:_____

Tel No:_____ Speciality:_____

If you would like information about other adverse reactions associated with the suspected drug, please tick this box ☐

* This is to enable you to identify the patient in any future correspondence concerning this report

Please attach additional pages if necessary

UK's yellow card

Example of Reporting form for suspected adverse reaction to medicines, including herbal medicines and vaccines

PLEASE NOTE: all consumer/patient and reporter information will remain confidential.

Patient/consumer identification (please complete or tick boxes below as appropriate)

Last name	First name(s)	Patient/record number
Ethnicity		
Address (place and region, or health facility may be used)		Date of birth
		Sex ☐ M ☐ F

List of all medicines/vaccines/herbal medicines used by the patient. Please indicate suspected medicines with an asterisk (*) (please complete boxes below)

Medicine(s)Vaccine(s) + batch no.	Daily dose	Route of administration	Date started	Date stopped	Reason for use

For herbal medicines please give detailed information on the product
Product name:

How was the product obtained?

List of product ingredients; attach product label if available:

Name and address of the manufacturer;

Name and address of the distributor:

Other relevant information:

Description of the suspected adverse reaction (please complete boxes below)

Date of onset of reaction (dd/mm/yy):
Description of reaction (please include results of laboratory tests if available):

Outcome of the suspected adverse reaction (please tick boxes as appropriate)

Recovered ☐	Not yet recovered ☐	Unknown ☐	Fatal ☐	Date of death
Severe? Yes ☐ No ☐		Rechallenge? Result:	Yes ☐	No ☐
Was the patient admitted to hospital? If yes, give name and address of hospital:			Yes ☐	No ☐

Other factors (please tick box or describe as appropriate)

Kidney disease ☐	Liver disease ☐	Allergy (please describe) ....
Other illnesses (please describe):		Malnutrition ☐

Reporter identification

Type (please circle): nurse/doctor/pharmacist/other health worker /manufacturer/ distributor/supplier
Name:
Address:
Telephone:
E-mail address:

Signature of reporter: ..... Date: .....

Please send completed form to: .....

WHO template for ADR reporting forms

Register of Chinese Herbal Medicine
Office 5, Ferndale Business Centre, 1 Exeter Street, Norwich
NR2 4QB.
Tel: 01603 623994
Fax: 01603 667557
Email: herbmed@rchm.co.uk
Website: www.rchm.co.uk

RCHM
THE REGISTER OF CHINESE HERBAL MEDICINE
中医药会

YELLOW CARD

for reporting suspected adverse events in confidence

Please fill in this form clearly in blue or black ink. **Please note that all information is completely confidential.**

1) About you, the practitioner completing the Yellow Card report

Surname..... First name.....

Address.....

..... Postcode.....

Telephone number..... Email address.....

2) About the patient who had the suspected adverse reaction

Initials of patient.....

Weight..... Height..... Ethnic group.....

Date of birth..... Male/Female ..... Pregnant? Yes/no

3) About the herbal medicine(s) that you think caused the adverse reaction

Type of prescription: raw herbs/concentrated powder/tincture/pills/cream/ delete as appropriate

or other (please describe).....

Prescription (please list all ingredients and brand name if applicable.....

.....

.....

.....

.....

.....

What was the herbal medicine prescribed for (e.g. asthma).....

.....

.....

Supplier of the medicine.....

Dosage of the medicine.....

Date prescription was started..... Date prescription was stopped (if stopped).....

RCHM's ADR reporting form

RCHM YELLOW CARD continued

4) About the suspected adverse reaction

Did you consider the reaction to be serious? Yes/no

Please describe the suspected adverse reaction in your own words including any treatment received for the reaction.....

.....

.....

.....

.....

.....

How bad was the suspected adverse reaction? – please tick:

- Mild or slightly uncomfortable
- Uncomfortable, a nuisance or irritation, but able to carry on with everyday activities
- Bad enough to affect day to day activities, i.e. persistent or significant disability or incapacity
- Bad enough to be admitted to hospital
- Life-threatening
- Caused death
- Caused congenital abnormality

Date adverse reaction started .....

Has the adverse reaction stopped? Yes/no If yes, what date did it stop?.....

How is the patient now? – please tick

- Recovered completely
- Getting better
- Still has reaction
- Recovered but with some lasting effects (please describe these below).....

.....

.....

Was the patient rechallenged? Yes/no..... If yes, at what dose.....

Did the adverse reaction re-occur? Yes/no

5) More information about the person who had the adverse reaction

Other medical conditions including known sensitivities .....

.....

.....

.....

.....

.....

RCHM's ADR reporting form

RCHM YELLOW CARD continued

6) Other medicines

Please list any other medicines (including your own previous prescriptions, prescribed medicines, self-prescribed medicines and other herbal remedies) used three months prior to the suspected adverse reaction including the name of the medicine, the dosage, what it was used for, when started, and when stopped

Name of medicine including brand name if known and type of medicine e.g. pill, powder, cream	Type of medicine e.g. external cream, raw herbs, powder	Source	Used for?	Dosage	Date started	Date stopped
.....	.....	.....	.....	.....	.....	.....
.....	.....	.....	.....	.....	.....	.....
.....	.....	.....	.....	.....	.....	.....
.....	.....	.....	.....	.....	.....	.....

7) Additional information and comments

Was a doctor, pharmacist or other health professional told about the suspected adverse reaction? Yes/no/don't know (please delete as appropriate)

If yes, did the health professional complete a Yellow Card report? Yes/no/don't know (please delete as appropriate)

Please give any other information that you think might be relevant including test results, oriental medical diagnosis e.g. patient yang xu treating for wind heat attack, dietary information, your conclusions and suggestions. For congenital abnormalities please state all other drugs taken during pregnancy and the last menstrual period. Please continue on a separate sheet if necessary.

.....

.....

.....

.....

Are you happy for the MHRA to contact you in the future to discuss the suspected adverse reaction or ask for more information?

Yes/no

8) Would you like your Yellow Card submission to be analysed by an expert?

The RCHM provides a service whereby the Yellow Card information that you have submitted, along with a full case history, can be analysed by an expert practitioner. **This process is completely anonymous and confidential.** If you wish for your Yellow Card report to be sent for analysis then please enclose a copy of your full case history notes and tick this box ☐

9) Finally, please sign and date this Yellow Card submission, thank you.

Signed (practitioner signature)..... Date.....

Please return this form to: Yellow Card Report, Register of Chinese Herbal Medicine, Office 5, Ferndale Business Centre, 1 Exeter Street, Norwich, NR2 4QB.

RCHM's ADR reporting form

THE NATIONAL INSTITUTE OF MEDICAL HERBALISTS

A PROFESSIONAL BODY OF PRACTITIONERS OF PHYTOTHERAPY

FOUNDED 1864

IN CONFIDENCE: SUSPECTED ADVERSE EVENT REPORTING CARD

PATIENT IDENTIFICATION (File No. or 1st three letters of surname & forename)	SEX	AGE	WEIGHT kg	HEIGHT m	PREGNANT? (Give trimester)

SUSPECT MEDICINE (Full name of herb and/or brand name)	PREPARATION (and strength)	ROUTE	DAILY DOSE	DATE Started	DATE Stopped

INDICATIONS	OTHER MEDICAL CONDITIONS (Including known sensitivities)

SUSPECTED REACTIONS (Diagnosis, Duration, Severity & Frequency)	REPORTING PRACTITIONER (Name & Address - PLEASE PRINT)
DATE Started / DATE Stopped / OUTCOME (Recovery/Referral/Fatal)	DATE: TEL NO:
	SIGNED:

Was patient rechallenged? YES [ ] NO [ ] At what daily dose? _____

Did the reaction recur? YES [ ] NO [ ]

PLEASE RECORD DETAILS OF ALL OTHER MEDICINES TAKEN IN PREVIOUS 2 MONTHS.
List your actual prescriptions, and include self-medication, with brand names if known.

MEDICINE (Herb and/or brand name, preparation & strength)	ROUTE	DAILY DOSE	DATE Started	DATE Stopped	INDICATION

ADDITIONAL INFORMATION AND COMMENTS (e.g., test results, dietary information, your conclusions & suggestions)

Please send to: THE DIRECTOR OF RESEARCH
(Address as given in the Directory of Members)

If you would like information about associated reports, tick here [ ]

NIMH's ADR reporting form

APPENDIX II

NATIONAL PHARMACOVIGILANCE CENTRE QUESTIONNAIRE

Pharmacovigilance of herbal medicines

ID code ☐-☐☐☐-☐

This questionnaire aims to collect information on spontaneous reporting for suspected adverse drug reactions (ADRs) associated with herbal medicines. Please answer the questions below; this should take less than 15 minutes. Your contribution towards this research is important.

Please work through the questionnaire, even if your centre does not accept suspected ADR reports for herbal medicines, as there is still information we would like to obtain about your national reporting system. As a general guide, the questions we would like you to answer are: Q1, 2, 3, 4, 13, 16, 17, 22, 23, 24 (column A), 26 (row A), 31-38.

Confidentiality. Your name will not be identified in any report arising from this study. If you do not want the name of your country to be revealed in association with these data, please tick this box: ☐

---

1. How does your national spontaneous ADR reporting scheme define herbal medicines?

Does not use a definition ☐

Uses WHO definition ☐

Uses own definition [*specify below*] ☐

.....

.....

.....

[*The rest of the questionnaire must be completed according to your centre's definition for herbal medicines outlined above*]

2. Does your national spontaneous ADR reporting scheme accept reports for herbal medicines?

Yes ☐ [*Go to Q6*] No ☐

3. Is there an independent centre/department/organisation in your country which administers spontaneous ADR reports for herbal medicines?

Yes ☐ [*specify who below*] No ☐ Don't know ☐

.....

4. Does your national spontaneous ADR reporting scheme have plans to accept reports for herbal medicines?

Yes ☐ No ☐ [*Go to Q13*]

5. When will these plans be introduced?

.....

6. Describe below how your scheme for herbal ADR reporting is/will be set up e.g. as a pilot scheme

.....

.....

.....

7. Are there any other schemes/organisations which send/provide suspected herbal ADR reports to your centre?

Yes ☐ [*specify which below*] No ☐ Don't know ☐

.....

8. Which of the following regulatory categories of herbal medicines are/will be included as part of your national spontaneous ADR reporting scheme? [*tick all that apply*]

Licensed/authorised/registered herbal medicines ☐

Unlicensed/unauthorised/non-registered herbal medicines ☐

Banned/prohibited/illegal herbal medicines ☐

Other(s) [*specify below*] ☐

.....

.....

9. Does your scheme have a separate spontaneous ADR reporting form for herbal medicines?

Yes ☐ *[please provide a copy]* No ☐

10. Does/will your scheme use any terms other than 'herbal medicines' to refer to/ describe herbal medicines?

Yes ☐ No ☐ *[Go to Q12]*

11. Which terms does/will your scheme use to refer to/describe herbal medicines? [*tick all that apply*]

Over the Counter (OTC) medicines	☐	Botanical medicines	☐
Self medication	☐	Medicinal plants	☐
Dietary supplements	☐	Phytomedicines	☐
Natural products	☐	Other(s) [*specify below*]	☐
Traditional medicines	☐	.....	
Complementary/Alternative medicines (CAM)	☐	.....	

12. For each of the following, indicate how it is/would be classified by your scheme. If herbal write 'H' on the dotted line, if non-herbal write 'NH', if both herbal and non-herbal write 'B' and if you do not know write 'DK'.

Animal product	.....	Gandhak Rasayana	.....	Opium	.....
Aristolochia species	.....	Glucosamine	.....	Senna	.....
Ayurvedic remedies	.....	Herb + mineral product	.....	St John's wort	.....
Biwen San	.....	Herb + animal part product	.....	Traditional Chinese Medicines	.....
Cranberry juice	.....	Homeopathic remedies	.....	Vitamins	.....
Digitalis leaf	.....	Melatonin	.....	Willow bark	.....
Essential Oils	.....	Minerals	.....	Zhi Bai Di Huang Wan	.....

13. Which of the following groups are recognised reporters to your spontaneous reporting scheme? [*tick the applicable reporter status for each group (column A) and provide the year each reporter group was first officially included in the scheme (column B)*]

Reporter group		(A) Reporter Status				(B) Year of first inclusion to the scheme
		Mandatory/ compulsory	Voluntary	Pilot	Not a recognised reporter	
Medical doctors	GPs/family physicians					
	Hospital physicians					
Community Pharmacists						
Hospital Pharmacists						
Nurses/Midwives						
Patients/Public/Consumers						
Herbal-medicine practitioners	Statutory regulated					
	Non-statutory regulated					
Other complementary /alternative medicine practitioners	Statutory regulated					
	Non-statutory regulated					
Manufacturers/ industry	Licensed products					
	Unlicensed products					
Other(s) [*specify below*]						

14. Are any of the above reporter groups asked or encouraged specifically to report suspected ADRs associated with herbal medicines?

Yes ☐ No ☐ [*Go to Q16*]

15. Which groups of reporters are asked or encouraged specifically to report suspected ADRs associated with herbal medicines?

.....

.....

16. How is your national spontaneous ADR reporting scheme organised? [*tick one box only*]

Divided into regional monitoring centres (RMCs) ☐

Comprises both a single national centre and RMCs ☐

Functions as a single national centre only ☐ [*Go to Q22*]

Collaboration between your centre and another organisation(s) [*specify below*] ☐ [*Go to Q22*]

.....

.....

Other(s) [*specify below*] ☐ [*Go to Q22*]

.....

.....

17. Into how many regional monitoring centres is your national spontaneous ADR reporting scheme divided?

.....

18. Do any of the regional monitoring centres have a special focus on herbal medicines?

Yes ☐ No ☐ [*Go to Q22*]

19. Which regional monitoring centre(s) has/have a special focus on herbal medicines?

.....

20. What activities with regard to herbal medicines does this centre/these centres undertake?

.....

.....

.....

