



Guiding Principles and Ethics in Pharmaceutical Medicine

Dr Keith Bragman FFPM

Ethical Issues Committee

The Faculty of Pharmaceutical Medicine has recently published the revised version of the Guiding Principles and Ethics in Pharmaceutical Medicine on our website*. Since the Guiding Principles were first published six years ago, there has been a collapse in public confidence regarding the activities of the pharmaceutical industry. Examples include major pharmaceutical companies and clinicians accused of concealing clinical trials data that showed increased risk of myocardial infarction in adults and in other trials, suicidal tendencies in children. Also the regulatory agencies have not been immune from criticism as the lay press and litigators have laid bare the extent of the perceived problem. And with the increasing globalization of clinical research have come accusations of exploitation of research subjects in resource poor countries. The pharmaceutical industry is now described by some as being on a par with the tobacco industry.

The vast majority of pharmaceutical physicians whether they are working in the pharmaceutical industry and associated service organizations, regulatory agencies or academia are dedicated to improving the lives of individuals through the provision of better healthcare. It is possible to have commercial responsibilities and still do the right thing. It is possible to publish clinical research (the currency of academia) in journals of repute without falsifying data or being economical with the truth. The Guiding Principles may not dramatically alter human behaviour. Most individuals should know the difference between right and wrong long before they reach medical or business school. However there is still an ongoing need to set out the ethical expectations placed upon pharmaceutical physicians and remind us that our duty is always to the individual, whether patient or research subject, and must take precedence over commercial or institutional research agendas. Until recently pharmaceutical physicians have been largely absent from this debate. We hope that you will read both the Guiding Principles and Ethics in Pharmaceutical Medicine and think about their relevance both to yourself and the organization that you represent. Can the content be improved upon? Certainly yes and we invite you to comment and join the debate.

*Guiding Principles for Pharmaceutical Physicians from the Ethical Issues Committee of the Faculty of Pharmaceutical Medicine of the Royal Colleges of Physicians of the UK, *Int J Clin Pract*, February 2006, 60, 2, 238–241

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, *Int J Clin Pract*, February 2006, 60, 2, 242–252

Copies of both of the above documents are available from the Faculty Office.

Ethical Guidelines and Legal Responsibility: Through a Glass Darkly

Jeremy Stuart-Smith QC

Lay Observer to Board, Faculty of Pharmaceutical Medicine

Introduction

Among the most fascinating aspects of acting as an English lawyer concerned with the field of medicine are the differences of language and emphasis that characterise the legal and medical professions. Thus the medical profession, while intensely concerned with questions of legal responsibility, speaks primarily in terms of ethics while the legal profession, while dependant upon ethical considerations, speaks primarily in terms of legal duties and liabilities. The task for a lawyer appointed to act as Lay Observer to the Faculty of Pharmaceutical Medicine is to bridge this cultural and linguistic gap recognising that medical ethics and legal responsibility have historically been linked as two sides of the same moral currency. In predicting how medical ethics and legal responsibility will develop in the future, however, it is essential to take pan-European cultural thinking into account.

The Traditional Approach

The English common law has developed by judicial decisions which have always reflected the ethical attitudes of the judges. Historically this has been masked by reference to “the reasonable man”, or to “the man on the Clapham Omnibus” or some other hypothetical and miraculous manifestation of ethical consensus. More recently the Judges have tried to achieve greater transparency about their approach. In the controversial case of **McFarlane v Tayside Area Health Authority** in 2000, the House of Lords considered whether damages should be awarded for the birth and existence of a healthy child whose conception and birth had been unwanted and caused by lack of care on the part of the Authority. When balancing the competing considerations, Lord Steyn asserted: “The court must apply positive law. But judges’ sense of the moral answer to a question, or the justice of the case, has been one of the great shaping forces of the common law. What may count in a situation of difficulty and uncertainty is not the subjective view of the judge but what he reasonably believes that the ordinary citizen would regard as right.”

The legal responsibility of physicians has primarily been developed in the context of the law of negligence. The central feature of this development has been consideration of what is reasonable conduct for a competent physician. When considering whether a physician’s conduct has been reasonable, the man on the Clapham Omnibus has not been thought qualified to provide a reliable answer; so the courts have sought to identify whether the physician’s conduct would be rationally be regarded as reasonable by a responsible and respectable body of medical opinion. This immediately brings into focus the question of medical ethics as defined by the medical profession. If a responsible and respectable body of medical opinion considers that a particular course of conduct is ethically acceptable, an individual physician who pursues that course of conduct is unlikely to be held to be negligent unless the Court takes the bold step of declaring that ethical stance to be irrational.

