Clinical trial safety committees: the devil's spoon

[Education and debate : Personal paper ]

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He who sups with the devil needs a long spoon. To cast the pharmaceutical industry in the role of the devil may seem a little unfair, but the British Biotech affair has shown all too clearly that there are times when the industry must be kept at arm's length from the development of its own drugs. This paper describes briefly the problems which beset British Biotech-reports of which have generally been confined to the financial pages of the daily press-and emphasises the need for the medical profession to recognise that the relation between drug development and patient care will always be an uneasy one.

British Biotech was (and still is) one of the new breed of companies based on high technology, "hype," and promise. Its market capitalisation-with a share price based solely on drugs under development-increased so much that the company nearly gained entry to the FTSE 100 index. When the director of clinical research, Dr Andrew Millar, told the principal shareholders that the clinical trials of two of their drugs were not going as well as the directors had claimed, he was dismissed and the share price collapsed. Millar was then sued by the company for breach of confidentiality. After nearly two years of legal wrangling British Biotech backed down and compensated him. The company's wrists were slapped by the Stock Exchange council-which is apparently what passes as "self regulation" in the City-and the story was over.

But all this need never have happened, and would not have done, had the two clinical trials in question been watched over by a data monitoring and safety committee. Although most companies and academics involved with clinical trials take the importance of data monitoring and safety committees as read, the British Biotech story is worth telling for the benefit of those who have never heard of one, and as a cautionary tale for those who have.

Methods

The information on which this article is based came from reports in the business sections of the daily press (for example, the Guardian of 19 June 1999 and the Times of 25 June 1999), from the protocols of the trials of marimastat and lexipafant, and from personal discussions with Dr Millar and Dr Frank Wells, former medical director of the Association
of the British Pharmaceutical Industry and adviser to Dr Millar, during the course of the legal action mounted by British Biotech.

**British Biotech trials**

The British Biotech saga is based on two drugs, marimastat, which was intended for the treatment of pancreatic cancer, and lexipafant for acute pancreatitis. In the pancreatic cancer trial, marimastat was compared with a conventional cytotoxic agent, gemcitabine. The administration and side effects of the two compounds were so different that conducting the study on a blind basis was impossible. However, marimastat was tested at three dosage regimens, and there was blinding in relation to these. The trial was set up without a data monitoring and safety committee. All data were kept in house, and Millar, as the senior medical employee, took the role of the data monitoring and safety committee and had access to the (dose blind) trial results at all times.

Millar observed an excess mortality in patients given marimastat, and he felt obliged to "unblind" the doses when a case of cardiomyopathy was reported. However, the fivefold higher mortality observed was not statistically significant, and because the highest dose of marimastat was associated with reduced mortality, Miller informed the directors but let the trial continue.

Gemcitabine and the highest dose of marimastat remained superior treatments, and this had important implications for the phase III trials which were due to start. Millar communicated this to the company directors, but they were unwilling to reconsider the phase III programme and he felt his only alternative was to inform the shareholders.

**Lexipafant**

The situation with lexipafant was complex and the details are not important here. The protocol of the trial did stipulate that a data monitoring and safety committee should be formed, but this committee met only once, reviewed data which had already been unblinded by Millar, and agreed that the trial should continue. As the study progressed, Millar knew that lexipafant was ineffective. He wanted to reconvene the data monitoring and safety committee, but the British Biotech directors would not allow this. These events coincided with the marimastat situation and Millar sought the support of the shareholders to rectify matters concerning both marimastat and lexipafant.

**Data monitoring and safety committees**

It is clear that the role of a data monitoring and safety committee and the need to appoint one are not widely appreciated. Had they been, the protocol for the trial of marimastat would never have been passed by the ethical committees of the participating centres, since it did not mention such a committee.

**Aim**

The main purpose of a data monitoring and safety committee is to protect patients—primarily those included in the trial but also other patients with the disease in question. The second responsibility of the data monitoring and safety committee is to ensure the
integrity of the study, but it has no other responsibility to the sponsors. Millar acted as a one man data monitoring and safety committee and attempted to protect the best interests of the patients. For his pains he incurred an expensive legal battle.

**Strength of purpose**

Had a data monitoring and safety committee been established and allowed to work properly in both trials, there would have been no need for a company employee to break the treatment code. A data monitoring and safety committee must be composed of a small number of strong individuals who insist on meeting regularly and who will not bow to company pressures. Companies always want to know trial results quickly so that if they are good, licensing can be fast tracked, and if they are bad, an expensive trial can be stopped. Pharmaceutical companies sometimes claim allegiance to stock market rules, and only a strong data monitoring and safety committee can protect them by allowing them honestly to claim that they do not know trial results.

**Stopping rules**

In a clinical trial, the unexpected often happens. A data monitoring and safety committee can be guided by predetermined rules on the limits of possible benefit and harm at which a trial should be stopped. However, a data monitoring and safety committee is not a substitute for a computer. In fact, stopping rules were not predefined in either of the British Biotech trials, making a data monitoring and safety committee even more important. In both trials, a data monitoring and safety committee would have come to the same conclusions and recommendations as Millar. If these recommendations had been ignored, the data monitoring and safety committee, being independent, would have been able to take whatever steps were necessary to ensure that the company complied.

**Maintaining the balance**

A data monitoring and safety committee has to be totally independent of both the trial investigators and the sponsoring company because it is responsible for the balance between individual and collective ethics. When a drug seems to be beneficial, should the trial be stopped early so that the treatment can be made available to all patients or should it continue so that the magnitude of the benefit can be measured accurately and some estimate made of the drug’s effect in different subgroups of patients? To make such a judgment a data monitoring and safety committee needs detailed information and the time to assess the consistency of the drug’s effects in subgroups of patients and in different centres. However much the sponsor might welcome it, stopping a study early because a drug seems beneficial is seldom a good idea in the long run. Stopping a trial prematurely because of a harmful effect or lack of efficacy is essential as soon as this is proved beyond doubt—but that proof has to be judged by the data monitoring and safety committee.

**Independence**

Members of a data monitoring and safety committee should be experienced and independent minded—and they must not be easily frightened by the pressure of unfolding trial events or by pressure from the sponsors. In the two British Biotech trials, the company was in a rush to get the drugs to the market, and apparently avoided
appointing a committee because it would slow the decision making cycle. However, not all company employees have the strength of mind shown by Millar. What would have happened if he had not blown the whistle remains a matter for conjecture.

The data monitoring and safety committee is the long spoon that allows patients and investigators to sup confidently with the pharmaceutical industry.

**Summary points**

Doctors working in the pharmaceutical industry have to contend with the competing demands of drug development and patient safety

The British Biotech affair has shown the pharmaceutical industry at its worst

As far as possible, company sponsored clinical trials must be run independently-data should not be kept in house and company employees should not have access to them

An independent data monitoring and safety committee should oversee trials

The committee should comprise experienced and strong minded clinicians and trialists whose remit is to ensure the welfare of patients in the widest sense