



Ethics and pharmaceutical medicine – the full report of the Ethical Issues Committee of the Faculty of Pharmaceutical Medicine of the Royal Colleges of Physicians of the UK

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SUMMARY

The practice of pharmaceutical medicine brings with it ethical challenges and dilemmas often very different from those encountered in the practice of clinical medicine. Having established a framework of guiding ethical principles, this report aims to look in some detail at specific areas of possible ethical concern to pharmaceutical physicians, offering practical advice and guidance on good practice. The report covers issues related to pharmaceutical research, including dissemination of research findings, communication

with other health professionals and patients and involvement of pharmaceutical physicians and companies in the provision of patient services. The primacy of the interests of patients and the wider public is emphasised, and the possible impact of new developments in pharmaceutical technology is explored. It is hoped that the report will help those working in pharmaceutical medicine and act as a stimulus for wider discussion and debate.

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1. INTRODUCTION

1.1 The ethical issues faced by medical practitioners are many and varied. The Faculty of Pharmaceutical Medicine (hereafter referred to as the Faculty) recognises that there are ethical issues which are of particular relevance to pharmaceutical physicians and believes that it has a responsibility to define and publish standards to which pharmaceutical physicians and others can refer.

1.2 This report draws attention to the particular ethical issues which face doctors practising within the discipline of pharmaceutical medicine. It deals, principally, with those issues which might face a pharmaceutical physician whether he or she is practising within a company, a contract research organisation, an academic department, a regulatory authority or acting as an independent consultant to any of the above, and seeks to offer guidance and support to members of the Faculty and others.

1.3 The Faculty recognises that there is a need for an international ethics network, involving pharmaceutical physicians working within the pharmaceutical and biotechnology industry, academic institutions and regulatory agencies. There is an

increasing need to take account of the progress achieved within therapeutics, the work already achieved by others in the field of bio-ethics and the texts already published.

1.4 Pharmaceutical physicians are essential members of the teams working throughout the life cycle of a therapeutic intervention, from the discovery research phase, through pre-clinical and clinical testing, licensing, launching, postmarketing studies and surveillance, new formulation and new indications work, through to its eventual demise whether on grounds of relative safety and efficacy or commercial non-viability. Being members of a team, there is an understandable tendency for pharmaceutical physicians to develop a strong interest in an intervention with which they have had a long or close association. Despite this, pharmaceutical physicians should recognise their ethical responsibility to stand aside from product loyalty when assessing factors affecting the product itself. They must remain aware at all times that the ultimate interests of both patients and their own employers are best served by an objective scientific attitude. The Faculty recognises that this may place a practising pharmaceutical physician in a position which demands considerable determination.

1.5 All clinical development activities and medical support services must be provided by appropriately trained individuals working to agreed standards in adequately staffed departments with clear responsibility and authority to take the necessary decisions. Ideally, professional accreditation of pharmaceutical physicians is an essential element of the demonstration of appropriate training in pharmaceutical

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medicine. As in all branches of medicine, accreditation should not be seen as a single event but is refreshed by continuing professional development to ensure that knowledge, skills and attitudes are current. Revalidation of pharmaceutical physicians is only one objective means of maintaining best practice. It should not replace personal responsibility and pride in professional standards.

1.6 Pharmaceutical physicians have a duty to apply standards of scientific rigour and to provide quality information wherever they may be working, be it in research, registration, marketing or as independent consultants. This includes those working with products such as herbal medicines, infant formulae and nutraceuticals, as well as those engaged in traditional pharmaceutical and biotechnology companies, the production of generic products or within academic departments or regulatory authorities.

1.7 The users of healthcare products are not necessarily aware of the costs and complexities involved in the development and registration of a therapeutic intervention and of the issues which may arise throughout its life cycle. Pharmaceutical physicians have a responsibility to raise awareness and understanding of the different pressures and constraints governing healthcare products.

1.8 This report therefore sets out a number of ethical issues which affect pharmaceutical physicians throughout their working lives, grouped by topic.

2. CLINICAL RESEARCH

2.1 General Issues

2.1.1 All those involved in the conduct of research on human subjects have a responsibility to put the interests of their patients first. It is unethical to change from an effective treatment to a trial medication unless there are sound medical reasons for doing so, approval is obtained from a research ethics committee, the appropriate explanation is given to any trial subject and consent obtained.

2.1.2 There are many guidelines on the conduct of studies to Good Clinical Practice (GCP) standards. These guidelines refer extensively to the scientific and ethical review procedures considered essential for the conduct of clinical trials. It is the responsibility of pharmaceutical physicians to ensure that these standards are constantly upheld. Pharmaceutical physicians should be completely familiar with all the principles and procedures of the current international GCP guidelines. They should in addition be completely familiar with any regional or local guidelines applicable to their intended study sites.

2.1.3 Medical ethics does not yet feature prominently in the syllabuses of all medical schools throughout the world, yet it is increasingly recognised as important. It follows that training in ethics in pharmaceutical medicine is itself important for all pharmaceutical physicians, healthcare professionals,

research ethics committee members and others involved in the research and development of therapeutic agents. The study and practice of research ethics should ideally start during undergraduate training and continue thereafter. The inclusion of ethics in undergraduate study provides a basis of understanding of the issues that will confront both the healthcare professional temporarily involved in clinical research and the future full-time professional researcher. The principle of universal access to standards of care would ideally become entrenched in basic medical practice and not just an issue to be considered in the context of therapeutic research. The Faculty strongly recommends that ethics should be included in the various training courses provided for individuals seeking recognition as a pharmaceutical physician, for example by gaining membership of the Faculty of Pharmaceutical Medicine in the United Kingdom. (www.fpm.org.uk).

