MEDIA/DIRECTOR v PFIZER

Celebrex study and meeting

An article in the BMJ, 5 September 2009, criticised a Celebrex (celecoxib) study and meeting. Celebrex was Pfizer's product for the symptomatic relief of osteoarthritis, rheumatoid arthritis and ankylosing spondylitis. In accordance with the Authority's Constitution and Procedure, the matter was taken up as a complaint by the Director.

The meeting, at a five star hotel resort in March 2009, had been held to encourage GPs to participate in a major study comparing the cardiovascular safety of Celecoxib vs non-selective non-steroidal anti-inflammatory drugs (NSAIDs). The author of the BMJ article had attended the meeting at the invitation of the study sponsor (a named university).

The BMJ article was critical that the invitation to the meeting did not mention Pfizer although it provided £26 million for the study. The study was described as an 'academic, investigator-initiated study, requested by the European Medicines Agency (EMEA) and sponsored by the (named university)'. The study application form submitted to the NHS research ethics committee indicated that Pfizer was the sole funder of the study.

According to the article, the Saturday morning meeting ended with a three course lunch. Attendees had complimentary drinks and dinner the night before, accommodation at the hotel on the Friday night and their travel reimbursed. The principal investigator stated that attendees received only 'standard set menus and no excessive hospitality was given'. He stressed that GPs had given up a Saturday without pay to be trained in trial methodology.

The article stated that thirty five doctors attended the meeting from 25 practices. Up to four GPs attended from a single practice. Some doctors said their practice had already signed up to the trial. One of them admitted coming along just for the hospitality. Practices that signed up received £1,000 and a further £5 every two months for each patient reporting progress on a web portal. The principal investigator noted that the money went to the practices not direct to the doctors.

The principal investigator defended the study's independence and noted that it was entirely run by the university with no pharmaceutical company involvement in any of its meetings. As such, the Code was inappropriate. A Pfizer spokesman supported the principal investigator's position stating, inter alia, that the study was an investigator driven research project sponsored by the university. Pfizer had financially supported the study, but it was managed and operated independently of the company. The meeting was not organised by Pfizer or on Pfizer's behalf; it was solely the initiative and responsibility of the principal investigator.

The article stated that the trial had been registered on ClinicalTrials.gov which encouraged transparency in clinical research by providing free access to information about funding, sponsorship, methodology, intervention, and research question. There was no mention of Pfizer in the trial registration form. The university had not commented on why it chose to leave out the funding source from the clinical register.

A professor of sociology was reported as being concerned that the study website did not mention Pfizer's funding – a fact also missing from some news pieces announcing the study. 'Neglecting to mention the financial sponsor of the research is deceptive', he stated and 'the recruitment of doctors via entertainment in five star luxury also appears to be ethically questionable'.

The article noted that the study was being conducted so that Pfizer could fulfil a regulatory commitment. COX-2 inhibitors had been monitored since 2004, when rofecoxib was withdrawn because of a risk of thrombotic cardiovascular events and questions were raised regarding the cardiovascular safety of other COX-2 inhibitors. The EMEA had decided to keep celecoxib on the market but to recommend a long term study to investigate its safety relative to non-selective NSAIDs.

The detailed response from Pfizer is given below.

The Panel noted Pfizer's submission and the comments of the principal investigator about their respective roles and responsibilities in relation to the study. The Panel considered that it was important to note the regulatory requirement for the study. Correspondence with the EMEA referred to Pfizer committing to perform a global cardiovascular study to confirm long term safety and to dialogue about the study design with EMEA/CHMP. The Panel noted Pfizer's submission that the principal investigator had acted as a global medical consultant on celecoxib for its parent company, Pfizer Inc, including attending the Oral Explanation before the CHMP. Pfizer explained that a study protocol was drafted by the principal investigator and his academic colleagues, although it was reviewed and amended by Pfizer and EMEA/CHMP. The university was the study sponsor for the purposes of the clinical trial regulations.

The Panel noted that the BMJ article criticised: the level of hospitality provided to potential clinical

investigators and the acceptability of the venue; whether the study was promotional including the acceptability of the level of payments to investigators and whether Pfizer's role in funding the study had been declared.

The first issue to be considered was the extent to which Pfizer was responsible, if at all, under the Code for any of the activities at issue. The Panel noted the regulatory requirement for the study. The Panel noted Pfizer's submission that the trial was an investigator initiated study, run independently of Pfizer; it was carried out at arm's length from Pfizer and without reference to the company.

The Panel noted that the study agreement between Pfizer and the sponsoring university described the parties as independent contractors. The university undertook to keep Pfizer updated on progress at regular intervals and provide quarterly written reports. Monthly teleconferences were also held with Pfizer. Under the study contract Pfizer undertook to provide two representatives to attend as observers to the Executive Committee and Steering Committee. The Panel noted that Pfizer by invitation had attended meetings of the Steering Committee as non voting observers but had rarely been invited to attend any meetings of the Executive Committee.

The Panel noted that Pfizer UK had little involvement in the matters subject to the complaint as its parent company Pfizer Inc led on this matter. The Panel was concerned that the first time Pfizer UK heard about the meeting at issue was when it was contacted by a journalist who wished to attend the meeting which was held in the UK and thus potentially subject to the UK Code. UK health professionals had attended the meeting. It was an established principle under the Code that UK companies were responsible for the acts and omissions of their overseas affiliates that came within the scope of the Code.