21. Are all reports associated with herbal medicines sent to this centre/these centres?

Yes ☐ No ☐

22. Are guidelines for your national spontaneous ADR reporting scheme available?

Yes ☐ [*please provide a copy*] No ☐

23. From which sources can your national spontaneous ADR reporting form and guidelines (if applicable) be obtained? [*tick all that apply*]

Source	Downloaded from the Internet	National Centre	Regional Monitoring Centre	Reference textbooks [*specify below*]	Other(s) [*specify below*] ....
ADR reporting form					
Guidelines					

24. Provide the following details for A) conventional and B) herbal medicines? [*tick all that apply and provide the number of spontaneous reports received by your centre. If your scheme does not accept herbal ADR reports complete column A only and then go to Q26*]

a) How can your scheme's ADR reports be submitted?	**A**	**B**
By post to the national system	☐	☐
By post to the regional monitoring centre	☐	☐
By telephone	☐	☐
Over the internet	☐	☐
Other(s) [*specify*]	☐	☐
b) In response to a submitted spontaneous ADR report what feedback does your national ADR reporting scheme provide to the individual reporter?	**A**	**B**
Acknowledgement letter	☐	☐
Replacement reporting form	☐	☐
Information on previously reported reactions, always/routinely	☐	☐
Information on previously reported reactions, only if requested	☐	☐
Other(s) [*specify below*].....	☐	☐
c) Total number of spontaneous ADR reports received since scheme first began		
d) Total number of spontaneous ADR reports received in 2003		

25. Which of the following data items would your centre consider essential for a herbal ADR report and are searchable on your database? [*tick all that apply for each data item*]

Data Item	**Essential**	**Desirable - but not essential**	**Not required**	**Searchable on your database**
Generic/common name e.g. Echinacea				
Brand/proprietary name				
Genus eg Echinacea				
Species e.g. *Echinacea purpurea*				
Plant part e.g. root				
Manufacturer				
Batch number				
Type of preparation/extract				
Ingredients (for combined products)				
Indication				
Details of supplier e.g. of practitioners				

26. How does/would your centre screen for signals for A) conventional and B) herbal medicines? [*If your scheme does not accept herbal ADR reports then complete row A only*]

	Each report is evaluated manually	**Automated system for signal detection**	**Other(s) [*specify below*] .....**
A) Conventional medicines			
B) Herbal medicines			

27. Has your centre ever detected any signals of safety concerns associated with herbal medicines?

Yes ☐ No ☐ [*Go to Q29*]

28. How many signals have been associated with herbal medicines?

..... since year .....

29. Has your scheme ever received information on herbal safety signals detected elsewhere?

Yes ☐ No ☐ [*Go to Q31 if also answered 'no' to Q27*]

30. Provide below details for the herbal safety signals identified at your centre or which have been detected elsewhere:

Source of signal		Name of Herbal Medicine	Suspected ADR	Year	Action Taken (State 'none' if no action taken)
Centre	External				

[continue on reverse or on a separate sheet if necessary]

31. Which of the following methods does/would your centre use to communicate information on safety concerns to relevant groups? [*tick all that apply*]

a) Direct national safety warning(s) ☐

⇨ Which of the following groups would receive the safety warning?

Recognised reporters ☐ Media ☐

Herbal medicine organisations ☐ Other(s) [*specify below*] ☐

Herbal practitioner organisations ☐ .....

Other CAM organisations ☐ .....

b) Centre's own newsletter ☐

⇨ How many issues are published each year? .....

⇨ Who are they distributed to? [*tick all that apply*]

Within the centre ☐ All reporter groups ☐

Specific reporter groups [*specify below*] ☐ Other(s) [*specify below*] ☐

....

....

c) Own website ☐

⇨Is there a specific herbal medicine section on your website?

Yes ☐ No ☐

⇨Are all internet users able to access this website?

Yes ☐ No ☐

d) Circulation of WHO SIGNAL publication ☐

⇨Who is this distributed to? [*tick all that apply*]

Within the centre ☐ All reporter groups ☐

Specific reporter groups [*specify below*] ☐ Other(s) [*specify below*] ☐

....

e) Other(s) [*specify below*] ☐

.....

.....

32. How many finished/marketed herbal medicines are licensed/authorised/registered in your country?

.....

33. What is the regulatory status of herbal medicines in your country? [*tick one box only*]

All are licensed/authorised/registered ☐
Some are licensed/authorised/registered ☐
None are licensed/authorised/registered ☐

34. From what sources can herbal medicines be obtained in your country? [*tick all that apply*]

Non-pharmacy retail outlets ☐
Registered pharmacies ☐
Medical doctors ☐
Complementary/alternative medicine practitioners ☐
Traditional healers ☐
Mail order ☐
Internet ☐
Other(s) [*specify below*] ☐
.....
.....

35. Please indicate your level of agreement with the following statements. [*tick one box for each statement*]

Statement	Strongly agree	Agree	Neutral	Disagree	Strongly disagree
Your current ADR reporting form **is suitable** for collecting reports for suspected herbal ADRs					
Your current ADR reporting form **needs modifying** in order to effectively collect data on suspected herbal ADRs					
There should be a **separate** ADR reporting **form** for herbal medicines					
There should be a **separate** ADR reporting **scheme** for herbal medicines					

36. We would welcome any other comments relevant to this study:

37. What is your position (job title) in the centre?

.....

38. Please send a copy of the following in the envelope provided together with this questionnaire:

Document	Checklist (✓)
ADR reporting form	
Herbal ADR reporting form (if applicable)	
Your scheme's guidelines for ADR reporting	

Thank you for your time. Please return this questionnaire in the envelope provided.

Miss AM Aggarwal MPharm MRPharmS & Dr J Barnes BPharm PhD MRPharmS FLS
Centre for Pharmacognosy & Phytotherapy, School of Pharmacy, University of London, 29/39 Brunswick Square, London WC1N 1AX, UK

APPENDIX III
FOCUS GROUP THEMES

Topic Guide: list of themes to be explored at focus group meetings.

Definitions

- **when you hear the term herbal medicines, what comes to mind?**
- how do pharmacists define herbal medicine
- what types of products/preparations do they consider to be herbal medicines (e.g. tea tree cream, garlic tablets, St John's wort tablets, senna tablets)
- by what other names do they refer to herbal medicines
- what do the terms phytomedicines, phytotherapeutics mean to you?
- are there any other types of remedies [essential oils, homoeopathy?] that they consider to be herbal

Now, I'd like to move on to aspects of your practice concerning herbal medicines. For example, do you recommend herbal medicines to patients/customers?

Pharmacists' practice

- do you recommend herbal medicines to patients/customers
- how often does that happen
- why do you recommend, or why do you not recommend?
- are there any groups you particularly would recommend or not recommend herbal medicines to [pregnant women; children; elderly; patients with chronic conditions]
- how frequently are you asked for advice on herbal medicines?
- what sort of questions are you asked about herbal medicines
- why do people ask pharmacists for advice on herbal medicines?
- how do you feel about giving advice on herbal medicines
- how can pharmacists encourage consumers to consult them for advice on herbal medicines?

- do you use herbal medicines for themselves or their immediate family
- importance of herbal medicines to pharmacy/pharmacists
- most pharmacies stock herbal medicines - how do you feel about that?
- Is the pharmacy the right place?

- what implications does the use of herbal medicines have for pharmaceutical care

- role in ADR reporting for herbals?
- role in disseminating information to consumers about safety concerns with regard to herbal products
- should advising on herbal medicines is/should be part of pharmacists' professional practice

That leads us into the question of training

Training, Knowledge, Information

- perceptions of knowledge
- what areas are you knowledgeable about?
- which areas are you not knowledgeable about?
- extent and type of training undertaken in aspects of herbal medicines
- what form should training take?
- specific training needs, e.g. content, formal qualification
- preferred method of undertaking training
- pharmacists' views on where pharmacists' training in herbal medicines should occur
- what information sources are available
- what would they like to have

- views on Code of Ethics
- pharmacists' knowledge of common herbal medicines, e.g. uses, evidence of efficacy, safety issues
- pharmacists' knowledge of licensing of herbal products
- pharmacists' knowledge of application of yellow-card scheme for ADR reporting to herbal

products

Views towards others

- pharmacists' views on consumers' knowledge of herbal medicines
- pharmacists' views on consumers' perceptions of pharmacists' knowledge
- what do you think about sales of HM in health-food stores, internet etc?
- **health-food stores** as sources of advice for consumers of herbal medicines
- **herbal practitioners** as sources of advice and herbal preparations for consumers of herbal medicines
- **doctors and other conventional health-care professionals** with regard to consumers of herbal medicines

Perceptions of and attitudes towards herbal medicines

- perceptions on quality, efficacy, safety of herbal medicines
- what do pharmacists perceive as 'quality' with respect to herbal medicines
- who do pharmacists perceive as being manufacturers of good-quality herbal medicines? Why?
- how are the quality, efficacy and safety of herbal medicines perceived relative to those of conventional medicines (OTC and prescription), complementary medicines, eg homoeopathic medicines etc.
- pharmacists' views on licensing of herbal products

Additional issues raised by focus group participants

We have about 10 minutes left now, I would just like to seek your views on ..... OR

We have about 10 minutes or so left now, are there any other issues concerning herbal medicines that any of you would like to raise?

Thank you for your time.

Freepost envelope for expenses.

APPENDIX IV

COMMUNITY PHARMACIST STUDY DOCUMENETS

From: "Queries" <queries@corec.org.uk>
To: "'Anjana Aggarwal'" <anjana.aggarwal@pharmacy.ac.uk>
Subject: RE: Ethics approval
Date: Thu, 23 Feb 2006 17:25:36 -0000
X-Mailer: Microsoft Outlook, Build 10.0.6626
X-Word-Score: 28 [194.66.95.40]
X-Word-Score-Reason: "* consultation *" (25), "* approval *" (3)
X-AntiSpam: Checked for restricted content by Gordano's AntiSpam Software

Thank you.
The following reply has been provided by Jo Downing, Information Officer

Thank you for your query. As community pharmacists are not NHS Staff this would not require ethical review by an NHS REC.

I hope this helps.

Regards

Queries Line
Central Office for Research Ethics Committees (COREC)
National Patient Safety Agency
Website: www.corec.org.uk <http://www.corec.org.uk>

Ref: 021/041/01
**
An information leaflet on the New Operational Procedures for NHS Research Ethics Committees from 1 March 2004 is available at <http://www.corec.org.uk/applicants/help/docs/Guidance_for_Applicants_to_RECs.pdf>. Request printed copies from the COREC office by email to: queries@corec.org.uk <mailto:queries@corec.org.uk>.

**
This reply may have been sourced in consultation with other members of the COREC team.
***

X-VirusChecked: Checked
X-Env-Sender: C.Cairns@kingston.ac.uk
X-Msg-Ref: server-3.tower-58.messagelabs.com!1155308290!84697776!1
X-StarScan-Version: 5.5.10.7; banners=kingston.ac.uk,-,-
X-Originating-IP: [141.241.2.18]
Subject: RE: RE: Questionnaire review
Date: Fri, 11 Aug 2006 15:58:09 +0100
X-MS-Has-Attach: yes
X-MS-TNEF-Correlator:
Thread-Topic: RE: Questionnaire review
Thread-Index: Aca7CQ0RSApWF2ZHQQm2FNTSknFP/wCTKTsk
From: "Cairns, Chris" <C.Cairns@kingston.ac.uk>
To: "Anjana Aggarwal" <anjana.aggarwal@pharmacy.ac.uk>
X-OriginalArrivalTime: 11 Aug 2006 14:58:09.0376 (UTC)
FILETIME=[8F2FF600:01C6BD56]
X-AntiSpam: Checked for restricted content by Gordano's AntiSpam Software

Dear Anjana,

Thanks for sending me your project for ethical review. In general, from an ethical point of view i felt it was well designed and all the major ethical issues well addressed. I have a few minor comments which I feel you should examine and have made some, hopefully, constructive suggestions. I attach these one the accompanying commentary. Some of the comments address the protocol and as such are not purely ethical in nature but it is my view that good research means good ethical standards, while poor methodology is not ethical as it will subject someone to research that may not be of use. Please take these comments in that spirit.

If you wish to discuss my comments or need a fuller explanation, please do not hesitate to contact me. Good luck with your research, you have a lot of work ahead of you.

Best wishes

Chris

Chris Cairns
Professor of Pharmacy Practice
Kingston University
Penrhyn Rd.
Kingston upon Thames
Surrey KT1 2EE
020 8547 8022

Community Pharmacists and Herbal Medicines

Ethics Opinion

1. **Protocol/plan of research**

4.2 Sampling

The protocol does not describe how the sampling is going to be done. There needs to be some description of the process to show that it is random and more importantly there is no coercion or abuse of positions of trust/power to recruit the subjects. From the PIL and letter of invitation neither of these appear to be present but it would be useful to describe how they are being avoided.

1.2 Ethnicity/nationality

The protocol states 'Ethnicity and nationality have also been included as these could be factors that greatly influence the perception and views of pharmacists ...' There is no evidence to support this statement and the study does not seem to be designed to test this hypothesis. Any conclusion drawn may not be valid. As declaration of ethnicity particularly can be sensitive the researcher should consider carefully whether this data is of benefit.

2. **Questionnaire**

4.2 General

The questionnaire overall does not appear to be intrusive or collect information or data that is particularly sensitive, with the exception of ethnicity and nationality (see below). It is completed anonymously and there are no obvious indicators of the respondents' identity. The demographic information is such that it would not be possible to identify individual respondents.

It is on the lengthy side and that may limit response but I note the researchers have a follow up strategy which may minimise this.

2.2 Demographic information

Questions 2.1 to 2.6 although not particularly intrusive or sensitive ask a number of personal questions about the respondent. None of them in themselves pose ethical issues. However, it may be best if these questions were asked after getting the respondents non personal views and information. Responses to Q2.1 to Q2.6 in their present position may influence subsequent responses. I would suggest putting them immediately before section 6.

2.3 Ethnicity

Please see my comments on ethnicity in 1.2 above. However, if the researchers feel that the collection of data on the ethnicity of the respondents is important, then one of the accepted ethnicity classifications should be used. That used in the latest UK census is routinely used by NHS organisations and in much clinical research. The present scale is too narrow. For example 'Asian' will include people of Middle Eastern, Indian, Pakistani & Sri Lankan, Chinese, Malay and Vietnamese origin, all of whom regard themselves differently. It makes no distinction between Black African and Black

Caribbean origin. Also it makes no differentiation between individuals who regard themselves as British or non British no matter their background. Also most surveys which ask for ethnicity data usually provide a decline to respond option. Last but not least the issue of mixed race should be handled sensitively. 'Mixed race' is now an accepted classification in the UK for example. I would simply use 'Other' rather than 'any other ...'

3. Consent

Consent is tacit as it is provided by the respondent returning the questionnaire. There are no material ethical issues with this approach in this study.

4. PIL

4.1 General

Overall the PIL is well laid out and covers all the important ethical issues. The explanation of how the coding would be anonymised is helpful and clear. Many studies do not deal with this. I have 2 minor comments to make.

4.2 Information on non responders

The information on the process for following up non responders does not read well. It presently reads in the third person as if it is an extract from the protocol. I would recommend re-writing in the second person in softer, more personal manner.

4.2 Taking part (section 4)

The sentence 'If you do decide to take part in the study ...' is cumbersome and refers to section 11, which I assume to be section 1.1. Can I suggest the following simpler text: 'If you decide to take part, please complete the questionnaire and return it to me in the enclosed reply paid envelope.'

5. Letter of invitation

There are no material ethical issues in the letter. In fact it is a model of good practice. I assume it will be on SoP headed notepaper.