2.1.4 Whilst recognising that the ethical review process should follow guidance set out in the current international GCP guidelines, it has to be accepted that the variability of the application of this process for clinical research country-by-country is considerable.

2.1.5 Although the implementation and day to day running of studies in a clinical research programme may well be delegated to a clinical scientist or other member of the investigational team, the ultimate responsibility should remain with the pharmaceutical physician. This person may typically be located within an organisation sponsoring the studies, for example a pharmaceutical company, a contract research organisation or an academic institution.

2.1.6 Prior to the start of a clinical trial, the pharmaceutical physician in overall charge has a duty of care to ensure the selection of appropriate investigators for the task in hand. In this regard, the training of investigators is particularly important, and it is essential that doctors who offer themselves as investigators for the conduct of clinical trials are recognisably trained to appropriate levels. It is equally important that experienced investigators, their staff and facilities adhere to GCP standards.

2.1.7 A clear statement should be made of the sponsor's policy with regard to the handling of suspect data, including the commitment to take appropriate action should evidence show beyond reasonable doubt that data has been falsified with an intent to deceive. Pharmaceutical physicians have a responsibility to ensure that no undue pressure is put on any investigator to meet deadlines. Sponsors should have a policy and standard operating procedure in place relating to the management of suspected fraud, with which all staff should be familiar. Furthermore, sponsors must clearly demonstrate their commitment to implementing the policy, if occasion demands.

2.1.8 Pharmaceutical physicians have an ethical responsibility to ensure that sufficient data are generated to allow the safe and effective use of a therapeutic intervention. Sometimes this

may mean that further studies are conducted beyond those needed solely for regulatory requirements.

2.1.9 A clinical trial cannot be ethically justified unless it is capable of generating scientifically valid results. Care should be taken to ensure study design and statistical methodologies are appropriate to the clinical stage of investigation. The pharmaceutical physician should take steps to ensure that the sensitivity of the trial, that is the ability to distinguish between an effective and a non-effective treatment, ensures that the trial may be expected to yield a meaningful answer to the hypothesis being tested. Ideally, subjects should be enrolled in randomised and controlled clinical trials to maximise the likelihood of obtaining useful and reliable results. The choice of comparator should be based upon best medical and regulatory practice, and any significant deviation from this principle should be discussed and agreed with the research ethics committee and institutional review board. All studies must be methodologically sound, and the inappropriate use of comparators, either qualitatively or by dose, is to be avoided.

The pharmaceutical physician must be clear in his/her mind on the primary end-points that will eventually determine the clinical indication and ultimately the regulatory claim. They must be clear whether the trial design is to test the equivalence, non-inferiority or superiority of the test product against the comparator, that the statistical

methodology is appropriate to the needs of the trial and that *a priori* decisions are maintained upon completion of the research.

2.1.10 Pharmaceutical physicians should ensure that studies involve placebos only when it is ethically appropriate to do so, recognising regulatory, scientific and patient support group pressures. A placebo control arm in a clinical trial may be ethically justified when no adequate, proven prophylactic, diagnostic or therapeutic method exists. The reasons for using placebos should be clearly stated and drawn to the attention of research ethics committees and institutional review boards.

Subjects participating in a control group within a clinical trial should receive an established and effective treatment unless:

- The risk of using a placebo is ethically acceptable.
- An effective and established treatment does not exist.
- The temporary withholding of an effective treatment would not expose the subjects to serious risk.
- There is no added risk of long-term harm.

The use of an established treatment in the control arm may prejudice the likelihood of obtaining a clear answer as to the potential benefit of an experimental therapy. In such cases, the use of placebo should not expose the subject to serious risk or potential long-term harm.

Placebo treatment should only be administered in the context of a properly randomised and controlled clinical

BOX 1

Existing Relevant Organisations

American Medical Association: <http://www.ama-assn.org>

Association of British Pharmaceutical Industry: ABPI: <http://www.abpi.org>

Biovision: <http://www.bivision.org>

Council for International Organizations of Medical Sciences/CIOMS: www.cioms.org

Council of Europe (COE): www.coe.int.org

EU National Authorities: <http://heads.medagencie.org>

European Commission (EC): <http://europa.eu.int>

European Consumer Group: <http://beuc.org>

European Federation of Pharmaceutical Industry Associations (EFPIA): <http://www.efpia.org/>

European Medicines Agency (EMA): <http://emea.eu.int>

Faculty of Pharmaceutical Medicine of the Royal Colleges of Physicians of the United Kingdom: www.fpm.org.uk

Food and Drug Administration (FDA): <http://www.fda.gov>

International Conference on Harmonization/ICH: www.ich.org

International Federation Pharmaceutical Manufacturers Associations/IFPMA: <http://www.ifpma.org>

Medical Research Council (MRC): <http://www.mrc.ac.uk/>

Medicine and Healthcare products Regulatory Agency (MHRA): <http://www.mhra.gov.uk>

