CONFLICTS OF INTEREST – DOES MONEY INFLUENCE SCIENTIFIC PUBLICATION?

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Conflict of interest in medical research: an introduction

Members of Parliament have long been concerned about conflicts of interest and must register their interests each year. If they fail to declare a relevant conflict of interest then opprobrium will follow. This has not until recently been the case with science. Scientists have perhaps thought that they were immune to conflicts of interest because science is objective. But science is full of judgements that are subjective, and science is undertaken not by machines but by human beings – and those beings are heir to the same weaknesses as all other humans. Increasingly we understand how conflict of interest does matter in science, and science is in the process of improving its processes for managing conflict of interest.

The perspective that follows is that of the editor of a medical journal. I worked for the BMJ (formerly the British Medical Journal) for 25 years and was the editor from 1991 to 2004. During that time there were many intense debates over conflict of interest, and I was involved in researching the subject. I have written on the subject in the BMJ,[1 2] a book on medical journals[3], and the forthcoming Principles of Health Care Ethics.

An illustration of how conflict of interest matters

Although most of those in business and politics do not need convincing that conflicts of interest matter, those in science do – and so I want to begin with an example. In the past 10 years there has been an intense debate about whether newer (third generation) contraceptive pills increase a woman's chance of developing thromboembolic disease (clots in the legs or lungs). This clearly matters to women and their doctors because clots in the lungs can kill. It also matters a great deal to the drug companies who manufactured the pills because they have invested tens, even hundreds, of millions of pounds in developing the drugs: if regulatory authorities were to ban the drugs or doctors advise patients against taking them then the business consequences would be severe – even forcing some companies out of business.

By the end of 1998 there were six studies of the question[4]. All of the three studies funded with public money found that the new contraceptive pills did increase the risk of thromboembolic disease, whereas the three funded by industry did not. In other words, there was a complete dichotomy. By 2000 there were nine publicly funded studies of which eight found an increased risk[4]. In contrast, three sponsored studies found no increased risk, and the one study that did find an increased risk was repeatedly reanalysed giving ever lower risks.

Conflict of interest has completely clouded this problem that is of great importance to women, doctors, drug companies, and health authorities.

What is conflict of interest?

Conflict of interest has been defined as "a set of conditions in which professional judgement concerning a primary interest (such as patients' welfare or the validity of research) tends to be unduly influenced by a secondary interest (such as financial gain)[5]." It is important to understand that it is a condition not a behaviour. It often operates unconsciously, and there is substantial and growing evidence of its influence on how doctors prescribe and treat patients, what research is undertaken, and how research is interpreted[3]. Conflicts may arise from many causes – academic, political, or religious, for example – but the best studied conflicts are financial. Science journals tend to concentrate on financial conflicts of interest, and in medicine the commonest source of financial is interaction with the pharmaceutical industry.

How common are conflicts of interest?

A quarter of medical researchers in the United States have received funding from pharmaceutical companies and half have received "research related gifts[6]." An analysis of 789 articles from major medical journals found that a third of lead authors had financial interests in their research – patents, shares, or payments for working on advisory boards or as a director. An important early study of conflicts of interest published in the New England Journal of Medicine in 1998 tracked

down 69 of 89 authors of 75 pieces in medical journals on new drugs for high blood pressure and found that 45 (63%) had financial conflicts of interest[7]. In other words, we have good evidence that most authors in medical journals have conflicts of interest.

Yet only two of the articles studied in the New England Journal of Medicine paper disclosed the conflicts of interest of the authors[7]. A study that I undertook with a medical student looked at 3642 articles in the five leading general medical jourtnals (Annals of Internal Medicine, BMJ, Lancet, JAMA, and the New England Journal of Medicine) and found that only 52 (1.4%) declared authors' conflicts of interest[8]. The proportion in those journals is now much higher – because the journals require authors to declare conflicts of interest and will report whatever the authors declare, making the authors vulnerable if they do in fact have conflicts of interest but have not declared them.

At the BMJ we began to ask authors to declare conflicts of interest in the late 90s, but they mostly didn't – until we asked very specific questions about reimbursement for attending a meeting, a fee for speaking, a fee for organising education, funds for research, funds for a member of staff, or fees for consulting. At the same time we changed our terminology from "conflict of interest" to "competing interest". For whatever reason the numbers declaring competing interests increased.