Chris Cairns
Professor of Pharmacy Practice
Kingston University

11th August 2006

ID code ☐☐☐-☐☐☐-☐☐

Community Pharmacists and Herbal Medicines

The aim of this questionnaire is to collect information on community pharmacists' experiences with and views on herbal medicines. Completion of all or part of the questionnaire indicates your consent for participation and use of the data you provide. Please note that your responses will be treated confidentially, and that your name or that of your pharmacy and your pharmacy colleagues, and any other identifying features, will not be revealed in any publications arising from this study.
Please complete all questions on the questionnaire as directed and in the order in which they appear; this should take around 20 minutes. Please return your completed questionnaire in the reply-paid envelope provided. Thank you for participating in this study.

SECTION 1: WHAT ARE HERBAL MEDICINES?

This section explores what you think are herbal medicines. Please complete this section FIRST.

1.1. How would you define or describe herbal medicines?

.....

.....

.....

1.2. For each of the following preparations, indicate whether you consider them to be 'herbal' [tick Yes] or not [tick No].

	Yes	No	Don't know
Dried root of *Aristolochia fangji*	☐	☐	☐
Aspirin	☐	☐	☐
Chondroitin	☐	☐	☐
Colpermin capsules	☐	☐	☐
Cranberry juice	☐	☐	☐
Digoxin	☐	☐	☐
Dried leaf of *Digitalis lanata*	☐	☐	☐

	Yes	No	Don't know
Fybogel sachets	☐	☐	☐
Capsules containing garlic powder	☐	☐	☐
Glucosamine	☐	☐	☐
Melatonin	☐	☐	☐
Senokot syrup	☐	☐	☐
St John's wort herb extract	☐	☐	☐
Willow bark extract	☐	☐	☐

1.3 For each of the following types of preparations, indicate whether you consider them to be 'herbal' [tick Yes] or not [tick No].

	Yes	No	Don't know
All complementary/alternative medicines	☐	☐	☐
Dried or fresh raw or crude plant material	☐	☐	☐
Extracts of plants or plant parts (e.g. leaves, roots)	☐	☐	☐
Essential oils	☐	☐	☐
All homeopathic (i.e. highly dilute) remedies	☐	☐	☐
Homeopathic (i.e. highly dilute) preparations of plant material	☐	☐	☐
Homeopathic (i.e. highly dilute) preparations of non-plant material	☐	☐	☐
Non-plant dietary supplements e.g. Co-enzyme Q_{10}	☐	☐	☐
Minerals	☐	☐	☐
Vitamins	☐	☐	☐

For the remainder of this questionnaire, please use the following description for herbal medicines. Herbal medicines are medicinal products containing as active plant ingredients, part of plants, and/or plant materials, whether in a crude (e.g. dried or fresh material) or processed (e.g. extract) state. This includes essential oils, plant juices, gums and other directly derived plant products, as well as 'dietary supplements' derived from plant material, e.g. garlic extract tablets. This includes plant materials used in various traditional systems of herbal medicines, e.g. Chinese herbal medicine. It does not include chemically defined isolated constituents, e.g. digoxin, or non-plant-derived substances, e.g. glucosamine.

SECTION 2: HERBAL MEDICINES IN YOUR PHARMACY
Please provide the following information about the pharmacy in which you work. If you are a locum or you work in or own more than one pharmacy, please provide answers for ONE pharmacy only: the pharmacy in which you work most often, have worked for the longest period of time, or is otherwise the main pharmacy with which you associate your work.

2.1. Which of the following categories would you use to describe your pharmacy? [Tick one only]

Independent	☐	Large ownership (26-100)	☐
Small ownership (2-15)	☐	National ownership (100+)	☐
Medium ownership (16-25)	☐		

2.2. How would you describe the LOCAL setting of your pharmacy? [Tick one only]

Village high street/village centre	☐	Supermarket	☐
Town high street/main shopping street	☐	Health centre/doctor's surgery	☐
Out-of-town shopping centre	☐	Housing estate	☐
Rural e.g. area without other shops	☐	Other [please specify .....]	☐

2.3. Over the last 7 days (use nearest previous 7-day period if you were on holiday/ill or otherwise away from work), how many hours did you work in this pharmacy? ..... hours

2.4. For how many years have you been working in this pharmacy? ..... years

2.5. What is your role in this pharmacy? [Tick all that apply]

Superintendent pharmacist	☐	Pharmacist	☐
Area manager	☐	Locum	☐
Store manager	☐	Other [please specify below]	☐
Owner	☐	.....	

2.6. Consider a typical day when you are working in this pharmacy. How many of the following pharmacy staff are also working? [Specify 'nil' where appropriate]

	Number
Other pharmacists [not including yourself]	
Trained dispenser	
Pharmacy counter staff	
Other [please specify.....]	

2.7. Does the pharmacy you have described above sell herbal medicines?

Yes ☐ No ☐ [If no, go to Q2.13] Don't know ☐ [If don't know, go to Q2.13]

2.8. If yes, which of the following categories of herbal medicines does the pharmacy sell? [Tick one only]

Licensed herbal medicines only	☐	Unlicensed herbal medicines only	☐
Both licensed and unlicensed herbal medicines	☐	Don't know	☐

2.9. If yes, which of the following dosage forms or types of herbal medicines does the pharmacy sell? [Tick all that apply]

	Yes	No	Don't know
Tablets/capsules	☐	☐	☐
Herbal tinctures	☐	☐	☐
Essential oils	☐	☐	☐
Herbal teas	☐	☐	☐

	Yes	No	Don't know
Crude/loose dried or fresh herbs	☐	☐	☐
Topical preparations of herbal medicines	☐	☐	☐
Other [please specify below]	☐	☐	☐
.....			

2.10. For the pharmacy you described above, who decides which herbal medicines are stocked in the pharmacy? [Tick all that apply]

	Yes	No	Don't know
Headquarters	☐	☐	☐
Superintendent pharmacist	☐	☐	☐
Non-pharmacist manager	☐	☐	☐

	Yes	No	Don't know
Pharmacist in charge	☐	☐	☐
Other [please specify below]	☐	☐	☐
.....			

2.11. Are you directly involved in the selection of these products? Yes ☐ No ☐ [If no, go to Q2.13]

2.12. If yes, please list the three most important criteria that influence your decision whether or not to stock a particular herbal medicine:

1. .....
2. .....
3. .....

2.13. For this pharmacy, over the last 7 days (use nearest previous 7-day period if you were on holiday/ill or otherwise away from work), how many times have you been asked by your patients and customers for advice or information on herbal medicines? [*Include instances where counter staff have referred queries to you, any proxy enquiries (i.e. those made by a customer on behalf of someone else) and those made by telephone or post or email*]

.....

2.14. For this pharmacy, over the last 7 days (use nearest previous 7-day period if you were on holiday/ill or otherwise away from work), how many times have you recommended and/or sold herbal medicines to your patients and customers? [*Include relevant instances from the previous question, and those where you sold or recommended herbal medicines to any proxy customers (i.e. those made on behalf of someone else) and any recommendations or sales made by telephone or post or email*]

.....

2.15. For this pharmacy, over the last 7 days (use nearest previous 7-day period if you were on holiday/ill or otherwise away from work), what types of enquiries did you receive? [Tick all that apply]

	Yes	No
Uses of specific herbal medicines	☐	☐
What herbal medicines to use for specific conditions	☐	☐
Side effects of herbal medicines	☐	☐
Interactions between herbal medicines and conventional medicines	☐	☐
Where to buy certain herbal medicines	☐	☐
Efficacy of specific herbal medicines	☐	☐
Dose/dosages for specific herbal medicines	☐	☐
Use of specific herbal medicines in pregnancy and/or breastfeeding	☐	☐
Cost of herbal medicines	☐	☐
Other [please specify]	☐	☐

2.16 In this pharmacy, what sources of information on herbal medicines are available to you and which do you use? [Tick all that apply]

	Available? (✓)		Use? (✓)	
	Yes	No	Yes	No
Martindale	☐	☐	☐	☐
Specific herbal medicine books [please specify below]	☐	☐	☐	☐
Pharmaceutical Journal articles	☐	☐	☐	☐
Fact sheets published by RPSGB	☐	☐	☐	☐
Manufacturers literature and brochures	☐	☐	☐	☐
Scientific databases (e.g. PubMed/Medline) [please specify below]	☐	☐	☐	☐
Specific websites (please specify below)	☐	☐	☐	☐
Internet search engines to find relevant internet sites [please specify below]	☐	☐	☐	☐
Telephone manufacturer directly	☐	☐	☐	☐
Telephone RPSGB information department	☐	☐	☐	☐
Telephone the NPA	☐	☐	☐	☐
Telephone/contact health-food store or herbal-medicine practitioner	☐	☐	☐	☐
Other [please specify.....]	☐	☐	☐	☐

2.17. Please describe up to THREE specific resources that you would like to have available to you to assist in advising on herbal medicines:

1. .....
2. .....
3. .....

SECTION 3: TRAINING, EDUCATION AND KNOWLEDGE IN HERBAL MEDICINES

3.1. Since registering as a pharmacist, what training, if any, have you undertaken in herbal medicines and for how many hours (include all forms of teaching/learning, including lectures, workshops, CPD activities)? [Tick all that apply]

	Yes	No	Hours
None	☐	☐	N/A
Employer-provided training	☐	☐	
Distance-learning packages (e.g. CPPE)	☐	☐	
Workshops, seminars, local branch lectures	☐	☐	
Formal postgraduate course [please specify details below] Name of course ..... Qualification ..... Institution	☐	☐	
Continuing professional development activities [please specify type of activity .....]	☐	☐	
Relevant research degree [please specify details below] Type (e.g. MSc) ..... Title of thesis ..... Institution	☐	☐	
Other [please specify .....]	☐	☐	

3.2. In your undergraduate pharmacy studies, did you receive any teaching/learning in herbal medicines and/or pharmacognosy?

Yes ☐ No ☐ [If no, go to Q3.4] Don't know ☐ [If don't know, go to Q3.4]

3.3. If Yes, please indicate which of the following YOU undertook during your pharmacy undergraduate studies as either part of the core curriculum, or as an option/elective topic. [Tick all that apply]

	Core curriculum (✓)		Elective/option (✓)	
	Yes	No	Yes	No
Specific stand-alone Pharmacognosy/natural products course	☐	☐	☐	☐
Specific stand-alone herbal and/or complementary medicines course	☐	☐	☐	☐
Pharmacognosy/natural products teaching/learning integrated as part of another course	☐	☐	☐	☐
Herbal and/or complementary medicines course integrated as part of another course	☐	☐	☐	☐

3.4. Which of the following best describes your level of competency in advising patients and the public on the safe and effective use of herbal medicines? [Tick one only]

Competent for most herbal medicines	☐	Quite competent for most herbal medicines	☐	Quite competent for a few herbal medicines	☐	Not competent for most herbal medicines	☐	Don't know	☐

3.5. What activities would <u>you</u> be willing to undertake to achieve a satisfactory level of competence in advising patients and the public on the safe and effective use of herbal medicines?

.....
.....
.....

SECTION 4: ADVERSE DRUG REACTION (ADR) REPORTING FOR HERBAL MEDICINES

4.1. While working as a <u>community pharmacist</u>, have you <u>ever</u> identified or received a report from a patient or customer of a suspected adverse drug reaction associated with <u>any type of medicine</u> (including herbal and complementary medicines)?

Yes ☐ No ☐ [If no, go to Q4.4] Don't know ☐ [If don't know, go to Q4.4]

4.2. If Yes, have you identified or received a report(s) from a patient or customer of a suspected adverse drug reaction associated with a <u>herbal medicine(s)</u> <u>in the last 12 months</u>?

Yes ☐ No ☐ [If no, go to Q4.4] Don't know ☐ [If don't know, go to Q4.4]

4.3. If Yes, how many such reports have you identified or received <u>in the last 12 months</u>? .....

4.4. While working as a <u>community pharmacist</u>, have you <u>ever</u> submitted a yellow card report for a suspected adverse drug reaction associated with <u>any type of medicine</u> (including herbal and complementary medicines) identified by you or reported to you by a patient or customer?

Yes ☐ No ☐ [If no, go to Q4.8] Don't know ☐ [If don't know, go to Q4.8]

4.5. If Yes, how many yellow card reports have you <u>ever</u> submitted while working as a community pharmacist?

.....

4.6. How many of these involved suspected adverse drug reactions, including interactions, associated with the use of herbal medicines? .....

4.7. How many such yellow card reports, associated with the use of herbal medicines, have you submitted <u>in the last 12 months</u>? .....

4.8. In your opinion, which of the following criteria should be met before you would submit a yellow card report for a suspected ADR associated with a herbal medicine? [Tick all that apply]

	Yes	No
The ADR must be serious	☐	☐
The ADR must be previously unknown for that herbal medicine	☐	☐
I must be certain that the herbal medicine caused the ADR	☐	☐
The herbal medicine has to be a licensed product	☐	☐
The herbal medicine has to be an unlicensed product	☐	☐

SECTION 5: PLEASE INDICATE YOUR LEVEL OF AGREEMENT WITH THE FOLLOWING STATEMENTS.
Tick one box for each statement

Statement	Level of agreement				
	Strongly agree	Agree	Neutral	Disagree	Strongly disagree
Community pharmacies should not sell any herbal medicines	☐	☐	☐	☐	☐
Herbal medicines should only be available from pharmacies	☐	☐	☐	☐	☐
Pharmacies should only sell licensed herbal medicines	☐	☐	☐	☐	☐
Herbal medicines should be required to have a product licence/marketing authorisation to be placed on the market	☐	☐	☐	☐	☐
Herbal medicines should be manufactured to Good Manufacturing Practice standards	☐	☐	☐	☐	☐
Herbal medicines should not be manufactured to the same standards as conventional medicines	☐	☐	☐	☐	☐
Licensed herbal medicinal products should be included in the British National Formulary	☐	☐	☐	☐	☐
Community pharmacists are in an ideal position to monitor for ADRs associated with herbal medicines	☐	☐	☐	☐	☐
Yellow card reports for suspected ADRs should not be submitted for unlicensed herbal medicines	☐	☐	☐	☐	☐
Patients/consumers should be able to submit yellow card reports for suspected ADRs associated with herbal medicines	☐	☐	☐	☐	☐
I am more likely to submit a yellow card report for a suspected ADR associated with the use of a conventional OTC medicine than for the same suspected ADR associated with the use of a licensed herbal medicine	☐	☐	☐	☐	☐
I am more likely to submit a yellow card report for a suspected ADR associated with the use of a conventional OTC medicine than for the same suspected ADR associated with the use of an unlicensed herbal medicine	☐	☐	☐	☐	☐
It is part of the pharmacist's role to disseminate information to patients/consumers about herbal safety concerns	☐	☐	☐	☐	☐
Staff in health-food stores are best placed to provide advice on herbal medicines	☐	☐	☐	☐	☐
Advising on herbal medicines should be part of pharmacists' professional practice	☐	☐	☐	☐	☐
I require more training on herbal medicines to be competent in advising patients/customers on herbal medicines	☐	☐	☐	☐	☐
Community pharmacists should only sell or advise on herbal medicines if they have undertaken formal training in herbal medicines	☐	☐	☐	☐	☐
Training in herbal medicines should be part of the pharmacy undergraduate compulsory curriculum	☐	☐	☐	☐	☐
Training in herbal medicines should be part of the pharmacy undergraduate optional curriculum	☐	☐	☐	☐	☐