Medlineplus (National Library of Medicine): <http://www.medlineplus.gov>; nlm.nih.gov

National Institute for Clinical Excellence (NICE): <http://www.nice.gov.uk>

National Institute of Health (NIH): <http://www.nih.gov>

PhRMA: <http://www.phrma.org>

Royal College of Physicians of Edinburgh: <http://www.rcpe.ac.uk/>

Royal College of Physicians of Glasgow: <http://www.rcpsglas.ac.uk/>

Royal College of Physicians of London: <http://www.rcplondon.ac.uk/>

The General Medical Council, United Kingdom: <http://www.gmc-uk.org/index.htm>

World Health Organization (WHO) (Main Office & European Office): <http://www.who.ch> & <http://www.who.dk>

World Medical Association (WMA): <http://www.wma.net>

trial to maximise the likelihood of obtaining statistically and clinically meaningful results. The use of placebo in diseases or conditions that may be associated with significant morbidity and/or mortality requires careful evaluation. The decision not to use an active comparator and/or a 'universal' standard of care must be justified and agreed with the research ethics committee, local stakeholders and the study participants.

2.1.11 Conducting therapeutic or prophylactic research in a resource-poor region of the world, where a universal standard of care for a serious disorder is not available, raises important questions regarding trial design and the use of placebo control as well as access to treatment outside or after the conclusion of the research. The proposed research should be responsive to the healthcare needs of the population or group from where the research participants are to be recruited. Careful evaluation of local medical practice and agreement with the local stakeholders and research ethics committee should be obtained prior to the initiation of the research in a population which is resource-poor and does not have access to a universal standard of care. The inclusion of a 'universal' standard of care in the control arm of a clinical trial may invalidate the trial regarding the relevance of the results to local healthcare practice. In these circumstances, a local research ethics committee may approve the use of a local treatment standard in the control arm even when it is known that a superior therapeutic option exists elsewhere.

There is a significant body of opinion that states that where an effective and proven treatment exists, the use of anything less in the control arm of a clinical trial cannot be justified on the basis of lack of patient access to treatment in a country or region of the world. There is an ethical concern that subjects in resource poor countries might be exploited in the drive to contain costs and more efficiently develop new drugs for use in the industrialised world. An alternative to the placebo-controlled trial is the equivalency trial design. This design evaluates whether an experimental treatment intervention is equivalent to a local standard of care. This trial design is more appropriate when a local standard of treatment has previously been defined and proven beneficial. It would be unwise to attempt to extrapolate the results of these local trials to other patient populations or to make comparisons to 'universal' standards of care evaluated elsewhere in the world.

The particular type of ethical dilemma illustrated above can be avoided by conducting work that is unambiguously relevant for the population of people involved as research subjects. Therefore, the sponsor and the research ethics committee should ensure that the clinical trial design and the choice of the comparator address local needs and are appropriate to the condition being studied and local conditions.

Pharmaceutical physicians should ensure that research ethics committees are provided with all relevant information to enable them to make a considered judgement on the ethics

of any given research protocol. They should encourage local research ethics committees to fulfil their important role of assessing the suitability of the local facilities and of the investigator to conduct any given study according to the proposed protocol and time scale. Payment for studies must be totally transparent and revealed to research ethics committees. The recipient should be identified, be it the investigator, the academic department, the hospital institute or whomsoever. There is nothing ethically wrong in providing payment so long as it can be justified by reference to guidance provided by a recognised body. Remuneration in the form of shares in a sponsoring company is a controversial issue which raises a specific ethical dilemma, given that even if the arrangement is transparent, the question of a damaging conflict of interest may arise. The guidance of the ethical committee or institutional review board should be requested.

2.1.12 Pharmaceutical physicians should also be aware of the possible conflict of interest faced by researchers who own shares in a company developing a product and who may therefore be tempted to report their findings in a stock-market-friendly manner. Any conflict of interest must be disclosed to the ethics committee or institutional review board concerned.

2.1.13 With regard to indemnity and compensation in the clinical trial context, pharmaceutical physicians should ensure that policies which safeguard the interests of the research subjects are clearly in place (for example the ABPI compensation guidelines in the UK). The applicability of 'no fault' compensation to human pharmacology phase I studies, and of product liability status to therapeutic use studies, should be routine.

2.1.14 There are major differences in attitudes throughout the world regarding payment to patients participating in clinical trials. There is no international agreement on such payments, but local guidelines may well exist, and the ethic committee or institutional review board concerned should certainly be informed and consulted. It is the responsibility of pharmaceutical physicians to ensure that patients are not inappropriately induced to take part in clinical studies.