Further evidence that conflicts of interest matter

An important study published in the Archives of Internal Medicine in 1994 found that among 69 randomised trials of non-steroidal anti-inflammatory drugs (which are used commonly to treat arthritis) sponsored by the manufacturers of the drugs in not a single trial was the drug being investigated (the sponsor's drug) worse than the comparative treatment[9]. In three quarters of the studies the sponsor's drug was better and in the other quarter of cases the same.

There have now been many studies comparing the outcomes of studies sponsored by industry and those not sponsored, and a review of 11 such studies found that sponsored studies were always more likely to have results favourable to the sponsor[10]. Overall the quality of the sponsored trials was higher. So sponsors are not getting favourable results by fiddling the results. Rather they are clever about the questions they ask and the design of the studies. They may compare their drug with placebo, conduct a comparison trial that will be too small to show an advantage to one treatment, or test their drug against a low dose of the comparison drug. It may also be that the companies are more likely to publish the positive results.

All of this matters greatly because two thirds of the randomised trials published in the major general medical journals are sponsored by the pharmaceutical industry[11]. I've argued elsewhere that in some ways medical journals have become the extension of the marketing arm of pharmaceutical companies[12].

Randomised trials are seen as one of the most important scientific designs for working out whether treatments work, but systematic reviews are as important – and maybe more important. A study of 71 systematic reviews of drugs for treating blood pressure did not find any difference between sponsored and unsponsored reviews in the results of the reviews, but 91% of the conclusions of sponsored reviews were positive and none negative compared with 72% that were positive and 8% negative in unsponsored reviews[13].

Another study compared 24 meta-analyses conducted by the Cochrane Collaboration (a worldwide not for profit collaboration) with 24 meta-analyses of the same two drugs in the same disease, eight of which were supported by industry[14]. The Cochrane reviews were of higher quality, and seven of the reviews sponsored by industry had conclusions recommending the experimental drug (the sponsor's drug) without reservation compared with none of the matched Cochrane reviews – even though the effect of the treatment was the same.

Evidence of the effects of conflicts of interest comes as well from studies other than drug studies. A study published in JAMA in 1998 investigated why of 106 reviews of passive smoking 37% concluded that it was harmful and the rest that it wasn't[15]. The authors thought that the most likely explanation was the quality of the article. They investigated article quality, the year of publication, whether the articles were peer reviewed or not, and the article topic and found that the only factor associated with the review's conclusion was whether the author was affiliated with the tobacco industry. The authors of the study had used a database to find out which authors were affiliated with the industry, but only 23% of the reviews disclosed the sources of funding for the research.

A very recent study looked at 206 studies of milk and soft drinks in which 111 declared financial sponsorship (22% all industry funding, 47% no industry funding, and 32% mixed funding)[16]. Studies funded by industry were seven times more likely to come up with results favourable to the sponsor than studies with no industry funding.

Most of the studies I've quoted on how conflict of interest affects the results of scientific studies have been completed in the past 10 years, but we now have overwhelming evidence of the influence of conflict of interest.

Conflict of interest and journals

Editors of journals have been prominent in exposing and responding to conflicts of interest, but the journals have their own conflicts. Many publish supplements sponsored by the pharmaceutical industry. These supplements are often highly profitable for the publishers, but studies have shown that the quality of such supplements are lower quality than the journals themselves[17 18]. Many journals also depend heavily on income from pharmaceutical advertising, and some sell advertising space off the back of the research they are publishing and will place advertisements beside articles.

But the biggest conflicts of interest for journals arise from "reprints," copies of articles that they publish that are sometimes purchased in huge numbers by pharmaceutical companies. The companies then give the articles to their sales representatives to use in selling their drugs. The reprints are rarely read, but the company can in effect use the brand of the journal to sell their drugs. Companies may buy more than a million dollars' worth of reprints, and the profit margin is high – meaning that publishers may make $700,000 profit on one sale. Increasingly editors have to meet financial targets, and – in stark terms – the choice could be publish the one study or make five editors redundant. Editors will deny that they are influenced by the financial incentive, but they know which articles will attract such sales (not least because they are usually funded by the company that will buy the reprints) – and, as I've said, conflict of interest operates subconsciously.