SECTION 6: PLEASE PROVIDE THE FOLLOWING DETAILS ABOUT YOURSELF

6.1. What sex are you? Male ☐ Female ☐

6.2 What is your country of birth? .....

6.3 What nationality are you? .....

6.4. To which of these ethnic groups do you consider you belong? [Tick one only]

i) White							
British	☐	Irish	☐	Scottish	☐	Other[please specify.....]	☐
ii) Asian or Asian British							
Indian	☐	Pakistani	☐	Bangladeshi	☐	Other[please specify.....]	☐
iii) Black or Black British							
Caribbean	☐	African	☐	Other[please specify.....]			☐
v) Mixed							
[Please specify.....]							☐
v) Chinese or other ethnic background							
Chinese	☐	Other[please specify.....]					☐
Please tick this box if you do not wish to answer this question							☐

6.5. What is your year of birth? .....

6.6. Which year did you register as a pharmacist? .....

6.7. For how many years in total have you worked as a community pharmacist? .....

6.8. Which of the following qualifications do you hold? [Tick all that apply]

	Yes	No
Undergraduate pharmacy degree from UK	☐	☐
Undergraduate pharmacy degree from Europe, other than UK	☐	☐
Undergraduate pharmacy degree from outside UK/Europe	☐	☐
Registered pharmacist in UK	☐	☐
Registered pharmacist in other country [please specify.....]	☐	☐
Postgraduate pharmacy qualification (certificate, diploma, masters) from UK	☐	☐
Postgraduate pharmacy qualification (certificate, diploma, masters) from outside UK	☐	☐
PhD in pharmaceutical discipline	☐	☐
PhD in other discipline	☐	☐

6.9. If you have any other comments about herbal medicines or comments relevant to this questionnaire that you would like to make, please write them in the box overleaf.

APPENDIX V

TRENDS IN TEACHING PHARMACOGNOSY QUESTIONNAIRE

The Teaching of Pharmacognosy/Natural products, Herbal Medicine and Complementary/Alternative Medicine: a cross-sectional survey of UK Schools/Departments of Pharmacy

This survey aims to gather information about the teaching of pharmacognosy/natural products and related areas, namely herbal medicines and aspects of complementary and alternative medicine (CAM), in the MPharm syllabus in UK schools of pharmacy. The questionnaire should be completed by a member of the academic staff who is directly involved with the teaching of these areas (or, for new schools, Head of School). It may be necessary for the respondent to consult colleagues and course co-ordinators in other disciplines (e.g. pharmacy practice) to determine all areas of the curriculum involving relevant teaching. Your contribution towards this research is important - please complete this questionnaire and return it in the addressed envelope provided. All information provided will be treated confidentially.

i) What is the current Royal Pharmaceutical Society of Great Britain accreditation status for your School/Department of Pharmacy?

Full	☐	(go to section 1 below)
Partial (subject to annual approval)	☐	(go to question ii below)
No accreditation at present	☐	(go to section 6 on page 5)

ii) For new Schools/Departments of Pharmacy (established in last five years), in what academic year did/will you receive your first intake of MPharm undergraduate students?

Academic year: ..... (continue below to section 1)

Section 1: CORE curriculum

Questions in this section relate only to the CORE curriculum (i.e. undertaken by all MPharm students) of the course

1a. Does the MPharm programme at your institution include teaching of pharmacognosy/natural products and related areas (herbal medicine and complementary/alternative medicine) as part of the CORE curriculum?

Yes ☐ No ☐ (please continue to section 2)

1b. If yes, in the table below, please indicate the number of hours teaching relevant to these subjects each student receives in each year of the MPharm programme and for each method of delivery. [*If none, please indicate ZERO*]

New schools of pharmacy should include proposed teaching here (e.g. for years 3 and 4) only if it is included in the accredited programme for that year. Details of other proposed teaching, or changes, will be collected in section 7.

Year	Formal Lectures	Laboratory-based practicals	Interactive tutorials/small group sessions	Assigned course-work	Other eg. Field visits. (Please specify)	Total number of hours per year
1						
2						
3						
4						
					Total	

1c. How is the CORE course material on pharmacognosy and related areas assessed? [*Indicate all that apply*] Please indicate whether or not each method of assessment contributes to the overall MPharm degree mark?

	Used in assessment		Contributes to MPharm degree mark	
	Yes	No	Yes	No
Examination(s)	☐	☐	☐	☐
Assessment of course work	☐	☐	☐	☐
Assessment of laboratory-based practicals	☐	☐	☐	☐
Other [please specify]	☐	☐	☐	☐

Section 2: OPTIONS/ELECTIVES

Questions in this section relate only to OPTIONS/ELECTIVES in the MPharm programme.

2a. Does the MPharm programme at your institution offer any option(s)/elective(s) on pharmacognosy/natural products and related areas (herbal medicine and complementary/alternative medicine)?

Yes ☐ [Please go to question 2b]
No ☐ [Please go to section 3]

2b. How many options/electives are available? .....

2c. What are the titles of the option(s)/elective(s), approximately how many students undertake each option and in which year of the MPharm programme are they taught?

Option	Title of option/elective	Approx. no. of students	Year of MPharm (e.g. 4th)
a			
b			
c			
d			

2d. For each of the options listed in 2c above please indicate the number of hours teaching each student receives for each method of delivery, specifying the year(s) in which the option(s) are taken.

Year	Formal Lectures	Laboratory-based practicals	Interactive tutorials/small group sessions	Assigned course-work	Other eg. Field visits. (Please specify)	Total number of hours per year
a						
b						
c						
d						
					Total	

2e. For each of the options listed in 2c above, list the 5 main topics/subjects taught/included.

Option a	Option b	Option c	Option d

2f. How are the OPTIONS/ELECTIVES on pharmacognosy and related areas assessed? [*Indicate all that apply*] Please indicate whether or not each method of assessment contributes to the overall MPharm degree mark?

	Used in assessment		Contributes to MPharm degree mark	
	Yes	No	Yes	No
Examination(s)	☐	☐	☐	☐
Assessment of course work	☐	☐	☐	☐
Assessment of laboratory-based practicals	☐	☐	☐	☐
Other [please specify]	☐	☐	☐	☐

Section 3: CONTENT of CORE and OPTIONS/ELECTIVES

This section aims to determine which subjects relevant to pharmacognosy/natural products, herbal medicine and complementary/alternative medicine are taught in the MPharm curriculum at your institution and the extent of teaching.

3a. For each of the following subjects, please indicate, whether the subject is taught on the core curriculum of the MPharm and/or as part of an option/elective and, if possible, the number of hours teaching for each.

	Core			Option		
	Subject taught		No. of hours	Subject taught		No. of hours
Subject	YES	NO		YES	NO	
History of pharmacognosy						
Botany: morphology and systematics						
Ethnobotany/ethnopharmacology						
Natural products in drug discovery						
Natural products chemistry						
Bioassay-guided isolation of natural products						
Thin layer chromatography involving herbal substances						
Other isolation methods for natural products						
Structure elucidation of natural products						
Microscopy of herbal drugs						
Macroscopy of herbal drugs						
Quality control of herbal medicines						
Efficacy of herbal medicines						
Safety and toxicity of herbal medicines						
Pharmacovigilance and ADR reporting for herbal medicines						
Licensing/regulation of herbal medicines						
Counselling patients on herbal medicines						
Chinese herbal medicine						
Ayurvedic medicine						
Homoepathy						
Essential oils/aromatherapy						
Flower remedies						
Anthroposophical medicine						
Vitamin/mineral/dietary supplements						
Other areas [Please specify]						

Section 3: CONTENT of CORE and OPTIONS/ELECTIVES *(continued)*

3b. Is your teaching of pharmacognosy/natural products, herbal medicine and complementary/alternative medicine on the CORE curriculum of the MPharm programme provided as a discrete course(s)?

Yes ☐ No ☐

If Yes, please list the name(s) of the discrete course(s) in pharmacognosy/natural products and related areas.

.....

.....

3c. Is your teaching of pharmacognosy/natural products, herbal medicine and complementary/alternative medicine on the CORE curriculum of the MPharm programme integrated with teaching provision from other disciplines?

Yes ☐ No ☐

If Yes, please list the name(s) of the course(s) into which teaching on pharmacognosy/natural products and related areas is integrated.

.....

.....

Section 4: RESEARCH PROJECTS

Questions in this section relate only to RESEARCH PROJECTS in the MPharm programme.

4a. Does the MPharm programme at your institution allow students to undertake a research project in pharmacognosy/natural products and related areas (herbal medicine and complementary/alternative medicine)?

Yes ☐ [Please go to question 4b]
No ☐ [Please go to section 5]

4b. On average, how many students each year undertake a research project in these areas?

..... students

4c. What is the total number of hours each student is advised to dedicate to the research project (including literature search, data collection/experimentation, writing up, preparation of presentation etc)?

..... hours

4d. What form do student research projects take? [*Please indicate all that apply*]

Literature based	☐
Laboratory-based	☐
Practice-type research	☐
Other [Please specify].....	☐

4e. How are RESEARCH PROJECTS on pharmacognosy and related areas assessed? [*Indicate all that apply*] Please indicate whether or not each method of assessment contributes to the overall MPharm degree mark?

	Used in assessment		Contributions to MPharm degree mark	
	Yes	No	Yes	No
Literature review	☐	☐	☐	☐
Project dissertation - written	☐	☐	☐	☐
Oral presentation	☐	☐	☐	☐
Poster presentation	☐	☐	☐	☐
Other [please specify].....	☐	☐	☐	☐

4f. What proportion of the overall MPharm degree mark is provided by the research project? .....%

Section 5: FUTURE PLANS - 'OLD' SCHOOLS OF PHARMACY (those established more than five years ago)

Questions in this section concern your institution's future plans for teaching of pharmacognosy/natural products, herbal medicine and complementary/alternative medicine as part of the MPharm program.

5a. Does your pharmacy institution have any plans to INCLUDE/INCREASE teaching of pharmacognosy/ natural products, herbal medicine and complementary/alternative medicine during the next FIVE YEARS?

Yes ☐ No ☐

If yes, please provide details below of the proposed changes, and the academic year in which they will be introduced.

Details of proposed increase in teaching provision	Year to be introduced

5b. Does your pharmacy institution have any plans to REMOVE or REDUCE teaching of pharmacognosy/ natural products, herbal medicine and complementary/alternative medicine during the next FIVE YEARS?

Yes ☐ No ☐

If yes, please provide details below of the proposed changes, and the academic year in which they will be introduced.

Details of proposed reduction in teaching provision	Year to be introduced

[NOW GO TO SECTION 7]

Section 6: FUTURE PLANS - 'NEW' SCHOOLS OF PHARMACY (those established less than five years ago)

Questions in this section concern your institution's future plans for teaching of pharmacognosy/natural products, herbal medicine and complementary/alternative medicine as part of the MPharm program.

6a. For schools with no RPSGB accreditation at present, in what academic year do you plan to seek accreditation?

accreditation application is currently being considered by the RPSGB ☐
2004 to 2005 ☐
2005 to 2006 ☐
2006 to 2007 ☐
Other (please state) ..... ☐

6b. In what academic year do you plan to receive your first intake of MPharm undergraduate students?

2005 to 2006 ☐
2006 to 2007 ☐
2007 to 2008 ☐
Other (please state) ..... ☐

6c. Does your pharmacy institution have any plans to introduce teaching on pharmacognosy/natural products, herbal medicine and complementary/alternative medicine as part of the MPharm program during the next FIVE YEARS?

Yes ☐ No ☐

6d. If yes, please provide details below of the teaching planned and its proposed date of introduction, and the academic year of the MPharm in which the teaching will be included.

Details of proposed increase in teaching provision	Year to be introduced

Section 7: YOUR VIEWS on teaching of pharmacognosy/natural products and related areas

This section seeks your views on issues relevant to the teaching of pharmacognosy/natural products, herbal medicines and complementary/alternative medicine. Please indicate your response to EACH of the following statements, even though some may seem similar, by ticking the appropriate box.

For the purposes of this study, pharmacognosy is considered to be the scientific discipline underpinning the use of herbal medicines and other natural products with relevance to medicines. It includes the study of the physical, chemical, biochemical and biological properties of drugs, drug substances, or potential drugs or drug substances of natural origin as well as the search for new drugs from natural sources.

7a. The term *pharmacognosy* is old-fashioned and should not be used by schools/departments of pharmacy to describe teaching and research activities in this area

Strongly agree ☐ Agree ☐ Neutral ☐ Disagree ☐ Strongly disagree ☐ Don't know ☐

7b. Pharmacognosy/natural products should be included on the indicative syllabus for the MPharm programme

Strongly agree ☐ Agree ☐ Neutral ☐ Disagree ☐ Strongly disagree ☐ Don't know ☐

7c. The term *natural products*, rather than *pharmacognosy*, should be used by schools/departments of pharmacy to describe teaching and research activities in this area

Strongly agree ☐ Agree ☐ Neutral ☐ Disagree ☐ Strongly disagree ☐ Don't know ☐

7d. It is important that schools/departments of pharmacy continue to use the term *pharmacognosy* to describe teaching and research activities in this area

Strongly agree ☐ Agree ☐ Neutral ☐ Disagree ☐ Strongly disagree ☐ Don't know ☐

7e. Community pharmacists have a professional responsibility to be able to provide reliable, objective information and advice to patients and the public on the safe, effective and appropriate use of herbal medicines

Strongly agree ☐ Agree ☐ Neutral ☐ Disagree ☐ Strongly disagree ☐ Don't know ☐

7f. Pharmacognosy should ONLY be offered for study as an option/elective on the MPharm program

Strongly agree ☐ Agree ☐ Neutral ☐ Disagree ☐ Strongly disagree ☐ Don't know ☐

7g. Pharmacognosy should NOT be included on the indicative syllabus for the MPharm program

Strongly agree ☐ Agree ☐ Neutral ☐ Disagree ☐ Strongly disagree ☐ Don't know ☐

[continues on next page]

7h. For each of the following subjects, please indicate whether you think it is essential that the subject is taught on the core curriculum of the MPharm or teaching the subject as an option/elective is sufficient.