2.2 Human Pharmacology (Phase I) Studies

2.2.1 When non-patient volunteers are recruited into human pharmacology or phase I studies, such individuals must be provided with summaries of all important and relevant findings on the therapeutic interventions concerned, whether they come from a company or academic institution or from elsewhere. Where volunteers are recruited from among employees of a sponsoring body, or among students, ethical safeguards must be in place to ensure that they are not exploited, coerced or inappropriately remunerated. Care should be taken to ensure that there is no perceived conflict of interest between those who design studies, including human pharmacology or Phase I studies, and the teams responsible for their

BOX 2**Existing Relevant Documents and Guidelines**

- ABPI. Clinical trials – developing new medicines. 2003
- ABPI. Introduction to the work of ethics committees. Second edition 2002. Council for International Organizations of Medical Sciences (CIOMS). *International Ethical Guidelines for Biomedical Research Involving Human Subjects*. Revised Edition. Geneva 2002.
- Association of the British Pharmaceutical Industry (ABPI). The Code of Practice for the Pharmaceutical Industry. 2003
- Council for International Organizations of Medical Sciences (CIOMS). *International Guidelines for Ethical Review of Epidemiological Studies*. Geneva 1991.
- Council of Europe. *Convention for the Protection of Human Rights and Dignity of the Human Being with Regard to the Application of Biology and Medicine: Convention on Human Rights and Biomedicine*. European Treaty Series – no. 164. Oviedo, 4 April 1997.
- Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use. *Official Journal* L121 34–44, 1 May 2001.
- Ethical Principles for Research Involving Human Subjects*. Adopted by the 18th World Medical Assembly, Helsinki, Finland, June 1964. Amended by the 29th World Medical Assembly, Tokyo, Japan, October 1975; the 35th World Medical Assembly, Venice, Italy, October 1983; the 41st World Medical Assembly, Hong Kong, September 1989; the 48th General Assembly, Somerset West, Republic of South Africa, October 1996; the 52nd General Assembly, Edinburgh, Scotland, October 2000; and Note of Clarification on Paragraph 29 added by the WMA General Assembly, Washington 2002.
- European Agency for the Evaluation of Medicinal Products (EMA). *Report of the EMA Workshop on Ethical Considerations in Clinical Trials*. London, 26 November 2001.
- European Commission, Detailed Guidance on the Application Format and Documentation to Be Submitted in the Application for an Ethics Committee Opinion on the Clinical Trial on Medicinal Products for Human Use [Brussels, April 2003: ENTR/F2/BLD (2003) Final]
- European Forum for Good Clinical Practice. *European Guidelines for Auditing Independent Ethics Committees*. Brussels: EFGCP, 2002.
- European Forum for Good Clinical Practice. *Guidelines and Recommendations for European Ethics Committees*. Revised Edition. Brussels: EFGCP, 1997.
- EuroSOCAP. *European Guidelines on Confidentiality and Privacy among Vulnerable Patient Populations*. Brussels: European Commission, expected 2005.
- Fluss, Sev S. *International Guidelines on Bioethics: Informal Listing of Selected International Codes, Declarations, Guidelines, etc. on Medical Ethics/Bioethics/Health Care Ethics/Human Rights Aspects of Health*. 2nd Revised Edition. Salve 2. Supplement to *The EFGCP News*, Autumn 2000.
- International Conference on Harmonization of Technical Requirements for the Registration of Pharmaceuticals for Human Use (ICH). *Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95)* 1 May 1996.
- Medical Research Council, United Kingdom. *MRC Guidelines for Good Clinical Practice in Clinical Trials*. London, 1998
- Ministry of Health, Labour & Welfare: <http://www.mhlw.gov.jp>
- Nuffield Council on Bioethics. Pharmacogenetics: ethical issues. 2003
- Nuffield Council on Bioethics. Stem cell therapy: ethical issues. 2000
- Nuffield Council on Bioethics. The ethics of research related to healthcare in developing countries. 2002
- Pharmaceutical Research & Manufacturers of America (PhRMA). *Principles on the Conduct of Clinical Trials and the Communication of Clinical Trial Results*. Washington, DC, July 2002.
- Royal College of Paediatrics and Child Health. Guidelines for the ethical conduct of medical research in children. *Arch Dis Child* 2000; **82**: 177–182
- Royal College of Physicians of London, Guidelines on the Practice of Ethics Committees in Medical Research involving Human Subjects. 1997
- Royal College of Physicians of London. Report on Relationships between Physicians and the Pharmaceutical Industry. 1986
- Royal College of Physicians of London. Report on Research Involving Humans. 1990
- The National Commission for the Protection of Human Subjects of Biomedical and Behavioural Research (Office of the Secretary, Department of Health, Education, & Welfare; United States), *The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research*. Washington, DC, 18 April 1979
- UNAIDS, *Ethical Considerations in HIV Preventive Vaccine Research*. Geneva, 2000.
- UNESCO, *Declaration on Universal Norms in Bioethics*. Paris, expected 2005.
- UNESCO, *The Universal Declaration on the Human Genome*. Paris: UNESCO, 1997.
- World Health Organization (TDR/WHO). *Operational Guidelines for Data & Safety Monitoring Boards* (expected 2004). Geneva: World Health Organization.
- World Health Organization (TDR/WHO). *Operational Guidelines for Ethics Committees That Review Biomedical Research*. Geneva: WHO, 2000.
- World Health Organization (TDR/WHO). *Operational Guidelines for the Development of Botanical Medicines* (expected 2005). Geneva: World Health Organization.
- World Health Organization (TDR/WHO). *Surveying and Evaluating Ethical Review Practices*, a companion guideline to the TDR WHO *Operational Guidelines for Ethics Committees That Review Biomedical Research* (2002). Geneva: World Health Organization.
- World Health Organization (WHO). Guidelines for Good Clinical Practice (GCP) for Trials on Pharmaceutical Products. Annex 3 of *The Use of Essential Drugs*. Sixth Report of the WHO Expert Committee. Geneva: World Health Organization, 1995: 97–137.
- World Medical Association, *Declaration of Helsinki*.

implementation. Independent ethics committee approval and relevant regulatory approval are required for all clinical studies.