Responding to conflict of interest

John Bailar, professor of statistics in Chicago, has famously said that "Disclosure is almost a panacea," and disclosure is the main way that most journals try to manage conflict of interest. Increasingly journals disclose the conflicts of interest of authors, but it's a minority that disclose the conflicts of interest of peer reviewers (not least because they are usually anonymous), editors, editorial boards, management committees, and owners[19]. Even when conflicts of interest are disclosed it's rare to give the amounts of money involved – even though most of us would think that the scale of the conflict is likely to influence the impact of the conflict.

Clearly disclosure alone will sometimes not be enough – for example, no journal would have an editorial on a new drug written by an employee of the manufacturer. But where is the point when the degree of conflict is unsupportable? Most journals have made no attempt to define that point.

The effect of conflict of interest on studies of drugs is particularly worrying, and various proposals have been made to try and respond. The Lancet, for example, reviews protocols of trials and then if the protocol of the trials is approved commits to publishing the results of the trial – in an attempt to avoid bias against trials that have negative results. Ian Roberts and I have argued that trial results should not be published in journals but rather with a full dataset on the web[20].

But there are increasing arguments on both sides of the Atlantic that drug trials should be funded with public money rather than by the companies themselves when they have a very clear conflict of interest.

Conclusions

Conflict of interest is common in medical research and has strong influences on the outcomes and conclusions of that research. Yet our response so far is inadequate. More needs to be done to counter the conflicts of interest, particularly the conflicts of the pharmaceutical industry.

REFERENCES

1 Smith R. Conflict of interest and the BMJ. BMJ 1994; 308: 4.

2 Smith R. Beyond conflict of interest. BMJ 1998; 317: 291 – 2.

3 Smith R. Conflicts of interest: how money clouds objectivity. In: Smith R. The trouble with medical journals. London: RSM Press, 2006.

4 Vandenbroucke JP. Competing interests and controversy about third generation oral contraceptives. BMJ 2000; 320: 381.

5 Thompson DF. Understanding financial conflicts of interest. N Engl J Med 1993; 329: 573-6.

6 Bekelman JE, Li Y, Gross CP. Scope and impact of financial conflicts of interest in biomedical research. A systematic review. JAMA 2003; 289: 454-65.

7 Stelfox HT, Chua G, O'Rourke K, Detsky AS. Conflict of interest in the debate over calcium channel antagonists. N Engl J Med 1998; 338: 101-5.

8 Hussain A, Smith R. Declaring financial competing interests: survey of five general medical journals. BMJ 2001;323:263-4.

9 Rochon PA, Gurwitz JH, Simms RW, Fortin PR, Felson DT, Minaker KL, et al. A study of manufacturer supported trials of non-steroidal anti-inflammatory drugs in the treatment of arthritis. Arch Intern Med 1994; 154: 157-63.

10 Lexchin J, Bero LA, Djulbegovic B, Clark O. Pharmaceutical industry sponsorship and research outcome and quality: systematic review. BMJ 2003; 326: 1167-70.

11 Egger M, Bartlett C, Juni P. Are randomised controlled trials in the BMJ different? BMJ 2001; 323: 1253.

12 Smith R. Medical Journals Are an Extension of the Marketing Arm of Pharmaceutical Companies. PLoS Med 2005; 2(5): e138

13 Yank V, Rennie D, Bero LA. Are Authors' Financial Ties With Pharmaceutical Companies Associated With Positive Results or Conclusions in Meta-analyses on Antihypertensive Medications? Abstract presented at fifth international congress on peer review and biomedical publication, Chicago, 2005. http://www.ama-assn.org/public/peer/abstracts.html#meta

14 Jørgensen AW, Hilden J, Gøtzsche PC. Cochrane reviews compared with industry supported meta-analyses and other meta-analyses of the same drugs: systematic review. BMJ 2006;333:782, doi:10.1136/bmj.38973.444699.0B

15 Barnes DE, Bero LA. Why review articles on the health effects of passive smoking reach different conclusions. JAMA 1998; 279: 1566-70.