	Subject should be taught on CORE curriculum		Teaching as part of an OPTION is sufficient	
Subject	YES	NO	YES	NO
History of pharmacognosy				
Botany: morphology and systematics				
Ethnobotany/ethnopharmacology				
Natural products in drug discovery				
Natural products chemistry				
Bioassay-guided isolation of natural products				
Thin layer chromatography involving herbal substances				
Other isolation methods for natural products				
Structure elucidation of natural products				
Microscopy of herbal drugs				
Macroscopy of herbal drugs				
Quality control of herbal medicines				
Efficacy of herbal medicines				
Safety and toxicity of herbal medicines				
Pharmacovigilance & ADR reporting for herbal medicines				
Licensing/regulation of herbal medicines				
Counselling patients on herbal medicines				
Chinese herbal medicine				
Ayurvedic medicine				
Homoepathy				
Essential oils/aromatherapy				
Flower remedies				
Anthroposophical medicine				
Vitamin/mineral/dietary supplements				
Other areas [Please specify]				
_____				
_____				

Section 8: SCHOOL/DEPARTMENT OF PHARMACY AND RESPONDENT CHARACTERISTICS

This section should be completed by ALL respondents.

8a. What is the current approximate number of students in each year at your pharmacy institution?

Year	Current number of students	Year	Current number of students
1		3	
2		4	

8b. Does your Pharmacy institution have a specific department/centre dedicated to the discipline of pharmacognosy/natural products?

Yes ☐ (continue to question 8c) No ☐ (Please go to question 8d)

8c. How many members of academic staff (full-time equivalents) are positioned within this specific department/centre?

.....

Please indicate the number of academic staff in each of the academic positions in the table below:

	Number of Staff		Number of Staff
Lecturer		Reader	
Senior Lecturer		Professor	
Principal Lecturer		Other.....	

8d. How many members of academic staff at your pharmacy institution teach solely in the areas of pharmacognosy/ natural products, herbal medicine and complementary/alternative medicine on the MPharm programme?

.....

8e. How many OTHER members of academic staff at your pharmacy institution contribute to teaching pharmacognosy/ natural products, herbal medicine and complementary/alternative medicine on the MPharm programme?

.....

8f.What is your academic position (e.g. Professor) and main discipline (e.g. Pharmacognosy)?

Position: ..... **Discipline:** .....

8g. Please provide the following information about yourself: Male ☐ Female ☐

8h. Which of the following qualifications do you hold? [*Tick all that apply*]

Registered pharmacist in UK	☐	Pharmacy degree from outside the UK	☐
Registered as pharmacist outside the UK	☐	Other science degree	☐
Pharmacy degree from UK	☐	Other relevant qualification [please specify below]	☐
		.....	

8i. Are you involved in the teaching of pharmacognosy/natural products, herbal medicines and/or complementary/alternative medicine to undergraduate students as part of the Mpharm programme at your institution?

Yes ☐ No ☐

8j. How long have you been teaching pharmacognosy/natural products, herbal medicines and/or complementary /alternative medicine on the undergraduate pharmacy programme at UK schools of pharmacy?

..... years

8k. If you have any further comments about teaching of pharmacognosy/natural products please write them below:

.....

THANK YOU for completing this questionnaire. Please return it in the addressed envelope provided.
If possible, please could you also include a copy of the MPharm programme document of your institution.

APPENDIX VI

COMMUNITY-PHARMACY BASED PHARMACOVIGILANCE OF AN OTC HERBAL MEDICINE

STUDY DOCUMENTS

(Study protocol, pharmacy participation form, consumer covering letter, information leaflet, consent form, recruitment questionnaire and 1-week follow-up questionnaire)

NHS

Hertfordshire Local Research Ethics Committee
Tonman House
63-77 Victoria Street
St Albans
Hertfordshire
AL1 3ER

Telephone: 01727 792 934
Facsimile: 01727 792 904

Email: andreas.marcou@bhsha.nhs.uk

20 January 2005

Dr Joanne Barnes

Lecturer in Phytopharmacy
University of London
School of Pharmacy
29-39 Brunswick Square
London
WC1N 1AX

Dear Dr Barnes

Full title of study: *A Pilot Study of community pharmacy bases pharmacovigilance of an over the counter herbal medicine Ginkgo (Ginkgo Biloba)*
REC reference number: *04/Q0201/41*
Protocol number:

Thank you for your letter of 10 January 2005, responding to the Committee's request for further information on the above research and submitting revised documentation.

The further information was considered at the meeting of the Committee held on 19 January 2005. A list of the members who were present at the meeting is attached.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation.
The committee would also like to thank Dr Barnes and Anjana Aggarwal for attending the meeting.
The favourable opinion applies to the research sites listed on the attached form. Confirmation of approval for other sites listed in the application will be issued as soon as local assessors have confirmed that they have no objection.

Conditions of approval

The favourable opinion is given provided that you comply with the conditions set out in the attached document. You are advised to study the conditions carefully.

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document Type:	Version:	Dated:	Date Received:
Protocol	2		10/01/2005
Covering Letter	2 health care provider		10/01/2005
Copy of Questionnaire	2 one-week follow-up questionnaire consumer		10/01/2005
Copy of Questionnaire	2 Week four follow-up questionnaire Consumer		10/01/2005
Copy of Questionnaire	2 3 month follow-up questionnaire consumer		10/01/2005
Copy of Questionnaire	2 6 month follow-up questionnaire consumer		10/01/2005
Copy of Questionnaire	2 patient follow-up questionnaire		10/01/2005
Copy of Questionnaire	2 Pharmacy Staff	12/01/2005	12/01/2005
Copy of Questionnaire	2 Recruitment Questionnaire Consumer		10/01/2005
Copy of Questionnaire	2 one week follow-up questionnaire		10/01/2005
Letters of Invitation to Participants	2 Customer		10/01/2005
Letters of Invitation to Participants	2 letter to Pharmacist		10/01/2005
Participant Information Sheet	2 Consumer Information Sheet		10/01/2005
Participant Consent Form	2 User Consent Form		10/01/2005
Participant Consent Form	2 health care providers consent form		10/01/2005
Response to Request for Further Information		10/01/2005	10/01/2005
Other	2 Flow Chart		10/01/2005
Other	2 one-week follow up questionnaire cover letter		10/01/2005
Other	2 one week Ginkgo sales record sheet	12/01/2005	10/01/2005
Other	2 SOP A		10/01/2005
Other	2 SOP B		12/01/2005
Other	2 Pharmacy Letter		10/01/2005
Other	2 Pharmacy Information Sheet		10/01/2005
Other	2 Participation Form		10/01/2005
Other	2 Consumers' views on the ginkgo study Introduction		10/01/2005
Other	2 cover letter 6 month		10/01/2005

	follow-up questionnaire participants		
Other	2 follow-up questionnaire letter week x Consumer		10/01/2005

Management approval

The study should not commence at any NHS site until the local Principal Investigator has obtained final management approval from the R&D Department for the relevant NHS care organisation.

Membership of the Committee

The members of the Ethics Committee who were present at the meeting are listed on the attached sheet.

Notification of other bodies

The Committee Administrator will notify the research sponsor that the study has a favourable ethical opinion.

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees (July 2001) and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

04/Q0201/41	**Please quote this number on all correspondence**

With the Committee's best wishes for the success of this project,

Yours sincerely,

Mrs Bridget Vickers
Chair

E-mail: andreas.marcou@bhsha.nhs.uk

Enclosures *List of names and professions of members who were present at the meeting and those who submitted written comments*

Standard approval conditions

Site approval form (SF1)

Enclosure 1

List of names and professions of members who were present at the meeting and those who submitted written comments

Mrs Bridget Vickers
Lay Chair

Mr Michael Buck
Lay Member

Dr Richard Dent
Consultant Thoracic Physician

Ms Margaret Eames
Statistician

Dr Anthony C Flind
Lay Member

Mr Gavin Ross
Lay member

Dr Mark Slater
Consultant Psychiatrist

Dr Mark Tanner
Consultant Psychiatrist

Ms Patricia Wilson
Senior Nurse Lecturer

Hertfordshire Local Research Ethics Committee

LIST OF SITES WITH A FAVOURABLE ETHICAL OPINION

For all studies requiring site-specific assessment, this form is issued by the main REC to the Chief Investigator and sponsor with the favourable opinion letter and following subsequent notifications from site assessors. For issue 2 onwards, all sites with a favourable opinion are listed, adding the new sites approved.

REC reference number:	04/Q0201/41	**Issue number:**	1	**Date of issue:**	20 January 2005
Chief Investigator:	Dr Joanne Barnes				
Full title of study:	A Pilot Study of community pharmacy bases pharmacovigilance of an over the counter herbal medicine Ginkgo (Ginkgo Biloba)				

This study was given a favourable ethical opinion by Hertfordshire Local Research Ethics Committee on 19 January 2005. The favourable opinion is extended to each of the sites listed below. The research may commence at each NHS site when management approval from the relevant NHS care organisation has been confirmed.

Principal Investigator	Post	Research site	Site assessor	Date of favourable opinion for this site	Notes [1]
Single Site application N/A	Single Site application N/A	N/A Host Organization not specified in database.	Hertfordshire Local Research Ethics Committee	20/01/2005	

Approved by the Chair on behalf of the REC:

..... (Signature of ~~Chair~~/Administrator*)

(*~~delete~~ as applicable)

Andrea Marcu... (Name)

[1] *The notes column may be used by the main REC to record the early closure or withdrawal of a site (where notified by the Chief Investigator or sponsor), the suspension of termination of the favourable opinion for an individual site, or any other relevant development. The date should be recorded.*

Study Protocol

A Pilot Study of Community-Pharmacy Based Pharmacovigilance of an Over-the-counter Herbal Medicine Ginkgo (*Ginkgo biloba*)

Aim:

The primary aim of this pilot project is to develop and assess the feasibility of a community-pharmacy—based method for pharmacovigilance of herbal medicines purchased over-the-counter (OTC), using ginkgo (*Ginkgo biloba*) products, for oral use as a model. The project's secondary aims are to describe the patterns of use and self-reported symptoms occurring during oral use of ginkgo products, purchased from community pharmacies.

Research Questions:

The specific research questions the study will explore are:

What is the response rate among community pharmacies in Hertfordshire invited to participate in the study?

What is the recruitment rate among purchasers of ginkgo identified in participating pharmacies and invited to take part in the study, for each of the two recruitment methods employed?

Is a greater consumer recruitment rate achieved through direct involvement of pharmacy staff or passive involvement by simply providing consumers with study documentation?

What are the reasons for and patterns of use of ginkgo purchased in pharmacies?

Can adverse event data for products containing the herbal ingredient ginkgo (*Ginkgo biloba*) be collected systematically from consumers using a community-pharmacy—based method of recruitment?

What is the frequency and types of adverse events that are self-reported by users of ginkgo purchased in pharmacies?

What are the pharmacists' and participating consumers' views towards this type of study?

Study design

This pilot project is an observational cohort study involving adult purchasers of oral preparations of the herbal medicine ginkgo (*Ginkgo biloba*) from participating community pharmacies in Hertfordshire. There is an experimental component to the recruitment phase of the study in that participating pharmacies will be randomised to use recruitment method A or B (see *Recruitment of consumer cohort* below).

Methods

Recruitment of pharmacies

Addresses and address labels for all community pharmacies (around 200) in Hertfordshire will be obtained from the RPSGB. The owner/pharmacy manager of all such pharmacies will be sent information about the study and an invitation to participate. The National Pharmaceutical Association (St Albans, Hertfordshire), RPSGB local branches in Hertfordshire, and the *Pharmaceutical Journal* will be approached to request assistance in encouraging participation. The project aims to recruit at least 50 pharmacies (participation rate of 25%); this is considered achievable on the basis that similar previous studies have achieved a participation rate of almost 50%.

Each participating pharmacy will be asked to record over a one-week period all sales of ginkgo products (including multi-ingredient preparations containing ginkgo) made from their pharmacy counter and requested to nominate a shop-floor pharmacist to oversee the running of the study. Each nominated pharmacist will be required to attend a training meeting at which the study will be discussed in detail and training materials provided; it is planned that three such meetings will be held in different locations in Hertfordshire (e.g. Watford, St Albans, Welwyn Garden City). They will also be directed to train their pharmacy staff, including any locum pharmacists, in the study procedures.

Characteristics of participating pharmacies (e.g. location, type of outlet) will be obtained in the pharmacy recruitment questionnaire. Based on this information, participating pharmacies will be stratified on location of pharmacy (urban, rural) and type of pharmacy (independent, small multiple, large multiple) before being randomly allocated to recruitment method A or B (see *Recruitment of consumer cohort* and *Sample size* below) using a computer-generated randomisation list. If insufficient pharmacies agree to participate in the study, stratification on both location and type of pharmacy may not be possible, in which case only location of pharmacy will be used. Participating pharmacies will be provided with a study pack containing all documentation required for their

method of consumer recruitment [standard operating procedures; training card; consumer recruitment packs; study reminder labels; diary to record any consultations with customers relating to ginkgo or with respect to the study and to record if any records have been made on the PMR system on the sale of a ginkgo preparation; logbook to record all sales of ginkgo and other details etc]. Pharmacies will be telephoned to ensure receipt of the pack and to answer any queries, and will be sent a faxed or telephone reminder to start consumer recruitment on the specified date. Recruitment will continue until 1050 consumers have been recruited (see *Sample size* below) or until the end of the recruitment period (8 weeks).

At the end of the consumer recruitment period, pharmacy staff from participating pharmacies will be invited to attend a focus group to provide their views on recruitment for the study and any other relevant issues. These data will then be used to develop a short questionnaire which will be distributed to all pharmacy staff involved in the study.

All participating pharmacies will be entered into a prize draw (one prize of books worth £250 from the Pharmaceutical Press) in recognition of staff time spent in consumer recruitment. However, entry into the draw will not be dependent on the number of consumers recruited.

Recruitment of consumer cohort

Similar previous studies involving purchasers of a conventional OTC medicine (ibuprofen) have found that consumer recruitment was highest using a method requiring greater pharmacy input;[15] however, it cannot be assumed that this will also apply to purchasers of an OTC herbal medicine.

Thus, two methods will be tested for consumer recruitment: A) consumers purchasing a ginkgo product will be approached directly by pharmacy staff, or B) materials regarding the study (Consumer information sheet, consent form, recruitment questionnaire, and reply-paid envelope) will be given to consumers with their ginkgo purchase. In each case, pharmacy staff will keep records of all ginkgo products sold to adult purchasers [sex; whether forms were handed out and reason if not; time taken with the potential research participant] and the number of forms given out. Where pharmacy staff are directly involved (method A), staff will explain the study to consumers meeting the inclusion criteria, distribute a consumer recruitment pack, and invite those interested in taking part to complete the consent form and recruitment questionnaire. Eligible consumers who prefer to complete the form off the pharmacy premises will be permitted to do so. Inclusion criteria for consumers are: those purchasing a ginkgo product; age 16 years or over; ability to give written informed consent. Proxy purchases will be included in the study provided the intended user meets

all other inclusion criteria - the purchaser will be asked to give the consumer information sheet, consent form and recruitment questionnaire to the intended user for completion. Existing and previous users will also be included in the study, provided that they meet all the other inclusion criteria. For existing users, the date when they first started taking ginkgo will be asked and taken into consideration during analysis.