2.3 Vulnerable Patient Groups

There is need for both sponsors and pharmaceutical physicians to evaluate medicinal products in populations where there may be the potential for significant off-label use. This is particularly relevant to the young and the elderly where the initial confirmatory clinical trials used for registration may not have included these subjects. The commitment to investigate the efficacy and safety of medicines in different patient populations may include sponsorship from either industry or the public sectors. The pharmaceutical physician is ideally placed to consider the needs of the patient in collaboration with the prescribing physician, regulatory agencies and patient advocacy groups. Sponsors should consider the potential for off-label use early on in the development of a new product and, where appropriate, include clinical studies in special populations to maximise the potential for rational prescribing that takes account of broad patient interests and needs.

These groups include but are not limited to children, pregnant or lactating mothers, the elderly, the mentally handicapped, those with terminal or life-threatening disease, those who are socially or economically disadvantaged or any condition or circumstance where informed consent may not be obtained easily. This also applies to non-therapeutic trials without direct benefit to the patients involved, for example those with cancer, those with chronic diseases including severe hepatic or renal impairment and the commonly acquired neurodegenerative disorders.

The ethical position regarding the use of special and vulnerable patient groups in clinical research should be clearly understood. The inclusion of such individuals in clinical research should address problems specific to the medical needs in these special populations, which might have altered pharmacokinetic disposition, efficacy and safety or prescribing practices.

Where a therapeutic intervention is being developed for use in children, studies involving children should normally follow those conducted in adults, unless the condition is unique to children, and/or the availability of an experimental treatment may be considered lifesaving. Where a therapeutic agent is not intended for use in children, paediatric studies must not be conducted. Any information available on off-label use in children should be available on request to doctors and pharmacists with a legitimate interest. The pharmaceutical physician should ensure that, where there is a likelihood that children will need treatment with a medicinal product being developed for an adult indication, those needs are addressed by the sponsor early on in the development process.

Obtaining informed consent from a parent or guardian should not substitute for appropriate explanation to the research subject, and the recording of verbal assent whenever possible. The sponsor and pharmaceutical physician have a special duty to ensure that the inclusion of the disadvantaged or special populations in clinical research is fully justified.

2.3.1 Research in disadvantaged populations. Pharmaceutical physicians should be aware of their ethical responsibilities towards patients taking part in clinical trials in disadvantaged populations wherever they might be found in the world. They should take particular note of the ethnic, social, public health and economic conditions prevailing in the areas or populations concerned at the time, when any form of clinical research is being considered. Ideally, externally sponsored research should fit within established healthcare priorities within the disadvantaged population being considered. As always, review by an independent research ethics committee and local stakeholders is essential for such studies.

The pharmaceutical physician should ensure that the research fulfils the ethical and scientific standards required of the sponsor both in the area where the work is to be conducted and in resource-richer areas of the world, and that the work will be of relevance to the participating individual volunteers or their society. In therapeutic research, the standard of care should be defined in consultation with those who work in the population. The level of care offered to research participants should, as a minimum, be the standard that is provided normally to them. However, when a resource-poor area either does not provide care or cannot afford care, the researcher may need to consider the provision of treatment within a clinical trial and continuing therapy upon completion of the study.

2.3.2 Orphan indications and off-label prescribing of medicines. A particular ethical dilemma arises with regard to orphan indications and to orphan therapeutic interventions. There are some rare conditions for which it is clear that there will never be a viable commercial return on investment. In such circumstances, the intervention may also not be assessable using the normal criteria. The pharmaceutical physician may make the ethical decision that on balance it is better to recommend that the intervention be made available than to deny anyone who might benefit from it. However, where this may lead to significant off-label use, the pharmaceutical physician has a duty to promote discussion between the sponsor and the regulatory agency regarding any clinical trial that would be required to ensure the safe use of a medicinal product in a limited indication.

The above should not be confused with the off-label prescription of medicines. Neither the sponsor nor the pharmaceutical physician should promote the off-label use of medicines. In the event of increased off-label prescribing, pharmaceutical physicians have an ethical responsibility to

consider and monitor any safety issues which may arise from such off-label use. They should ensure that such use is not encouraged either by omission or by commission. They should also ensure that the sponsor re-evaluates in a timely manner the need to conduct additional clinical research which may eventually lead to changes in the original label for that product.

2.4 Therapeutic Use Studies (formerly also known as Phase IV studies) and Postmarketing Surveillance

2.4.1 Once a therapeutic intervention has reached the stage where it is available for prescription use, pharmaceutical physicians have an ethical responsibility to ensure that any studies they design, either as observational postmarketing surveillance studies or therapeutic use (Phase IV clinical) trials, will provide useful information regarding appropriate use in real-life situations.

2.4.2 Pharmaceutical physicians have an important ethical responsibility to ensure that no marketing exercise should ever masquerade as a scientific study, be it a Phase IV clinical trial or an observational postmarketing surveillance study. With regard to the nature of such studies, those responsible for current guidelines should pay due regard to the need for guidance on hypothesis generation and confirmation. Thus studies should not be set up to confirm a hypothesis which is scientifically unsound.