16 Lesser LI, Ebbeling CB, Goozner M, Wypij D, Ludwig DS. Relationship between Funding Source and Conclusion among Nutrition-Related Scientific Articles PLoS Medicine 2006; 4. e5 doi:10.1371/journal.pmed.0040005

17 Rochon PA, Gurwitz JH, Cheung M, Hayes JA, Chalmers TC. Evaluating the quality of articles published in journal supplements compared with the quality of those published in the parent journal. JAMA 1994;272: 108-13.

18 Cho MK, Bero LA. The quality of drug studies published in symposium proceedings. Ann Intern Med 1996;124: 485-9.

19 Haivas I, Schroter S, Waechter F, Smith R. Editors' declaration of their own conflicts of interest. CMAJ 2004; 171 (5). doi:10.1503/cmaj.1031982.

20 Smith R. Roberts I. Patient safety requires a new way to publish clinical trials. PloS Clinical Trials 2006; 1: 1.

When does clinical science cease to exist?

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Why are conflicts of interest in clinical science worth bothering about?

In 2004, a former editor of the highly regarded *New England Journal of Medicine*, Jerome Kassirer, published a book for the public entitled *On the take: how medicine's complicity with big business can endanger your health.* From his vantage point at the heart of the medical establishment, Kassirer felt that the time had come to speak publicly about conflicts of interests within clinical science.

These conflicts are worth bothering about because they are associated with biased design and reporting of research. A comparison of information in confidential pre-licensing records of new drugs in Sweden and Finland with information reported publicly in medical journals showed that studies in which researchers had looked for adverse effects were less likely to be published. A similar study of recently introduced drugs concluded that any attempt to develop treatment recommendations using analyses based only on publicly available data was likely to be biased. These two studies are not exceptional: there is now substantial evidence showing associations between industry-sponsorship and research results favouring products made by the companies funding the research.[1] These observed associations sometimes also reflect comparisons of new treatments with existing treatments which are given either in doses too low to be effective, or in doses higher than necessary, with consequent higher incidence of adverse effects than with the new drugs.

Marcia Angell, another former editor of the *New England Journal of Medicine,* discusses these disturbing features of modern clinical research in her 2004 book entitled *The truth about the drug companies: how they deceive us and what to do about it.*

Why is biased design and reporting of clinical science important?

Biased design and reporting of biomedical science is important because it can result in avoidable suffering and death. In 1993, for example, Cowley and his colleagues published a study that had been completed thirteen years previously:

"… When we carried out our study in 1980 we thought that the increased death rate that occurred in the (anti-arrhythmic drug) group was an effect of chance…The development of (the drug) was abandoned for commercial reasons, and this study was therefore never published; it is now a good example of 'publication bias'. The results described here … might have provided an early warning of trouble ahead." [2]

The 'trouble ahead' was a major medical disaster: at the peak of their use in the late 1980s, anti-arrhythmic drugs were causing – every year – comparable numbers of deaths to the total number of Americans who died in the Vietnam war. [3]

When does clinical science cease to exist?

Most research evaluating the effects of medical treatments is sponsored by companies that have an interest in selling treatments. Jan Vandenbroucke has spelled out the consequences of this kind of research having received so little independent support, from public and charitable sources for example. [4]

"In all scientific debates all sides always have their own biases: we have no other way to look at data but to interpret them. However, in usual clinical or epidemiologic research, studies are repeated by others, in different settings and by different means, looking for biases, flaws, and ways of remedying them, endlessly arguing whether the biases are remedied or not. That is the essence of open scientific debate and criticism. That is no longer possible with pharmaceutical products because of the monopoly of the pharmaceutical industry of studies of its own products. This leads to persistently one-sided studies that can no longer be questioned by studies from other sides. Moreover, the one-sidedness cannot be seen from the public record, that is the published papers. Without the possibility of open debate, science simply ceases to exist."

An Italian initiative is addressing this unsatisfactory state of affairs. The Agenzia Italiana per il Farmaco is the first European drug regulatory agency to fund independent clinical research on proprietary and unregistered drugs. Italian legislation now requires pharmaceutical companies to contribute 5% of promotion costs to fund this research. In March 2006, €35m were used to commission 54 clinical research projects evaluating orphan drugs, head to head comparisons of drugs, and for pharmacoviligance (http://tinyurl.com/yfph5l).