All study documents will be returned to the study team. During the consumer recruitment phase, as part of quality assurance, a random check will be made on 10% or 10 of the participating pharmacies (whichever is the greatest) to ensure that procedures are being followed. Participating pharmacies will be informed at the beginning of the study that this may occur.

Study documentation and procedures

The consumer information sheet will describe the study team, explain the aim and procedures of the study, and advise consumers to consult their GP or pharmacist if their symptoms persist, if they experience new symptoms that concern them (i.e. they should behave as they usually would) or if they have any concerns about the ginkgo product they have purchased. To ensure data confidentiality, each consumer recruitment pack will be coded with a unique number for each participating pharmacy and for each set of forms, and this number will be used for the participant throughout the study. The consent form will include the usual statements regarding data confidentiality, freedom to withdraw from the study at any time etc. The recruitment questionnaire will request consumer details (gender, name and address etc), information on the ginkgo purchase (product details: name, manufacturer, type of preparation, batch number etc), and where the form was completed. Copies of forms used in a previous study have been obtained and were used to assist in the design of the questionnaires to be used in the proposed study. The authors of the previous study will be acknowledged in any publications arising from the proposed study as agreed.[20] All forms and questionnaires have been piloted on several lay individuals known to us (mostly non-academic staff at the School of Pharmacy), to identify any problems with comprehension, and amendments have been made in accordance with their comments.

Once completed recruitment documents (consent form and recruitment questionnaire) have been received by the study team and eligibility has been confirmed, the consumer will be considered to be enrolled in the study. They will be sent a signed copy of the consent form to keep and a one-week follow up questionnaire which will seek information on previous medical history and use of health services for six months before the ginkgo purchase, usage of the ginkgo product purchased as well as any other medication and supplements taken, any symptoms experienced, opinion as to

which symptoms (if any) were related to use of ginkgo, and use of health services. If a participant reports consulting their GP, pharmacist, or any other healthcare provider, with respect to a specific symptom/side effect experienced, they will be contacted by post to seek permission to contact and obtain details of the healthcare provider concerned with the consultation. Similar questionnaires (excluding questions on previous medical history etc) will be sent at 4 weeks, 3, 6 and 12 months following the initial purchase. Non-responders will be telephoned after 2 and 4 weeks and/or sent a duplicate copy of the questionnaire as necessary.

If a participant has consulted their GP, pharmacist or any other healthcare provider and, where written consent is given, the healthcare provider will be contacted to confirm details of the consultation, and to ascertain whether or not they submitted a yellow card report of a suspected adverse drug reaction to the CSM/MHRA. MHRA will be contacted in an attempt to confirm that any such yellow card reports were received. We will contact the relevant individual at the CSM/MHRA with anonymous details of these suspected adverse drug reactions in an attempt to confirm whether or not the CSM/MHRA did actually receive these yellow card reports.

At the end of the study, all participants (including any study withdrawals) will be asked about their willingness to attend a focus group meeting to provide their views on the study. Depending on the number of volunteers, a range of individuals (different ages, sex) will be invited to attend a focus group session. It is intended that 8 focus groups with an invited number of 8 research participants per session (target of 6 attending to take into account for last minute withdrawals) to take place.

Sample size

As this is a feasibility study, a sample size calculation is not relevant. However, the aim will be for 21 consumers to be enrolled through each pharmacy,† providing a total target sample of 1050 consumers (i.e. 50 pharmacies x 21). With a sample of this size, the study will have 95% power to detect a difference of 10% in recruitment between the two methods (i.e. 55% vs 45% of subjects recruited by different methods; 2-tailed).

† In practice, recruitment rates are likely to vary between pharmacies, so once the 1050th consumer has been enrolled by the study team or at the end of the 8 week recruitment period, pharmacies will be informed that recruitment has ended and will be directed to return any study materials to the study team. If any consent and recruitment forms are still 'live' [i.e. given out by pharmacy staff but not yet received by the study team], these consumers will still be accepted into the study once completed forms are received.

Although this is not based on the 'cluster' design, the numbers are approximately valid. An approximate sample size calculation based on clustering has been carried out, but as reliable data on recruitment rates for individual pharmacies are not available in the context of a study involving a herbal medicine, the approximation above has been used.

Given resource limitations, and the pilot nature of this study, recruitment will be closed once 1050 participants are enrolled or at the end of 8 weeks from the start of recruitment, whichever is the sooner.

Data analysis

Data will be input by AA; checks data entry for 5% of the study participants, selected at random will be made by JB. Data will be stored and analysed using SPSS version 12 or STATA version 8 for Windows. All hard copies of study documentation and computer data will be stored to protect consumer confidentiality.

Descriptive statistics for the cohort will be calculated. Recruitment and response rates for methods A and B (number of recruitment packs given out/number of completed forms received by the study team) and other categorical variables will be compared using the Chi-squared test. Continuous variables will be compared using appropriate statistical methods.

Patterns of ginkgo use will be presented descriptively. Comparisons between male/female, and between older/younger consumers may be relevant, in which case categorical/continuous variables will be compared as described above. Frequency and types of adverse events occurring during/after ginkgo use will be presented. Cases of inappropriate use of ginkgo [e.g. concurrent use with medicines potentially interacting with ginkgo] will be described. Data on previous medical history, concurrent medication, symptoms experienced and use of health services will be presented descriptively. Qualitative data on pharmacists' and participants' views on the study will be explored using content analysis.

[Name]
[Address]
[Address]
[Address]
[Address]

[Our ref]
[Date]

Dear.....

Ginkgo Study

The School of Pharmacy at the University of London, is conducting a pilot study to assess the feasibility of a community-pharmacy-based method for monitoring the safety of herbal medicines purchased over-the-counter (OTC), using ginkgo (*Ginkgo biloba*) products, for oral use, as a model.

As the owner/manager of this pharmacy, we are writing to ask if you are willing for your pharmacy and its staff to be involved with this study. We appreciate you are a busy professional with many demands on your time, but the involvement of your pharmacy is crucial for the success of this study.

The study has been specifically designed to minimize the level of work required by participating pharmacies. Pharmacists and pharmacy counter staff will only be involved with recruiting consumers into the study, as all further follow-up will be carried out by us. Time required will therefore be kept to a minimum and participating in the study should not disrupt usual activities.

As a small incentive all pharmacies who participate in the study will be entered into a prize draw to win £250 worth of books from the Pharmaceutical Press.

I have enclosed an information sheet which contains further details about the study. If after reading this, you are interested in participating I would be grateful if you could complete the enclosed form and nominate a shop floor pharmacist (this could be yourself) to oversee the management of the study. A reply-paid envelope is enclosed for your reply.

If you would like any further information about the study or have any further questions please contact me.

Thank you for your time

Anjana M. Aggarwal MPharm MRPharmS

Tel: 0207 753 5893
Email: anjana.aggarwal@ulsop.ac.uk

Enclosures:
Study information sheet
Participation form
Reply-paid envelope

Version 2

The School of Pharmacy
University of London

Ginkgo Study

PHARMACY INFORMATION SHEET

We would like to invite your pharmacy to take part in this pilot study. This sheet is provided to give you more information about the purpose of the study and what it will involve. If there is anything that is not clear, or if you would like more information, please contact the study investigator Miss Anjana Aggarwal (details at the end of the leaflet).

1. What is the purpose of the study?

Increasingly patients and the public are using herbal medicines as well as, or instead of conventional medicines for the prevention and treatment of illness. The perception that these products are natural and safe is in part responsible for their popularity.

Alongside the widespread use of herbal medicines there have been several high-profile public health concerns about their safety. In 2000, evidence emerged of drug interactions between St John's wort (*Hypericum perforatum*) and certain prescription medicines and, in 2003, reports emerged of liver problems, including liver failure associated with the use of kava (*Piper methysticum*).

At present, the identification of herbal safety concerns relies heavily on spontaneous reporting systems such as the Committee on Safety of Medicines (CSM)/Medicines and Healthcare products Regulatory Agency's (MHRA) yellow card scheme for suspected adverse drug reaction (ADR) reporting. However, the scheme has well recognised limitations, particularly under-reporting of suspected ADRs. For several reasons, under-reporting of suspected ADRs associated with herbal medicines is likely to be greater compared to conventional medicines. In addition, the yellow card does not lend itself well to collecting data on suspected ADRs associated with herbal medicines, as important information (e.g. plant part used, type of preparation) are not requested.

Against this background, there is a clear need to develop new methods for monitoring the safety (pharmacovigilance) of herbal medicines. The aim of this study is to assess the feasibility of a community pharmacy based method for the pharmacovigilance of herbal medicines purchased over-the-counter, using ginkgo (*Ginkgo biloba*) products for oral use, as a model. We have chosen to use ginkgo, not because of any specific concerns about its effects, but because it is a popular herbal medicine, used for a variety of conditions, and as it is widely available from community pharmacies.

2. How have I been selected?

For a certain period of time, we are inviting all community pharmacies in Hertfordshire to take part in this study. In total, we aim to recruit at least 50 community pharmacies. Names and addresses have been obtained from the RPSGB, although the RPSGB otherwise is not involved with this study.

3. Do I have to take part?

It is for you to decide whether or not you are willing for your pharmacy and its staff to be involved with this study. If you do not want to take part in this study, please indicate this on the enclosed form. If you do decide to take part in the study, details of what you need to do next are provided in section 10.

4. What does the study involve?

If you are willing for your pharmacy and its staff to be involved in this study, and if your pharmacy meets the inclusion criteria, please complete the enclosed form and return it to me in the reply paid envelope provided.

Each participating pharmacy will be asked to record over a one-week period all sales of ginkgo products (including multi-ingredient preparations containing ginkgo) made from their pharmacy counter and requested to nominate a shop-floor pharmacist to oversee the running of the study.

Each nominated pharmacist will be required to attend a training meeting at which the study will be discussed in detail and training materials provided; it is planned that three such meetings will be held in different locations in Hertfordshire (e.g. Watford, St Albans, Welwyn Garden City). They will also be directed to train their pharmacy staff, including any locum pharmacists, in the study procedures.

On completion of this, all participating pharmacies will be stratified on location of pharmacy (urban, rural) and type of pharmacy (independent, small multiple, large multiple) before being randomly allocated to one of two recruitment methods: A) consumers purchasing a ginkgo product will be approached directly by pharmacy staff, or B) materials regarding the study (consumer information sheet, consent form, recruitment questionnaire, and reply-paid envelope) will be given to consumers with their ginkgo purchase. In each case, pharmacy staff will keep records of all ginkgo products sold to adult purchasers [sex; whether forms were handed out and reason if not; time taken with the potential research participant] and the number of forms given out. Where pharmacy staff are directly involved (method A), staff will explain the study to consumers meeting the inclusion criteria, distribute the study documents, and invite those interested in taking part to complete the consent form and recruitment questionnaire.

Participating pharmacies will be provided with a study pack containing all documentation required for their method of consumer recruitment. Pharmacies will be telephoned to ensure receipt of the pack and to answer any queries, and will be sent a faxed or telephone reminder to start consumer recruitment on the specified date. Recruitment will continue until 1050 consumers in total across all participating pharmacies have been recruited or until the end of the recruitment period (8 weeks).

At the end of the consumer recruitment period, pharmacy staff from participating pharmacies will be invited to attend a feedback meeting to provide their views on recruitment for the study and any other relevant issues.

5. What are the possible disadvantages of taking part?

Some time will be required in training all members of staff and in implementing the study procedures. However, this study has been specifically designed to minimise the level of work required by participating pharmacies, as all consumer follow-up will be carried out by the study investigators.

In addition, as a result of this study, it is possible that more advice on ginkgo or herbal medicines may be sought by customers.

6. What are the benefits of taking part?

The results of this study will help us to assess whether or not this method could be useful in monitoring the effects of herbal medicines. Therefore, if your pharmacy and its staff takes part, they will be contributing to research that may have some benefits for the public health. In addition, your pharmacy's involvement in the study may help you to consider its current practices regarding herbal medicines and the training provided may help your staff increase their knowledge and awareness of this area.

7. Will my taking part in this study be kept confidential?

All the information you give us will be treated confidentially, and the requirements of the Data Protection Act will be followed at all times.

8. What will happen to the information collected during the study?

If you agree for your pharmacy and its staff to be involved in this study, all data provided will be accessed only by the study team. The data may be inspected by other authorised individuals, such as a representative from the ethics committee that approved the study, to ensure that the study is being carried out correctly. Individual staff names or your pharmacy's name, however, will not be identified in the event of this.

You may notice that we have coded each form with a number. This identification code is used solely for the purposes of administering the study. Once the data have been entered on to our computer system it will not be possible to identify or link personal medical information with participants names. All documents received will be stored securely in the research office and will be archived securely at the end of the study. We are required to keep our records for a defined period of time.

We aim to publish the results of the study in a reputable scientific journal. No details will be revealed from which you could be identified. A copy of a summary of the findings will be sent to all study participating pharmacies.

9. Who has reviewed the study?

Ethical approval to carry out this study was granted by the Hertfordshire Local Research Ethics Committee on 20 January 2005. Research management and governance approval was granted by the Hertfordshire PCTs on 25 April 2005.

10. What should I do now?
Thank you for considering taking part in this study. Please could you complete the enclosed form and return it to us in the reply-paid envelope provided.

9. Contact for further information
If you would like to discuss the study in more detail, please contact the **study investigator**;

Miss Anjana M. Aggarwal
Centre for Pharmacognosy and Phytotherapy
School of Pharmacy
University of London
29/39 Brunswick Square
London WC1N 1AX

Telephone: 0207 753 5800 ext 4837; **Mobile:** 07748962323; **E-mail:** anjana.aggarwal@ulsop.ac.uk

ID code: 250-02-a

Ginkgo Study

PARTICIPATION FORM

Please take a couple of minutes to answer the questions below.

1. *In BLOCK CAPITALS* provide the following details about yourself;

a) Title and name:.....

b) Position in the pharmacy:.....

2. Does your pharmacy sell herbal medicines?

Yes ☐ No ☐ *[If no - thank you, we cannot include your pharmacy in the study. Please go to question 6]*

3. Does your pharmacy sell any herbal products for oral use containing ginkgo (*Ginkgo biloba*)?

Yes ☐ No ☐ *[If no - thank you, we cannot include your pharmacy in the study. Please go to question 6]*

4. Are you willing for your pharmacy to take part in this study?

Yes ☐ No ☐ *[If no - thank you. Please answer questions 6 - 8]*

***5. In BLOCK CAPITALS* provide the following details of the nominated shop floor pharmacist who will oversee the management of the study (if different from above):**

a) Title and name:.....

b) Position (job title) in the pharmacy:.....