2.4.3 In all areas of postmarketing surveillance, it is essential that the handling of observational databases and extracting of, interpretation, documentation and reporting from them be of the highest standard, and pharmaceutical physicians have an ethical responsibility in this regard.

2.4.4 If, despite the approval that will have been given to any study by a relevant research ethics committee, a pharmaceutical physician comes across any potentially unethical study being conducted by another person, that doctor should contact the sponsor of the study to point out the causes for concern. If, despite this, the concern remains, the appropriate ethics committee should be fully informed.

2.5 Risk Management

2.5.1 If the pharmaceutical physician has uncertainty regarding the overall status and direction of a clinical research programme, even in the light of acceptable efficacy or safety, it is appropriate to delay making decisions on future plans until any doubts have been resolved. Making an inappropriate decision before such doubts are resolved is unethical. Thus, both when assessing the outcome of a clinical trial programme and when reviewing the postmarketing safety profile, pharmaceutical physicians must actively fulfil their scientific and ethical responsibilities. They must make forthright decisions where, for example, the relative evidence of efficacy is less

than acceptable or where there is an unexpectedly high incidence of adverse reactions, recognising their overriding responsibility as doctors to put the interests of patients as their top priority.

2.5.2 The management of new information suggesting the possibility of an adverse safety profile for an intervention may be difficult. The pharmaceutical physician must ensure that the evaluation of the benefit/risk profile of a therapeutic intervention represents an honest and transparent assessment of all available information. It is essential that adequate pharmacovigilance and systems are in place to ensure the timely capture and analysis of relevant data upon which a decision to withdraw or modify an intervention might be based. The sponsor must ensure that pharmacovigilance is practised to mandated regulatory standards. The pharmaceutical physician should have received training to assure the standard of practice within his/her institution.

There are situations where the potential benefit to a larger number of patients has to be balanced against the possible harm done to a smaller number. The pharmaceutical physician has an ethical responsibility to ensure that all parties are aware of any significant risk associated with a medicinal product. Pharmaceutical physicians involved in the withdrawal of a therapeutic intervention must ensure that all relevant information is made available to enable the clinical care of patients who are affected by the withdrawal to continue with the minimum of disturbance to them.

2.5.3 It is important to appreciate that the evidence available to formulate a benefit/risk assessment increases with time as use of the new intervention increases. This is particularly true in the case of risk assessment, where the available information enlarges and becomes more relevant to general prescribing. In the past, risk assessment has generally depended upon intervention studies backed by spontaneous reporting schemes for adverse reactions. More recently, observational cohort studies, disease registers and record linkage schemes are increasingly being used to refine the available information on risk assessments. It is the duty of the pharmaceutical physician to utilise all such information resources to maximise the quality of information used to assess benefit/risk profiles and to minimise the time taken to achieve an optimum assessment of a benefit/risk profile.

2.6 Other Approaches to Clinical Research

2.6.1 There are new technologies of which pharmaceutical physicians should be aware, such as pharmacogenetics, which may be used for selecting and classifying or treating patients, which may well have ethical implications. In the design of research protocols using such tools, pharmaceutical physicians should be vigilant in protecting patient rights.

The application of powerful molecular techniques has the potential to provide tailored therapy to individual patient

needs but may also label an individual with far-reaching consequences for themselves and their families. There are ethical and legal considerations which cover this situation, but which vary from region to region (e.g. among Europe, the USA and other countries). Pharmaceutical physicians have a responsibility to know and respect all local regulations and conventions which apply.

2.6.2 Pharmacoepidemiology involves the collection, management and analysis of clinical data where patients may not have specifically consented to the collection or use of their information. The anonymity of all subjects must be maintained, and data reporting should respect the anonymity of research subjects and groups of subjects.

2.6.3 Clinical data management now involves the electronic transfer of information. These modern management tools facilitate clinical development and, in using them, pharmaceutical physicians have a duty to ensure that there is no deviation from the maintenance of high ethical standards or from the fulfilment of all legal requirements concerning privacy.

2.7 New Therapeutic Approaches

Pharmaceutical physicians must be aware of controversial and new therapeutic approaches in the wider context of the practice of medicine where ethical and medico-legal issues arise. These include, for example, the use of human tissues, gene therapy, medically assisted conception and *in vitro* fertilisation, prenatal diagnosis, abortion, the collection of human stem cells with potential therapeutic intent, as well as the interface with medical devices and delivery mechanisms.

The collection of genetic information from specific populations and the recent sequencing of the human genome provide for potentially important therapeutic advances and understanding of the biology of disease. However, with these advances come significant ethical issues relating to ownership of data, intellectual property and who may eventually know and benefit from these advances. The ownership of archived human tissues and their future use raise important questions relating to the content of informed consent.

Ideally, these issues should be addressed early on in the informed consent process before human tissues and/or their products are subjected to future analysis. If consent was not obtained in advance, then the use of such materials must be carefully considered with an ethics committee and their written approval obtained.

3. COMMUNICATION

3.1 Promotion

3.1.1 Pharmaceutical physicians have a professional and, at times, a legal responsibility to ensure that any promotional

material or activity does not contravene the advertising regulations of the countries concerned. Their ethical and scientific duty to their employer, prescribing physicians and patients is to ensure that they do not allow claims to be made which cannot be substantiated.