What can be done to reduce the adverse effects of conflicts of interest in clinical science?

In an article published last year I reviewed relevant developments over the previous decade. [5] During the

mid-1990s, some individuals working within the pharmaceutical industry recognised that the situation outlined above is indefensible, ethically as well as scientifically. The ethics committee of the Faculty of Pharmaceutical Medicine, for example, stated that:

"Pharmaceutical physicians…have a particular ethical responsibility to ensure that the evidence on which doctors should make their prescribing decisions is freely available….the outcome of all clinical trials on a medicine should be reported."

Schering Health Care and GlaxoWellcome endorsed this view, introduced disclosure policies, and published information about their clinical trials programmes. However, the subsequent efforts of the Association of the British Pharmaceutical Industry to persuade other companies to follow GlaxoWellcome's lead met with very limited success. The situation changed when the attorney general of New York State charged GlaxoSmithKline with suppressing information suggesting that one of the company's products might have serious adverse effects. As other examples of suppressed evidence began to emerge, the public became increasingly conscious of the impact of conflicts of interest in clinical science.

What has Parliament done to reduce conflicts of interest in clinical science?

The growing public awareness that all was not well was reflected in the decision of the Health Committee of the House of Commons in 2004 to examine the influence of the pharmaceutical industry. The Committee's investigation and report were wide ranging. Among other problems, they drew attention to the problem of publication bias.

"If pharmaceutical companies only publish clinical research that is positive and hold back on publishing clinical research which is negative, then patients may well be given treatments which, unknown to either the patient or the doctor, are likely to do more harm than good."

The Committee introduced its recommendations by quoting Sir Richard Sykes, formerly chief executive of GlaxoWellcome, who had told the Committee that "Today the industry has got a very bad name", and that there had to be "some big changes." The Committee noted that "the situation would be much improved by more transparency". Specifically, it called for a register of all clinical trials to be established, maintained by an independent body; and that "the results of all clinical trials data, containing full trials information, be put on the register at launch as a condition of the marketing licence."

Although declaring its shared commitment to "transparency and accountability relating to registration of clinical trials and publication of their results", the Government rejected the Committee's call for an independently maintained register. Instead, it referred to a number of other initiatives which, it claimed, "will soon make comprehensive information about the safety and effectiveness of medicines much more easily accessible."

Comprehensive information about the safety and effectiveness of medicines remains far from easily accessible, and information about ongoing clinical research remains extremely limited. Several years ago I proposed a 'patient-led good controlled trials guide', suggesting that "Researchers and research sponsors will need to realise that one of the preconditions for consumer endorsement of and partnership in their trials is likely to be that protocols and other trial documents should be made public". [6] More recently, in a book for the public, which I co-authored with a medical journalist and a breast cancer patient, [7] our advice to our readers was very explicit:

"Agree to participate in a clinical trial only on condition (i) that the study protocol has been registered publicly on www.controlled-trials.com; (ii) that the protocol refers to the systematic reviews of existing evidence showing that the trial is justified; and (iii) that you receive a written assurance that the full study results will be published, and sent to all participants who indicate that they wish to receive them."

What should parliamentarians do to reduce conflicts of interest in clinical science?

Conflicts of interest are associated with biased reporting of research, and biased reporting of clinical research can result in avoidable suffering and death. These facts have already been acknowledged by British parliamentarians, who have proposed ways of dealing with them. However, further action is required to protect the interests of patients and the public by building on the Health Committee's recommendations. Here are three suggestions:

(i) support the Health Committee's call for "greater transparency" and continue to press for a "register of all clinical trials…maintained by an independent body."

(ii) hold the Government to its 2005 assurance that its initiatives "will soon make comprehensive information about the safety and effectiveness of medicines much more easily accessible."

(iii) promote increased public and charity support for designing, conducting and reporting clinical research of relevance to patients and the NHS, and free from conflicts of interest.