6.How many of the following staff does your pharmacy currently employ? [*If none, please enter nil*]

	Full-time	Part-time		Locum
		Weekday	Weekend	
Pharmacists				
Dispensing technicians				
Healthcare assistants/counter staff				

7. How would you describe the LOCAL setting of your pharmacy? [*Tick one only*]

Rural ☐ Urban ☐

8. Which of the following types of pharmacy would you use to describe your pharmacy? [*Tick one only*]

Independent ☐ Small multiple ☐ Large multiple ☐

Thank you for your time. Please return this form in the reply-paid envelope provided

Miss AM Aggarwal MPharm MRPharmS & Dr J Barnes BPharm PhD MRPharmS FLS
Centre for Pharmacognosy & Phytotherapy, School of Pharmacy, University of London, 29/39 Brunswick Square, London WC1N 1AX, UK

The School of Pharmacy
University of London

Dear Customer

The School of Pharmacy at the University of London, is conducting a study to monitor the use of an over-the-counter herbal medicine, ginkgo, (also known as *Ginkgo biloba*); the study involves collecting information directly from people who have bought ginkgo.

As you have bought a product containing ginkgo we are inviting you to take part in this research study. The enclosed information sheet provides full details as to why the study is being done and what it will involve.

If after reading the information sheet you are interested in participating, then please complete the enclosed consent form and recruitment questionnaire. These forms should take less than 10 minutes to complete. Once they have been completed please return them to The School of Pharmacy (not to the pharmacy where you bought ginkgo) in the reply-paid envelope provided.

If you require any further information about the study, please contact me.

Thank you for your time

Yours sincerely

Anjana M. Aggarwal MPharm MRPharmS

Telephone number: 0207 753 5989
Mobile number: 07748962323
Email address: anjana.aggarwal@ulsop.ac.uk

Enclosures:
Consumer information sheet
Consent form
Recruitment questionnaire
Reply-paid envelope

The School of Pharmacy
University of London

CONSENT FORM

Title of Project:
Ginkgo Study

Name of Researchers:
Miss Anjana M Aggarwal
Dr Joanne Barnes

TO BE COMPLETED BY THE USER OF THE GINKGO PRODUCT

PLEASE INITIAL BOX

1. I confirm that I have read and understood the consumer information sheet dated January 2005 (version 2) for the above study, have had the opportunity to ask questions and that any questions have been answered satisfactorily. ☐
2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason and without this affecting any future treatment. ☐
3. I understand that I will be asked to complete further questionnaires during the next 6 months. ☐
4. The Hertfordshire Local Research Ethics Committee has approved this study and may wish to inspect sections of the data collected. I give permission for authorised individuals to have access to my data if necessary. ☐
5. I understand that all information that I provide will be kept confidential and that my identity will be kept anonymous at all times. ☐
6. I agree to take part in the above study. ☐

Name of participant	Date	Signature
Researcher	Date	Signature

Please return this form with the recruitment questionnaire in the reply-paid envelope provided.
A photocopy of this form will be posted to you for you to keep.
Thank you for your time

FOR OFFICE USE ONLY:

ID Code: ☐☐☐-☐☐☐☐-☐☐-☐
Date received: ...../...../.....

The School of Pharmacy
University of London

Ginkgo Study

CONSUMER INFORMATION SHEET

As you have bought a product containing ginkgo we are inviting you to take part in this research study. Before you decide whether or not you wish to take part, it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and feel free to discuss it with your family and friends, and your GP or pharmacist, if you wish. If there is anything that is not clear, or if you would like more information, please ask the study investigator Miss Anjana Aggarwal (details at the end of the leaflet).

1. What is the purpose of the study?

Many people in the UK use herbal medicines to maintain health and to help treat a wide range of different conditions.

Many people assume that herbal medicines are entirely safe as they originate from plants, a natural source. However, like other medicines, herbal medicines can have adverse effects (sometimes called 'side effects') and can interact with certain conventional medicines. While many people who take herbal medicines do not experience any adverse effects, some people may experience new symptoms or side effects. Therefore, as with all medicines, there is a need to monitor the effects of herbal medicines during and after use.

Furthermore because herbal medicines are usually bought over-the-counter without the need to consult a doctor or pharmacist, usual ways of monitoring the effects of medicines such as through a GP or community (high-street) pharmacist, are not always possible for herbal medicines.

Therefore, the aim of this study is to explore whether it is possible to collect information on the effects of herbal medicines directly from people using them. In the study, we are monitoring the use of ginkgo products bought from community pharmacies. We have chosen to use ginkgo, not because of any specific concerns about its effects, but because it is a popular herbal medicine, used for a wide range of conditions, and as it is widely available from community pharmacies.

2. Why have I been chosen?

For a certain period of time, we are inviting every customer above the age of 16, who buys a ginkgo product from this pharmacy to take part in this study. Several other pharmacies in Hertfordshire are also involved in the study and, in total, we aim to recruit 1050 participants.

3. What does the study involve?

If you do decide to take part in the study, and if you meet the inclusion criteria you will need to complete the enclosed consent form and recruitment questionnaire and return them to us in the reply-paid envelope provided. Once we have received these forms we will check that you are eligible to take part in the study and, if so, send you a copy of the consent form for you to keep.

Over the next 6 months we will then send you 4 questionnaires to fill in and return to us. These will be sent at intervals of approximately; 1 week, 4 weeks, 3 and 6 months from now. Each questionnaire should take around 20 minutes to complete. You will be asked for information on the following areas:

- Previous medical history and use of health services for the six months before you bought ginkgo (first questionnaire only)
- Usage of the ginkgo product bought
- Usage of any other medication and supplements taken
- Any symptoms experienced
- Use of health services (e.g. whether you consulted your GP)

It is important that each questionnaire is completed as fully as possible. However, we do understand that you may be unable to answer certain questions or, there may be questions that you do not wish to answer.

If you consult a GP, pharmacist or any other healthcare provider during the study, we may need to contact them for further information. If this occurs, we will contact you by post to obtain your permission to contact the healthcare provider concerned. If you give us your permission, we will ask the healthcare provider for information on the consultation and any action taken by them.

At the end of the study you will be invited to take part in a focus group meeting to put forward your views regarding the study.

4. What are the possible disadvantages and risks of taking part?

Some time will be required to complete the questionnaires. This has been kept to a minimum as the questionnaires have been designed to skip over questions that are not applicable for each individual completing the questionnaire and most of the questions are tick box styled.

Regarding ginkgo itself, available evidence suggests that products containing ginkgo are usually well tolerated when taken at recommended dosages. However, like other medicines, ginkgo may not be suitable for every individual. It is generally recommended that individuals planning to take a herbal medicine or a non-prescription medicine should consult their GP and/or pharmacist, particularly if taking conventional medicines, or if they have any serious existing diseases. As you have bought a product containing ginkgo, you may have already discussed with your GP or pharmacist whether it is suitable for you.

If you do have any concerns about using ginkgo, either now or whilst taking it, it is important that you discuss them with your GP or pharmacist. As with all medicines, if your symptoms persist, or if you experience any new symptoms that cause you concern, you should contact your GP or pharmacist as soon as possible.

5. What are the benefits of taking part?

The results of this study will help us to assess whether or not this method could be useful in monitoring the effects of herbal medicines. Therefore, if you take part, you will be contributing to research that may have some benefits for the public health. In addition, during the study you may find that completing the questionnaires helps you to consider whether or not ginkgo is helping you.

6. Do I have to take part?

It is for you to decide whether or not you would like to take part in this study – your participation is completely voluntary. If you do decide to take part in the study, details of what you need to do next are provided in section 10. If you take part and then decide you do not wish to continue in the study, you are free to withdraw at any time without giving a reason (although it would be useful for us if you can) and without it affecting any treatment you receive now or in the future. If you do not want to take part in the study, you do not need to take any further action.

7. Will my taking part in this study be kept confidential?

All the information you give us will be treated confidentially, and the requirements of the Data Protection Act will be followed at all times.

8. What will happen to the information collected during the study?

If you agree to take part in the study your data will be accessed only by the study team. The data may be inspected by other authorised individuals, such as a representative from the ethics committee that approved the study, to ensure that the study is being carried out correctly. Your name, however, will not be identified in the event of this.

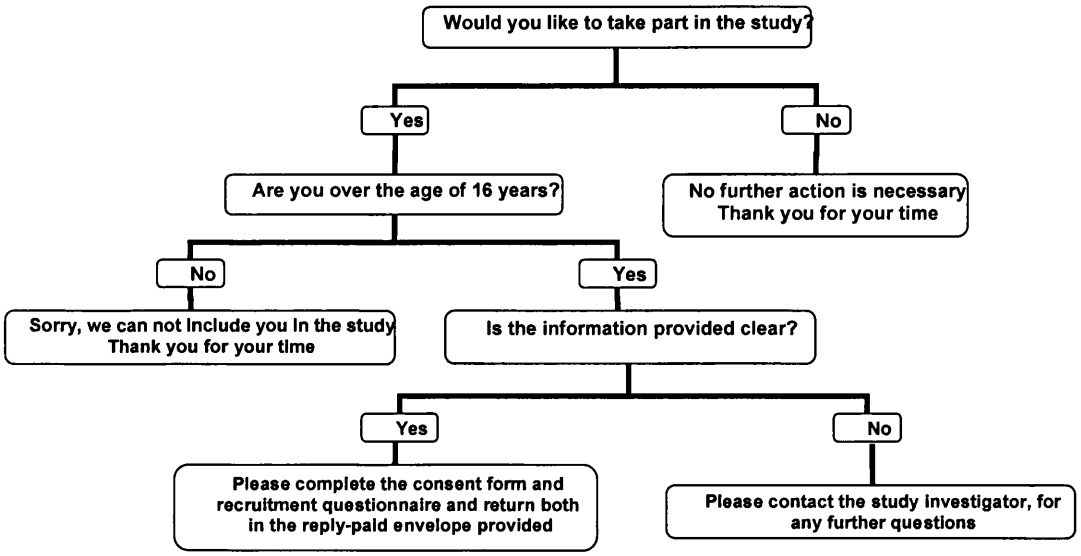
You may notice that we have coded each form with a number. This identification code is used solely for the purposes of administering the study. Once the data have been entered on to our computer system it will not be possible to identify or link personal medical information with individual participants' names. All documents received will be stored securely in the research office and will be archived securely at the end of the study. We are required to keep our records for a defined period of time.

We aim to publish the results of the study in a reputable scientific journal. However, no details will be revealed from which you could be identified. A copy of a summary of the findings will be sent to all study participants.

9. Who has reviewed the study?

Ethical approval to carry out this study was granted by the Hertfordshire Local Research Ethics Committee on 20 January 2005. Research management and governance approval was granted by the Hertfordshire Primary Care Trust on 25 April 2005.

10. What should I do now?



11. Contact for further information

If you would like to discuss the study in more detail, please contact the **study investigator;**

Miss Anjana M. Aggarwal
Centre for Pharmacognosy and Phytotherapy
School of Pharmacy
University of London
29/39 Brunswick Square
London WC1N 1AX

Telephone: 0207 753 5989; **Mobile**: 07748962323; **E-mail**:anjana.aggarwal@ulsop.ac.uk

ID Code: GGG-GGGG-GG-G

Ginkgo Study

RECRUITMENT QUESTIONNAIRE

Please answer the questions below in BLOCK CAPITALS

1. Provide the following details about the ginkgo product you have just purchased:

Date purchased	
Brand/full name	
Manufacturer's name	
Batch number [*this can be denoted by BN or LOT*]	
Expiry/use by/best before date [*circle as appropriate*]	

2. What type of product is it?

Tablets ☐ Liquid/tincture ☐ Capsules ☐ Other [*specify*]................................☐

3. What is the ginkgo strength of the product? [***This information should be on the pack and on the patient leaflet (if there is one), under the 'active ingredients/constituents', or just 'ingredients' section***]

For tablets or capsules: .... mg ginkgo per tablet/capsule [*circle as appropriate*]
For liquid or tincture: .... mg ginkgo in .... mls/drop [*circle as appropriate*]
For others [*specify*]: ....

4. Did you go to the pharmacy in person to purchase the ginkgo product?

Yes ☐ No ☐ [*someone else bought them for my use*]

5. Provide the following details about yourself:

Title: ” ” ” ” **Surname:** ” ” ” ” ” ” ” ” ” ” ” ” ” ” ” ” ” ”

Sex (M/F): ” **Forename:** ” ” ” ” ” ” ” ” ” ” ” ” ” ” ” ” ” ”

Address: ”

” ”

Postcode: ” ” ” ” ” ” ” ” ” ” ” **Date of birth:** Day ” ” / Month ” ” / Year ” ” ” ”

Telephone: Area code ” ” ” ” ” ” Number ” ” ” ” ” ” ” ” ” ” ” ”

Ethnic group e.g. White, Chinese etc:...

6. Did you complete this form in the pharmacy? Yes ☐ No ☐

7. Date of completing this questionnaire: ....

Please return this questionnaire and the consent form in the reply-paid envelope provided.
Thank you for your time.

Miss AM Aggarwal MPharm MRPharmS & Dr J Barnes BPharm PhD MRPharmS FLS
Centre for Pharmacognosy & Phytotherapy, School of Pharmacy, University of London, 29/39 Brunswick Square, London WC1N 1AX, UK

[Name]
[Address 1]
[Address 2]
[Address 3]
[Address 4]

[Date]

[Our ref]

Dear [Surname]

RE: Ginkgo Study

Please find enclosed your one-week follow-up questionnaire with regard to the above study. The questionnaire asks for information on your recent purchase of ginkgo and on your health and use of health services.

Please complete the questionnaire as carefully and completely as possible. This should take around 20 minutes. If there is anything that is not clear, or if you have any questions, please contact me.

Once you have completed the questionnaire please return it in the reply paid envelope provided. All information will be treated confidentially.

I have also enclosed a signed copy of your consent form for you to keep.

Thank you for taking part in this study.

Yours sincerely

Anjana M. Aggarwal

Telephone number: 0207 753 5893
Email address: anjana.aggarwal@ulsop.ac.uk

Enclosures:
Consent form
One week follow-up questionnaire
Reply-paid envelope

ID code ☐☐☐-☐☐☐-☐☐-☐

Ginkgo Study

One Week Follow-up Questionnaire

These questions relate to your recent purchase of a ginkgo product, and your experiences for the first seven days after buying the product. Please answer all the questions as indicated below, as completely as possible. We do understand that you may be unable to answer certain questions or, there may be questions that you do not wish to answer. Once you have completed the questionnaire please return in the reply-paid envelope provided.