Pharmaceutical physicians must be able to demonstrate due diligence in this regard, recognising that it is unethical for them to do otherwise, and they must use their ethical judgement to advise those responsible throughout the life-cycle management of a medicinal product.

The pharmaceutical physician should be fully aware of local codes of practice and should not be party to practices that are designed to influence inappropriately the researcher and/or prescribing clinician, or support over-extended claims or covert advertising practices for medicinal products. This includes the provision by the sponsor of excessive hospitality or gifts which might be interpreted as an inducement.

Market research is a well-established method of obtaining information about patterns of use of specific therapeutic interventions and is entirely acceptable in principle. Some market research exercises, however, might be disguised as scientific research. This is not acceptable practice, and the pharmaceutical physician has an ethical responsibility to ensure that the purpose of the market research is clear, and the research is conducted in a transparent manner.

3.1.2 Provision of Information

3.2.1 It is the professional responsibility of pharmaceutical physicians to ensure that information provided to doctors, pharmacists, patients and members of the public is appropriate and accurate. They have an ethical responsibility to ensure that, while complying with any relevant regulations, such information is comprehensive and comprehensible. For patient information leaflets, such as package inserts, they have to make the fine distinction between providing information which is detailed enough to satisfy legal and regulatory requirements, but which is not so detailed that it affects the confidence of a patient or their family in the product and therefore negatively affects treatment adherence or compliance. Low risk events, where the causality remains unknown, frequently fall into the category of adding nothing to the understanding of a product by the prescriber or the consumer and can be omitted justifiably on ethical grounds. Information may, however, have to be included on legal or regulatory grounds.

3.2.2 With regard to promotion in third-world or developing countries, pharmaceutical physicians have an ethical responsibility to understand the risks involved in promoting a product which may deviate from accepted practice and cultural norm. Harmonisation of medical practice between developed and developing countries may be counterproductive, and the implications of introducing a new treatment or

practice should be evaluated prior to implementation in a resource-poor country. Pharmaceutical physicians have an ethical responsibility to ensure that products can be used appropriately in the target countries.

3.2.3 The Summary of Product Characteristics is a legal document in the United Kingdom and describes the essential characteristics of the medicinal product. Similar documents are usually approved by the respective regulatory agencies of the intended country for approved distribution of a medicinal product. The format and content are subject to regulatory approval, but the document is owned by the sponsor who has responsibility for ensuring that it is accurate and up to date. The pharmaceutical physician has an essential role in the writing of these documents, and an ethical obligation to ensure that the information contained therein is accurate and includes all materially relevant prescribing information.

3.3 Information to Healthcare Professionals

3.3.1 Doctors are increasingly being encouraged to practise medicine based on all the available evidence in an attempt to improve further the quality of healthcare. Pharmaceutical physicians have a particular ethical responsibility to ensure that all the evidence on which doctors should make their decisions is freely available.

3.3.2 Data to support marketing position statements should be of the same quality regardless of whether they are published or unpublished. The same scientific criteria should apply to unpublished data, made available to prescribers on request, as to published data.

3.3.3 It is well recognised that doctors sometimes prescribe medicines for indications or in dosage regimens that are not in accordance with the terms of the product's marketing authorisation. Although there can be no question of promotion of interventions for such off-label use, nor should this be encouraged, relevant information which is on file should be provided on request to physicians and pharmacists.

3.3.4 Pharmaceutical physicians may be aware of information regarding a therapeutic intervention which, for various reasons, has not been published. This may be because of editorial decisions or, more controversially, because of commercial decisions. Selective publication is therefore a dilemma which can only be resolved by encouraging the provision of all information known about an intervention to those entitled to it. Indeed, it is unethical for a pharmaceutical physician to endorse the withholding of such information. In this regard, the Faculty strongly recommends that pharmaceutical physicians encourage the reporting of all clinical trial outcomes and endorses the move towards the registration of clinical trials before study initiation. Publication of trial results should be agreed between the sponsor and the researcher before initiation of a clinical trial. In addition, sponsors have an ethical responsibility to publish, or make available, negative research findings

which may affect prescribing practices, especially with regard to the safety of medicines already available for prescription.

3.4 Information to Patients

3.4.1 There is increasing freedom, in some parts of the world, in the provision of information and the encouragement given to patients to seek as much information as they wish. This should certainly be permitted, for ideally a patient and their personal medical advisors should be able to discuss treatment options on a level playing field of information. However, the provision of such information should not be promotional in content.

Moreover, provision of information to patients should not be done with the intent to undermine the confidence of patients in the advice and treatment given by their doctors. Pharmaceutical physicians have an ethical duty to ensure that there is a clear understanding of the difference between providing information and offering advice, and that advice to patients must come from their own personal physician.

3.5 Information to the Media

3.5.1 With regard to public relations, pharmaceutical physicians have an ethical responsibility to ensure that expectations are not inappropriately raised as a result of the release of media briefings. Pharmaceutical physicians should be involved in the drafting of any briefings about potential therapeutic interventions provided to financial analysts or to the media.

3.5.2 A pharmaceutical physician may be aware of the distribution of a medicine, for example via the Internet, which bypasses national legislation and control. In these circumstances, the pharmaceutical physician has a duty to draw this to the attention of the legal sponsor and regulatory authorities.