REFERENCES

1 Hemminki E (1980). Study of information submitted by drug companies to licensing authorities. BMJ 280:833-6; Djulbegovic B, Lacevic M, Cantor A, Fields KK, Bennett CL, Adams JR, Kuderer NM, Lyman GH (2000). The uncertainty principle and industry-sponsored research. Lancet 356:635-638; Melander H, Ahlqvist-Rastad J, Meijer G, Beermann B (2003). Evidence b(i)ased medicine - selective reporting from studies sponsored by pharmaceutical industry: review of studies in new drug applications. BMJ 326:1171-3; Lexchin J, Bero LA, Djulbegovic B, Clark O (2003). Pharmaceutical industry sponsorship and research outcome and quality: systematic review. BMJ 326:1167-70; Bhandari M, Busse JW, Jackowski D, Montori VM, Schünemann H, Sprague S, Mears D, Schemitsch EH, Heels-Ansdell D, Devereaux PJ (2004). Association between industry funding and statistically significant pro-industry findings in medical and surgical randomized trials. CMAJ 170:477-480; Lesser LI, Ebbeling CB, Goozner M, Wypij D, Ludwig DS (2007). Relationship between funding source and conclusion among nutrition-related scientific articles. PLoS Medicine 4: e5 doi:10.1371/journal.pmed.0040005.

2 Cowley AJ, Skene A, Stainer K, Hampton JR (1993). The effect of lorcainide on arrhythmias and survival in patients with acute myocardial infarction: an example of publication bias. International Journal of Cardiology 40:161-166.

3 Moore T (1995). Deadly Medicine. New York: Simon and Schuster.

4 Vandenbroucke JP (2005). Without new rules for industry-sponsored research, science will cease to exist. Rapid response on bmj.com, posted 14 December, available at http://bmj.bmjjournals.com/cgi/eletters/331/7529/1350.

5 Chalmers I (2006). From optimism to disillusion about commitment to transparency in the medico-industrial complex. Journal of the Royal Society of Medicine 99:337-341.

6 Chalmers I (2000). A patient-led good controlled trials guide. Lancet 356:774.

7 Evans I, Thornton H, Chalmers I (2006). Testing treatments: better research for better healthcare. London: British Library.

Publish and be damned…

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When the big pharmaceutical companies overstep themselves in published claims of safety and efficacy of the medicines that they sell, the media and the public shout loudly. Attracting criticism and judicial disapproval through a string of disputes, especially involving state court actions in the USA, hangs the dirty laundry of the marketing departments out to dry and tarnishes reputations. The tightrope of worthiness is apparently, very easy to fall from. A healthcare company proudly boasts the ethic of serving the patient first, whilst the unstated duty as a properly structured organisation must be to employees and shareholders. More than most, the companies are seen to engage in activities which bring them little public sympathy: the use of animals in research, making a profit from illness and finally over-promoting the benefits of very expensive medicines against cheaper alternatives.

Conflicts of interest

The need to recognise conflicts of interest and manage them in a transparent way has exercised all disciplines of medicine. Few experts are without potential conflicts of interest since the circumstances rather than deliberate action lays the field expert open to a consideration of motive when recommending a particular therapy. It is extremely difficult to avoid and in my view, entirely undesirable to ignore those events and interactions which are sponsored by the pharmaceutical industry. Most have valid educational content and provided that the marketing component is clearly recognised and not excessive, help shape the view of an intelligent practitioner. The key is perhaps to avoid a monopolistic situation and the following unacceptable situations are well trodden:

- Failure to disclose a financial interest in a publication seeking to promote a drug or product.
- Failure to disclose ownership or being a direct beneficiary of an invention promoted in peer-reviewed literature.
- Having a high personal dependency on a single sponsor of a major research programme through institutional employment.

There is a general agreement that more transparency is necessary since the situation of potential conflicts of interest are extremely pervasive, and in the case of international experts, probably invisible beyond the state level.[1]

Research and data ownership

The forum for structured consideration of the benefits of treatments and new pharmacological agents is medical publishing. This too is big business, with organisations making significant profits from authors who often receive little financial recompense for their effort. In practice, medical researchers do not publish for the purpose of penning the next best-seller, more for recognition of their contribution and for continuing grant support of their institution. As mentioned earlier, the precarious finances of some university departments provide potential pressure points which can distort the relationship between independent researcher and employer. An independent research worker may regard the stewardship of data gathered during a contract between university and a sponsor as their own, but since the ownership is frequently transferred in the agreement to the sponsor, the worker becomes dis-enfranchised; moreover, raw data used in a meta-analysis may not be openly available. From internal and fairly soon afterwards external viewpoints, the bias and veracity of data becomes challenged and the independence of the field expert questioned.