For pharmaceutical physicians, issues of legal responsibility have most commonly arisen in the context of whether it was reasonable to distribute a product which is subsequently alleged to have caused injury. This has focused attention upon the risk benefit ratio and the steps that should be taken to determine what that ratio may be. The concept of reasonableness applies at both stages: have reasonable steps been taken to determine the risk benefit ratio, and is it reasonable to distribute a product which is understood to have that ratio of risk to benefit? Only if a Claimant can prove that the Defendant’s behaviour was unreasonable in these respects can compensation be recovered for any injuries that may be proved to flow from that unreasonable behaviour. A moment’s consideration will show that this is a demanding standard for a Claimant to achieve: whether that is desirable or not is well outside the scope of this article. It is also obvious that, in such an enquiry, legal responsibility will be inextricably linked to issues of medical ethics and how they have changed with time.



The European Influence

Against this common law backdrop, it is no surprise to find that two speakers at the Faculty's Annual Symposium in November 2005 are reported to have touched on the risk benefit ratio. Dr Thomas Löngren noted that the way decisions are reached when assessing risk benefit will be changing; while Professor Sir Michael Rawlins noted that the conventional approach failed to capture the judgments of the consumer. The critical feature, in the context of this article, is that these changes are substantially driven by European cultural influences which will inevitably affect the profession's ethical stance and the scope of legal responsibilities.

In the field of Consumer Protection, the common law is now subservient to the statutory protection provided by the Consumer Protection Act 1987 which embodies European Directive 85/374. The philosophy behind the Directive is radically different from the approach of the common law. Under the Act, a producer is liable for damage caused by a defect in his product. The test of whether a product is defective has nothing whatsoever to do with reasonableness: a product is defective when it does not provide the safety which a person is entitled to expect. Thus the consumer's expectation of safety determines the question of defect. Carefully constructed arguments that would have reintroduced notions of reasonable conduct were rejected by the English court in the Hepatitis C litigation and it cannot be assumed that a different approach will be adopted by other courts in the future.

This seismic shift in the approach to legal responsibilities must necessarily affect future consideration of medical ethics, as the brief report of Sir Michael Rawlins' contribution to the symposium amply demonstrates. The consumer-oriented approach to responsibility finds another philosophical manifestation in the precautionary principle, which holds that, if there is a risk that is not quantified or qualified then, as a precaution, that risk should be obviated. The principle has already been

considered in the first of the Anorectic cases: CFI case T – 74/00 (Artegodan et al – 26 November 2002). The case concerned the authority of the commission to amend the summary of product characteristics and, if necessary, to revoke marketing authorization of a medicinal product found to be unsafe. It was held that:

“The precautionary principle requires the suspension or withdrawal of a marketing authorization where new data give rise to serious doubts as to either the safety or the efficacy of the medicinal product in question and those doubts lead to an unfavourable assessment of the benefit/risk balance of that medicinal product. Against that back ground, the competent authority need do no more than provide... solid and convincing evidence which, while not resolving the scientific uncertainty, may reasonably raise doubts as to the safety and/or efficacy of the medicinal product.” [Emphasis added]

Conclusion

Any profession must develop and promulgate ethical guidelines. Under the common law, compliance or non-compliance with ethical guidelines will in many cases be the touchstone for judges when deciding where legal responsibility should lie. However, the cultural influence of Europe is likely to become all-pervasive and is already dominant in the sphere of consumer protection. Although the future scope of legal liabilities cannot be predicted with any precision or confidence, an overtly consumer-oriented philosophy will affect the legal responsibilities of manufacturers, regulators and therapeutic physicians alike.



Faculty of Pharmaceutical Medicine of the Royal Colleges of Physicians of the United Kingdom

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1 St. Andrew's Place, Regent's Park, London NW1 4LB


Tel: +44 (0)20 7224 0343

Fax: +44 (0)20 7224 5381

E-mail: fpm@fpm.org.uk

Website: www.fpm.org.uk

Registered Charity No 1011631



Ethics and Pharmaceutical Research

Dr TKG Mant FFPM
Senior Medical Advisor,
GDRU, Quintiles Limited, London, UK

Injury to Research Volunteers – The Clinical Research Nightmare, in the May 4th edition of the New England Journal of Medicine [1] is aptly titled. Healthy volunteer Phase I trials have an excellent safety record [2], but the serious adverse events that followed the administration of TGN1412, which caused six volunteers to require intensive care at Northwick Park hospital is a nightmarish reminder of drug toxicity to all those involved in the development of new medicines.

With the current public, government, lay and scientific media interest in Pharmaceutical Industry sponsored research, it was timely that the Ethics Issues Committee of the Faculty of Pharmaceutical Medicine of the Royal College of Physicians published “Guiding Principles for Pharmaceutical Physicians [3] and their full report on “Ethics and Pharmaceutical Medicine” [4] in February. The fundamental ethical principles of human medical research are “laid in stone” in the World Medical Association Declaration of Helsinki. The Ethics Issues Committee has endeavored, I feel successfully, to describe many areas of pharmaceutical research where ethical issues may arise as well as providing pertinent advice.