Thank you for taking part in this study.

SECTION A: THESE QUESTIONS RELATE TO USE OF GINKGO IN THE PAST

1a. Had you ever taken ginkgo before you made your recent purchase of ginkgo?

No ☐ → [If no, go to Q3a]

Yes ☐

1b. When did you first start to take ginkgo?

...../...../.....
(Day) (Month) (Year)

2a. Were you already taking ginkgo when you made your recent purchase?

No ☐

Yes ☐ → [If yes, go to Q2c]

2b. When did you did you stop taking ginkgo?

...../...../.....
(Day) (Month) (Year)

2c. How frequently did you take ginkgo before your recent purchase? [Tick one box only in each table]

Once	
Twice	
3 times	
4 times	
Other [specify]	

per

Day	
Week	
Month	
Year	
Other [specify]	

SECTION B: THESE QUESTIONS RELATE TO YOUR RECENT PURCHASE OF GINKGO

If you are already taking ginkgo or have previously taken ginkgo please refer to your purchase this time round.

3a. Did anyone recommend ginkgo to you, or advise you to buy ginkgo?

No ☐ → [If no, go to Q4]

Yes ☐

3b. Who recommended/advised you to use ginkgo? [Tick the main one only and then go to Q5a]

Friend/relative	☐	Health food store staff	☐
Hospital doctor	☐	Herbal medicine practitioner (herbalist)	☐
GP/family physician	☐	Complementary/alternative practitioner [specify below]	☐
Hospital pharmacist	☐	.....	
Community (high-street) pharmacist	☐	Other [specify below]	☐
Pharmacy counter staff	☐	.....	

4. How did you choose to use ginkgo? [Tick the main reason which applies]

I knew somebody else using it	☐	I was already taking it	☐
I saw it advertised	☐	Other [specify below]	☐
By browsing	☐	.....	

5a. Did you ask for advice or information from any of the following healthcare professionals/providers specifically about using ginkgo? [Tick all that apply]

Type of healthcare professional	At the time of this purchase	Previously	Since purchasing it
Hospital doctor	☐	☐	☐
GP/family physician	☐	☐	☐
Hospital pharmacist	☐	☐	☐
Community (high-street) pharmacist	☐	☐	☐
Pharmacy counter staff	☐	☐	☐
Health food store staff	☐	☐	☐
Herbal medicine practitioner (herbalist)	☐	☐	☐
Nobody	☐	☐	☐
Other [specify]	☐	☐	☐

5b. What information did you ask for and who from?

Information requested	Type of healthcare professional/provider e.g. doctor

6a. Did you buy ginkgo to use for a specific symptom, medical condition or health reason?

No ☐ → [If no, go to Q7]

Yes ☐

6b. For which specific symptom, medical condition or health reason did you buy ginkgo? [Tick the main one only]

Poor circulation	☐	Colds/flu	☐	Sexual problems	☐
To improve my memory	☐	Back pain	☐	General well being	☐
High blood pressure	☐	Headaches	☐	For no specific reason	☐
Alzheimer's disease	☐	Asthma	☐	Other [specify below]	☐
Tinnitus	☐	Diabetes	☐	.....	
To combat ageing	☐	Insomnia	☐	.....	

6c. How long have you had this symptom, medical condition or health reason?

.....days/weeks/months/years [circle one] Not applicable ☐

7. What was the main reason you chose the particular ginkgo product that you recently purchased? [Tick one only]

Saw it advertised	☐	Cheapest product available	☐
Already using it	☐	Easy to use formulation eg easy to swallow	☐
Only one in stock	☐	Known brand/manufacturer	☐
Attractive packaging	☐	Better quality than the other brands	☐
The product is standardised	☐	Product is a licensed preparation	☐
Recommended by the pharmacist	☐	Other [specify below]	☐
Recommended by the Pharmacy counter staff	☐	.....	
Most expensive product available	☐	.....	

SECTION C: THESE QUESTIONS RELATE TO YOUR CURRENT USE OF GINKGO

8a. Have you started to take the ginkgo product that you recently purchased?

Yes ☐ → [If no, go to Q9]

No ☐

8b. If no, why not? [Tick the main reason only]

I am finishing off my old pack	☐	[Go to Q9]
I have not got round to taking it yet	☐	[Go to Q11]
The problem went away by itself, so I decided not to take it	☐	[Go to Q11]
I was advised not to take it [specify by who below]	☐	[Go to Q11]
.....		
I changed to a different medicine [specify name of medicine below]	☐	[Go to Q11]
.....		
Other [specify below]	☐	[Go to Q11]
.....		

9. How often did you take ginkgo on each of the 7 days following your purchase? [Complete for each day - write 'none' if you did not take any ginkgo that day]

Day	Tablets/Capsules	Liquids/Tinctures	
	Total number taken	Quantity/Volume taken	Unit e.g. mls/drops
1			
2			
3			
4			
5			
6			
7			

10a. Are you still taking ginkgo?

Yes ☐ → [If yes, go to Q11]

No ☐

10b. On what date did you stop taking ginkgo?

...../...../.....
(Day) (Month) (Year)

10c. What was the main reason you stopped taking ginkgo? [Tick the main reason only]

I kept on forgetting to take it	☐	I did not feel well after taking it	☐
I found it too expensive	☐	I was advised not to take it [specify by who below]	☐
I felt it wasn't helping me	☐	.....	
I heard it was bad for you	☐	Other [specify below]	☐
My problem went away	☐	.....	

10d. Would you use ginkgo again? [Tick one box only]

Yes	☐	[Go to Q10e]
Not sure	☐	[Go to Q11]
No	☐	[Go to Q11]

10e. What for?

The same condition	☐
For another condition	☐
Not sure	☐

PLEASE GO ON TO THE NEXT PAGE

SECTION D: THESE QUESTIONS RELATE TO YOUR GENERAL HEALTH

11. With regard to the specific symptom, medical condition or health reason for which you purchased ginkgo, indicate whether or not you think it has improved or became worse since then. [Tick one box only]

Much worse	Worse	No change	Improved	Much improved	Don't know	Not applicable
☐	☐	☐	☐	☐	☐	☐

12a. In the month before your recent purchase of ginkgo, did you experience any symptoms e.g. headaches, diarrhoea etc?

No ☐ → [If no, go to Q13a]

Yes ☐

12b. What symptoms did you experience during/ in the month before your recent purchase of ginkgo? [For each symptom state when it started, whether or not you reported it to anyone, who you reported it to, if applicable, and whether or not you are still experiencing the symptom]

Symptom	Date when this symptom started?			Did you report this symptom to anyone ? (✓)		Who did you report this symptom to?	Are you still experiencing this symptom? (✓)	
	Day	Month	Year	Yes	No		Yes	No

[continue on reverse or on a separate sheet if necessary]

13a. Did you experience any new symptoms or side effects in the first 7 days after your recent purchase of ginkgo? [Answer this question even if you did not take or have stopped taking ginkgo]

No ☐ → [If no, go to Q14a]

Yes ☐

13b. What <u>new</u> symptoms/side effects did you experience? [For each symptom/side effect specify when it started, whether or not you reported it to anyone about it, who you reported it to, if applicable, and whether or not you thought the symptom/side effect was related to the use of ginkgo if applicable].

Symptom/side effect	Date when this symptom started?		Did you report this symptom to anyone ? (✓)		Who did you report this symptom to?	Do you think it is related to your use of ginkgo? (✓)		
	Day	Month	Yes	No		Yes	No	Not sure

[continue on reverse or on a separate sheet if necessary]

14a. Did you visit/consult any of the following healthcare professionals in the <u>six months before</u> your recent purchase of ginkgo? [Answer each line]

Type of healthcare professional	Did you visit/consult them?		How often did you visit/consult them?	For what reason(s) did you consult/visit them?
	Yes (✓)	No(✓)		
Hospital doctor				
GP				
Hospital Pharmacist				
Community Pharmacist				
Traditional Chinese Medicine Practitioner				
Homeopath				
Herbalist				
Other complementary/ alternative healthcare professional				

15a. Have you ever been diagnosed (by a doctor) with any medical conditions?

No ☐ → [If no, go to Q16a]

Yes ☐

15b. What are your existing medical conditions?

Medical condition e.g. diabetes	When were you diagnosed (by a doctor) with this condition?		
	Day	Month	Year

[continue on reverse or on a separate sheet if necessary]

16a. During the last 12 months, have you experienced any significant medical events e.g. heart attack?

No ☐ → [If no, go to Q17a]

Yes ☐

16b. During the last 12 months, have you experienced any of the following medical events? [Answer each line]

Medical event	Yes (✓)	No (✓)	When did this event occur?		
			Day	Month	Year
Heart attack					
Stroke					
Bleeding stomach ulcer					
Other bleeding episode					
Blood clot in the lungs (Pulmonary embolism)					
Deep vein thrombosis					
Loss of consciousness					

16c. If you have experienced any other significant medical events over the last 12 months, list them here. [If none, write none]

Medical event	When did this event occur?		
	Day	Month	Year

[continue on reverse or on a separate sheet if necessary]

17a. Are you currently taking any medicines prescribed for you by your doctor?

No ☐ → [If no, go to Q18a]

Yes ☐

17b. List all of your prescribed medicines:

Name of medicine	What type of the product is it? e.g. tablet, cream	What is the strength of the product? e.g. 75 mg, 1%	How often do you take or use it? e.g. every day	What are you using it for?	When did you start taking it?		
					Day	Month	Year

[continue on reverse or on a separate sheet if necessary]

18a. Are you currently taking any other medicines, remedies or supplements, including any you've bought from a pharmacy, health-food store or elsewhere e.g. over the internet? [Include all herbal or homeopathic remedies, vitamins and minerals, dietary supplements etc.]

No ☐ → [If no, go to Q19a]

Yes ☐

18b. List all of your other medicines, remedies or supplements that you are currently taking:

Brand/full name	What is the formulation of the product? e.g. tablets	What is the strength of the product? e.g. 75 mg, 1%	How often do you take or use it? e.g. every day	What are you using it for?	When did you start taking it?		
					Day	Month	Year

[continue on reverse or on a separate sheet if necessary]

SECTION E: THESE QUESTIONS RELATE TO YOUR GENERAL LIFESTYLE

19a. Do you smoke tobacco?

No ☐ [If no, go to Q20a] Yes ☐

19b. Specify below how many you smoke on average per day:

..... cigarettes/cigars/pipe [delete as appropriate]

20a. Do you drink alcohol?

No ☐ [If no, go to Q21a] Yes ☐

20b. Specify below how many units you consume on average per week:

.....units [1unit = ½ pint of standard strength beer, lager or cider
= 1 pub measure (25ml) of spirits
= 1 small glass (125ml) of wine]

21a. What is the highest level of education you have achieved?

To secondary school level or below ☐
Some education after secondary school, but not higher education ☐
Higher education or more ☐

21b. What is your total annual household income (your income plus that of your partner/spouse, if applicable)?

<£10k ☐ £10k to £20k ☐ >£20k to £35k ☐ >£35k ☐

21c. What are your and, if applicable, your partner's/spouse's occupations? [If you or your partner/spouse are unemployed, retired, housewife etc. write this in the relevant box]

Your occupation	Partner's/Spouse's occupation

21d What is your marital status? [Tick the one that most closely matches]

Single (never married) ☐ Separated/divorced ☐
Cohabiting ☐ Other [specify below] ☐
Married ☐ .....

SECTION F: THIS QUESTION IS FOR FEMALES ONLY. IT REQUESTS SOME FURTHER INFORMATION WHICH IS USEFUL FOR US

22. Do any of the following currently apply to you?

	No	Yes		
Pregnant	☐	☐	⇨ When is the baby due:	......../........./............
Breast feeding	☐	☐	⇨ When was the baby born:	......../........./............
Going through menopause	☐	☐	⇨ When was your last period:	......../........./............
Post menopausal	☐	☐	⇨ When was your last period:	......../........./............

SECTION G: OTHER RELEVANT INFORMATION

23. We would welcome any further information you would like to provide or comments about the study:

24a. Are you currently involved in any other research studies?

No ☐ [If no, go to Q25] Yes ☐

24b. If yes, please provide the following details:

Name of the study	
Who is running the study?	

25. If any of your contact details are incorrect on the accompanying letter or need updating please write your correct details below:

Title (Mr etc): ☐☐☐☐

Surname: ☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐

Forename: ☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐

Address: ☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐
☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐

Postcode: ☐☐☐☐ ☐☐☐☐☐☐

Area code Number

Telephone: ☐☐☐☐☐☐ ☐☐☐☐☐☐☐☐☐☐☐

25. Date of completing this questionnaire: ..../.............../.............
(Day) (Month) (Year)

Thank you for completing this questionnaire
Please return this questionnaire in the envelope provided

Miss AM Aggarwal MPharm MRPharmS & Dr J Barnes BPharm PhD MRPharmS FLS
Centre for Pharmacognosy & Phytotherapy, School of Pharmacy, University of London,
29/39 Brunswick Square, London WC1N 1AX, UK

APPENDIX VII
LIST OF PUBLICATIONS

1. Barnes J, Aggarwal AM. Spontaneous reporting of ADRs associated with herbal medicines: final results of a cross sectional survey of national pharmacovigilance centres. Pharmacovigilance of Herbal Medicines: Current State and Future Directions 2006. Abstract published in Drug Safety 2006; 29 (4): 359.

2. Aggarwal AM, Barnes J. A pilot study of Community-Pharmacy-Based Pharmacovigilance of an Over –the-Counter Herbal Medicine Ginkgo (*Ginkgo biloba*): Methodological Issues from Work in Progress. Pharmacovigilance of Herbal Medicines: Current State and Future Directions 2006. Abstract published in Drug Safety 2006; 29 (4): 358.

3. Barnes J, Aggarwal AM. An assessment of undergraduate pharmacy students' knowledge of spontaneous reporting for suspected ADRs associated with herbal medicinal products. International Society of Pharmacovigilance 2004. Abstract published in Drug Safety 2005; 28 (10): 943.

4. Barnes J, Aggarwal AM, Morzaria J. Trends in teaching of pharmacognosy and related subjects: a cross-sectional study of UK schools of pharmacy. BPC 2005. JPP 2005; 57 (supplement): 33 [abstract]

5. Barnes J, Aggarwal AM. Spontaneous reporting of ADRs associated with herbal medicines: a cross-sectional survey of national pharmacovigilance centres. International Society of Pharmacovigilance 2004. Abstract published in Drug Safety 2004; 27(12):917.

6. Frassetto LA, Thai T, Aggarwal AM, Bucher P, Jacobsen W, Christians C, Benet LZ, Floren LC. Pharmacokinetic interactions between cyclosporine and protease inhibitors in HIV+ subjects. Drug Metab Pharmacokin 18(2):114-120, 2003.