Why don't companies publish more about their failures?

Researchers in the pharmaceutical industry rarely write papers as the work pressure demotes this activity to a tertiary objective. There is little enthusiasm to reveal thought processes as the intellectual property must be carefully considered for patent filing and the financial clampdowns restrict the attendance at scientific meetings to a fortunate few. We hear little of failures in public-access literature but obviously there must be many projects that have to be curtailed at an early stage. Those that do make it through the sieve have proved themselves in a vast battery of tests but identification as a star performer in a pivotal animal model of disease does not necessarily translate into the next blockbuster drug. In any case, disclosure of these less fruitful paths in drug discovery to a competitor makes poor business sense.

The commercial and scientific premise for initiation of a clinical trial is that the compound will be found superior because the cost of a study in the US or UK swallows up huge chunks of the project budget. It is debatable whether clinical research starts from a true null hypothesis and external critics have proposed that conditions may be selected to show the drug works well in a particular scenario to establish proof of concept. In an ideal world, the whole gamut would be tested as

early as possible, in a diverse population of patients. If that is the objective the process would have to be less bureaucratic, more effective and above all, much cheaper.

The partnership between publisher and academic

The partnership between publishing and the researcher is extremely important as the primary vehicle of peer group appraisal. In this system, publishing in medical journals is highly regarded as it will then be extensively cited, a process measured by "impact factor". It is therefore an essential component of the researcher's progression through a career, with universities holding off promotion until the required weight of published work or height of impact factor has been gained. An objective element of assessment for a lecturer or medical researcher, it is the key to international fame and recognition whereas performing as a good teacher has a more parochial radius. The ideal portfolio is mixed, with research council funding accompanied by charity and industry support indicating relevance of research to society's needs.

As the trinity of drug company, impartial and independent researcher and editor might be seen as the engine for the generation of misleading data, all three now engage in codes of practice to allow public scrutiny of motive and financial interest. In the Western World, bigger pharmaceutical companies publish the summaries of all current trials on the web and so move towards more openness. The professional organisations, specifically the ABPI for the industry and the RPSGB for the pharmacists attempt, with some degree of success, to police the industry. Up to now, it has been a steadily improving process but recently the medical treatment spectrum lurched backwards to an earlier, less certain time.

Could we judge alternative therapy by the standards imposed for allopathic medication?

The growth of public interest in alternative medical therapy has blossomed, fostered by the considerable profits in nutraceuticals and "feel good" therapy. This is not just placebo therapy as many herbal products contain oils and actives in sufficient quantities to act pharmacologically. There have been reports of adulteration of herbal products with steroids and one report quoted by Ernst suggested 24% of Taiwanese medicines are adulterated with at least one conventional pharmacological agent.[2] This leaves a confusing mix of the innocuous and the active marketed as modern panaceas as alternatives to "harmful" allopathic remedies. If we accept that evidence-led medicine is a rational progression, is there any generation of peer-reviewed literature that could be useful in the management of this new public-led enthusiasm for ancient pharmaceutical practice?

There are scholarly journals on the web which attempt to address the proof of new medical therapies. One, published by Elsevier in the Science Direct library, is entitled "Phytomedicine" and attracts "innovative and expert" findings in therapy, toxicology and formulation associated with plant-based medicine. The publishers comment that "The papers published in this journal are also useful to drug regulatory authorities in deciding whether to approve certain phytomedicines or not." This sets a public role for the journal as such decisions affect policy and individual well being. Unfortunately potential conflicts of interest, judged by the ethical considerations which we currently apply to allopathic medicines, are equally evident in a sample of papers from this journal particularly in the supplements section. Supplements are often used by publishing houses and are welcomed by young researchers as they concentrate information on a new drug or product in a single issue. They are, almost without exception, moneymakers for publishers.