As a Phase 1 investigator and past Research Ethics Committee member I should like to add a personal view to the section on Human Pharmacology (Phase 1) Studies with a particular reference to monoclonal antibodies. Whereas in most clinical trials involving treatments there is the concept of “ equipoise ” between different treatments as a major ethical consideration, this is not the case in healthy volunteer studies. In comparison to most clinical trials involving new medicines, as the volunteers are healthy, there can be no therapeutic benefit to the participants to “balance” any risk associated with the experimental drug or study procedures. Consequently that risk must be considered minimal for the study to be ethical. ICH and regulatory authority guidelines assist in determining the preclinical studies that are necessary to help minimise risk before first administration to man.

Although not always predictive, the preclinical testing, when combined with the design and conduct of Phase 1 studies and Ethics’ Committee review in the UK have resulted in unexpected serious toxicity in healthy volunteer studies being very rare.

Relatively recent advances in science have led to the introduction of a number of biologicals being used as therapeutic agents. For example recombinant-derived products have replaced many products previously derived from animal or human tissue; monoclonal antibodies have already made a significant contribution to the quality of life in many patients with rheumatoid arthritis, certain cancers and other diseases. With most biologicals interspecies variation is much more significant so extrapolation from the traditional preclinical tests in animals to determine effects and risk in humans, is more tenuous and difficult than for the more conventional small molecules. The potential benefits of many of the biologicals under development appear extraordinary. The regulatory authorities, the pharmaceutical industry, many academic institutions, some clinical units and some contract research organisations have already accumulated considerable experience of biologicals. In my opinion this knowledge, expertise and hard data must be shared to expedite the safe introduction of effective new biologicals whilst terminating the development of ineffective or unsafe biologicals at the earliest opportunity. The MHRA made certain information, including their interim report, available on their website [5], concerning the TGN1412 healthy volunteer trial mentioned above under the Freedom of Information Act. It must be a tribute to the medical staff of Northwick Park Hospital that all six volunteers survived the acute multi-organ failure thought to be secondary to a cytokine release syndrome. I hope the lessons that have been learnt from the medical management of these volunteers will also be released. I strongly recommend that all pharmaceutical physicians and other scientists involved in the development of monoclonal antibodies read and note well the “Testing Antibody Therapies: Position



Paper” written by the Academy of Medical Sciences [6] as well as the Wood and Darbyshire perspective [1]. The ABPI has already instigated a multidisciplinary safety biomarkers group to help determine the value of a variety of tests. The scientific media, Pharmaceutical medical and academic departments can help by encouraging the publication of “negative” as well as “positive” data at the earliest opportunity.

These are exciting and challenging times for pharmaceutical physicians involved in clinical research. In my opinion they have not only a professional, but also a moral duty to read, understand and act upon the Faculties report on ethics.

Ref 1. Woods A, Darbyshire J. Injury to Research Volunteers – The Clinical Research Nightmare. *N Engl J Med*, May 2006, **354**, **18**, 1869-1871.

Ref 2. Stein C. Managing Risk in Healthy Subjects Participating in Clinical Research. *Clin Pharmacol Ther*, 2003, **74**, 511-512

Ref 3. Bickerstaffe R, Brock P, Husson J-M, Rubin I, Bragman K, Paterson K, Sommerville A. Ethics and pharmaceutical medicine – the full report of the Ethical Issues Committee of the Faculty of Pharmaceutical Medicine of the Royal College of Physicians of the UK. *Int J Clin Pract*, February 2006, **60**, **2**, 242-252

Ref 4. Bickerstaffe R, Brock P, Husson J-M, Rubin I, Bragman K, Paterson K, Sommerville A. Guiding Principles for Pharmaceutical Physicians. *Int J Clin Pract*, February 2006, **60**, **2**, 239-241

Ref 5. www.mhra.gov.uk – *Clinical trial suspension: latest findings*

Ref 6. www.acmedsci.ac.uk – *Testing Antibody Therapies: position paper.*

The letter reflects the personal views of the author. The author is a Phase I Investigator who performs research on behalf of many pharmaceutical companies and other sponsors.

How to contact us

Address:

Faculty of Pharmaceutical Medicine
1 St Andrews Place, Regents Park
London NW1 4LB, United Kingdom

Telephone: +44 (0)20 7224 0343

Fax: +44 (0)20 7224 5381

E-mail: fpm@fpm.org.uk

Web-site: www.fpm.org.uk

Chief Executive

Mrs Kathryn Swanston Tel Ext.22
K.Swanston@fpm.org.uk

Membership and Finance

Administrator

Mr Barry Muzzeroll Tel Ext.21
B.Muzzeroll@fpm.org.uk
Subscription and membership enquiries

Education Administrator

Ms Laura Thornton Tel Ext.23
L.Thornton@fpm.org.uk
HMT, examinations

Deputy Education Administrator

Mr Konrad Obiora Tel Ext. 20
K.Obiora@fpm.org.uk
CPD

Registered charity 1011631

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