4. PROVISION OF PATIENT SERVICES

4.1 The pharmaceutical physician involved in conducting a Phase II or Phase III study must ensure that it is clearly set out in the protocol as to whether or not the company will provide continuation of support and interventions once a patient's involvement ends. This should be included in the patient's information sheet and be understood by the investigator. The decision to provide continuation of an unlicensed intervention after a study is completed must be made on a study-by-study and a case-by-case basis; the ethical responsibility is to ensure that this is made abundantly clear to all concerned, including the institutional review board or research ethics committee conducting the review of the protocol. Such use must be justified on the basis of a clearly defined unmet medical need. Whatever the circumstances, there must be proper ongoing collection of safety and efficacy data. Therefore, in the absence of an appropriate protocol or a

named-patient arrangement being in place, no continuation should be provided.

4.2 As far as therapeutic use (or Phase IV) studies are concerned, continuation will always be by purchase from the market. However, the financial implications of continuing within restricted resources must be considered in consultation with the investigator and research ethics committee before such a study is started, as the continuation may be unaffordable.

4.3 Disease management packages may provide comprehensive care in a specified disease area for patients in a given locality and may involve one or more commercial companies. Pharmaceutical physicians have an ethical responsibility to ensure that any conflict between competing interests is minimised, recognising that the issues may be many and diverse, ranging from professional freedoms to return on capital employed. When these issues are handled effectively, then such packages may be of great clinical value and are welcomed. However, it must always be remembered that patients are whole persons, not a series of pathological events strung together, and that the management package available for just one pathological event may be disadvantageous for others and thus for the patient as a whole. The management of, for example, a child's asthma, must not be taken in isolation, recognising that the child may well have other diseases for which other treatment will be necessary.

4.4 There is potential for considerable conflict of interest for a pharmaceutical physician and other healthcare workers in the context of disease management packages, where the treatment of choice may be a medicinal agent manufactured by a competitor. As long as the decision to prescribe remains with the patient's own doctor, clinically and ethically there may be a place for these packages. Any payment to a pharmaceutical physician or other healthcare worker which is contingent on the use of a product is unethical and in many countries may be illegal.

4.5 Whenever a pharmaceutical physician is also responsible as a clinician for individual patients, the best interests of those individual patients must always prevail, for example, over those of the employer.

4.6 There is an increasing tendency to move towards clinical management guidelines, but these must never be imposed at the risk of discouraging individual clinical judgement, particularly where it can be demonstrated that an alternative course of action is more appropriate for an individual patient. On the other hand, where treatment as set out in the guidelines is clearly more desirable or efficacious for a patient, the

doctor's own clinical opinion should not override this. Pharmaceutical physicians have an ethical responsibility to ensure that information is provided in accordance with the principles of evidence-based medicine, to optimise the acceptability of those products for which they are responsible, but within appropriate clinical management guidelines.

4.7 Where clinicians demonstrate new uses for established therapeutic interventions which are outside existing clinical management guidelines or even any marketing authorisation, and such new uses appear feasible, it must be remembered that it is unlawful for a pharmaceutical physician to seek to extend the uses without conducting appropriate clinical trials and/or obtaining the necessary regulatory clearance.

4.8 The Faculty believes it may be in the interests of industry to be able to make financial contributions towards an appropriate academic or healthcare project or facility as long as this is transparent. Justifiable financial contributions to academic or healthcare projects or facilities should meet local criteria.

4.9 Pharmaceutical physicians have a duty of care regarding unlicensed or unproven interventions, whoever is suggesting them. In all cases, it is physician investigators who are legally responsible for any patients under their care, while the providers of the interventions carry responsibility for the quality of whatever they supply.

4.10 It is unethical to supply unlicensed or unproven interventions for commercial gain. This is not incompatible with making an administrative charge to cover the cost of the medicine and/or distribution on a 'named patient' basis. When this happens, it is the ethical responsibility of the pharmaceutical physician involved to make all relevant information available to the clinician. Doctors should note that the supply 'for particular patient use' is clearly intended only in very limited circumstances, which are meant to be exceptional.

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APPENDIX

The Ethical Issues Committee of the Faculty of Pharmaceutical Medicine, London UK comprised the following members at the time of writing this report:

Dr Roger Bickerstaffe (Chairman)

Global Vice President Communications, Solvay Pharmaceuticals, Belgium and past chairman of the European Forum on Good Clinical Practice, Brussels

Dr Peter Brock

Medical Director, European Vice-President, Medical Affairs, Wyeth Lederle and Member of Association of British Pharmaceutical Industries Medical Committee

Professor Jean-Marc Husson

Consultant Pharmaceutical Physician and Director of the European Diploma in Pharmaceutical Medicine. Past President of the International Federation of Associations of Pharmaceutical Physicians and past Medical Director, Roussel-Uclaf, Paris

Dr Ian Rubin

Chief Executive Officer, Matrix, past Medical Director, Fisons Pharmaceuticals and Chief Operations Officer and Medical Director, Phytopharm plc

Dr Keith Bragman

Consultant Pharmaceutical Physician. Past Director and Head of Global Development, UCB S.A, Brussels, Belgium

Dr Ken Paterson

Department of Clinical Pharmacology, Royal Infirmary, Glasgow and past Secretary to the Royal College of Physicians and Surgeons of Glasgow

Professor Ann Sommerville

Visiting Professor of Medical Ethics at Queen Mary College, London, and Head of the British Medical Association's Ethics Department.