A sample supplement in 2006 reviews a medicine composed of ethanolic extracts of plant materials, a preparation with a long heritage and used by patients for the treatment of gut motility disorders (Allescher, 2006).[3] The papers are an interesting mix of clinical trial, meta-analysis and some fairly highly technical analysis which attempts to look at mechanism of action. In these refereed papers, the authors are tempted to extemporise beyond the data and suggest that laboratory findings will be directly translated to a clinical effect (Schempp et al, 2006).[4] Moreover, other contributors propose that functional bowel disease may represent a suitable target for a mixture of substances with multiple targets although the claim of clinical superiority is not explicit. This is arguably a different tack to that in conventional gastroenterological research, and in my view must remain highly speculative. On at least one of these papers, authorship included representation from the sponsoring company. There were no statements of financial links disclosed in the individual publications and even if none exist, we should apply the same rules to reassure the public that there are no conflicts of interest.

Small pharmaceutical companies producing "alternative" medicine are therefore in the spotlight. The possibility of inappropriate claims in medical scientific literature and the risk that editorial advisors are less aware of issues of conflicts of interest poses a problem if healthcare policy in the United Kingdom places the two systems side-by-side. Moreover, if it is the stated editorial policy that a journal's output could be used to influence decision making in Government, then the publishers as well as the editor bear a serious responsibility to maintain appropriate standards of scientific evidence and extrapolation.

Clive G Wilson is a consultant for Allergan Inc (USA), Aspire (USA), Egalet a/s (Denmark), GSK (UK), Intec (Israel) and is working on programmes financed by Pfizer and other major pharmaceutical companies. He has no financial interest in the material discussed in this article and acknowledges the assistance of the Royal Pharmaceutical Society Great Britain and ABPI in providing background information relating to the preparation of this material. There were, unfortunately, no "ghost writers" available.

REFERENCES

1 Papanikolaou G. et al. (2001) Reporting of conflicts of interest in guidelines of preventive and therapeutic interventions. BMC Medical Research Methodology 2001, 1:1-3.

2 Ernst E. (2002) Adulteration of Chinese herbal medicines with synthetic drugs: a systematic review. J. Int. Med. 252:107-113.

3 Allescher H D. (2006). Functional dyspepsia-a multicausal disease and its therapy. Phytomedicine 13: SV 2-11.

4 Schempp H., Weiser D., Kelber O., Elstner E F (2006). Radical scavenging and anti-inflammatory properties of STW 5 (Iberogast) and its components . Phytomedicine 13: SV 36-44.

In discussion the following points were made:

Although there was a representative speaking on behalf of the Royal Pharmaceutical Society of Great Britain, the need was expressed for a speaker to represent the pharmaceutical industry. There are major problems in the interpretation of data resulting in a collapse of trust. This requires industry to be more open. The Medicines and Healthcare products Regulatory Agency (MHRA) is unbiased although funded by industry. However, there is still a need for some public funding for the evaluation of drugs. But why spend scarce public money on drugs when the companies have so much? It is very important to acknowledge the failures of the current drug appraisal system. It is considered bizarre by the public that manufacturers control product availability. Research blind alleys are often not disclosed for reasons of commercial competition and confidentiality, and lack of transparency results in much wasted effort by researchers.

Homeopathic testing by the MHRA has slipped from previous high standards in that only homeopathic proof is now required and not scientific testing. Transparency through publication is not possible since if you publish your results you cannot patent them. Non-financial conflicts also exist and may bias outcomes. Nevertheless, despite the difficulties, 25% of all useful drugs were developed in this country. According to Sir Richard Sykes the pharmaceutical industry has a bad name – that is the reality – and industry has a job to do to put it right.

Journals are controlled by the Editors in Societies, who are not under commercial pressure, and not by commercial publishing houses who also have their own standards of ethics. However, reprints of key articles may have a very high commercial value to the publishers and are protected as the source of valuable profits to journal publishers. There are pressures for these to be more freely available on the worldwide web. Peer review also received criticism for the amateurish way it is sometimes conducted, as it may give rise to conflicts between the reviewer and author. Indeed, ideas may be stolen, or suppressed; the drug company may have power of veto over the final published paper, which may not contain all relevant data. This situation might be improved by publishing the reviewers' names.