Taking all the circumstances into account, the Panel did not accept that Pfizer had absolutely no responsibility under the Code for any aspect of the arrangements. It was not a strictly arm's length arrangement. Pfizer was obliged to initiate the study to satisfy regulatory requirements. On the evidence before the Panel, Pfizer Inc had not included a provision about Code compliance as part of the contract. The Panel noted Pfizer UK's proposal to subsequently amend the contract by adding a relevant provision that the university conduct the study in accordance with 'all applicable laws, regulations and codes of practice'. The Panel noted that on finding out about the meeting Pfizer UK had advised the principal investigator that there was a very high likelihood of Pfizer being associated with it and that it could not allow study funds to be used to hold meetings at a venue such as that proposed. The Panel also noted that, at the university's request, Pfizer had provided it with guidance on how to run an event within the ABPI guidelines. The Panel noted that there might be certain activities which fell solely within the investigator's remit on which the company quite properly had absolutely no influence. However, in the particular circumstances of this case, the Panel considered that it was beholden on Pfizer to use its best endeavours to ensure the contract provided that certain activities such as arrangements for meetings complied with the Code, otherwise the omission of such provisions would be a means of circumventing the relevant Code requirements. This would be unacceptable.

Taking all the circumstances into account the Panel considered that Pfizer UK was responsible under the Code for the matters raised in the article at issue.

The Panel noted that the hotel meeting was designed to educate UK potential trial investigators about the study. The meeting started at 8.30am with registration followed by the first presentation on the study at 9am. The meeting finished at 1pm for lunch. Overnight accommodation and dinner had been provided for 34 doctors, one journalist and 6 study staff. Three GPs, 4 study staff and 1 public relations person attended but did not stay overnight. The overall cost was £215.63 per attendee, including study staff and investigators or £278.01 for delegates. The Panel considered that irrespective of the content, the impression given by holding a half day meeting at the hotel which was a renowned, deluxe venue, including an overnight stay for most delegates, was inappropriate. High standards had not been maintained. The impression given by the arrangements was such that they brought discredit upon and reduced confidence in the pharmaceutical industry. Breaches of the Code were ruled including Clause 2.

A declaration of Pfizer's role in relation to funding the study did not appear on the invitation, agenda or other meeting papers. Pfizer Inc's observer status was referred to on a slide which discussed the organisation of the study but not the company's financial role. A breach of the Code was ruled. The Panel noted that other study material should have clearly indicated Pfizer's role. The Panel noted that the only other relevant piece of material before the Panel was the GP template contract which referred to the Pfizer funding in the first paragraph. The Panel ruled no breach of the Code in relation to the GP template contract.

The only issue to be considered by the Panel in relation to the study was whether it was disguised promotion. In this regard particular reference was made in the article at issue to the run-in period. The study was run independently of Pfizer. Nonetheless the Panel considered that in the particular circumstances of this study it was beholden on Pfizer, before it provided the finance, to satisfy itself that the study was not disguised promotion. The protocol stated that the study was powered to demonstrate that celecoxib was not inferior to standard NSAID therapy in relation to cardiovascular safety. Eligible patients were subject to a 2 week open-label run-in of treatment with

celecoxib. At the end of this period subjects who had taken at least one dose and who did not express a strong preference for either their previous treatment or celecoxib were eligible for randomisation. Appendix 1 to the protocol explained some of the rationale behind the study design and explained that chronic NSAID users who were not taking 'coxib' medicines had demonstrated tolerance to NSAIDs and randomisation without an open phase was thought to introduce a bias in that such subjects would be more likely to tolerate their old medicine than a new one. For this reason the open label phase allowed those who had relatively similar tolerability and efficacy to both therapies prior to randomisation to be included. The Panel noted that the regulators had considered and approved the protocol before recruitment commenced. The Panel did not consider that the points of concern raised in the BMJ article were sufficient to demonstrate that the study was disguised promotion. A reasonable explanation appeared in an appendix to the protocol. No breach was ruled.

The Panel noted that given its ruling of no breach above it thus followed that on the narrow allegation in the article, Pfizer had funded the study for research purposes and the funding to the university did not constitute an inducement to prescribe, supply, administer, recommend, buy or sell any medicine. No breach was thus ruled.

The Panel noted Pfizer's submission about the modest nature of the payments to practices participating in the study. The practice received a one-off payment of £1,000 to search records and contact patients followed by £5 per month for each participant recruited by the practice and £1 per month for the provision of data in relation to each participant. Given its finding of no breach of the Code above, and noting that the level of the payments was not unreasonable, the Panel ruled no breach.

Upon appeal by Pfizer the Appeal Board noted Pfizer's submission and the comments of the principal investigator about their respective roles and responsibilities in relation to the study. The Appeal Board considered that it was important to note the regulatory requirement for the study. The EMEA had reviewed the safety of the COX-2s, including celecoxib (Celebrex) in 2004/5. In June 2005 the CHMP recommended the maintenance of the marketing authorization for Celebrex on the basis that Pfizer initiated a global study to investigate the long term cardiovascular safety of celecoxib relative to non-selective NSAIDs. The Appeal Board noted Pfizer's submission that the principal investigator had acted as an external medical consultant on celecoxib for Pfizer Inc including attending a meeting of the CHMP on Pfizer's behalf and it was in this capacity that he was aware of the CHMP requirement for a study and become involved. Pfizer had initially planned to sponsor the study itself which it submitted was the more usual approach. However, the principal investigator presented a proposed study design which was ultimately accepted by CHMP as suitable in order to meet Pfizer's regulatory commitment. The protocol was reviewed and amended by Pfizer and the CHMP.

The study agreement stated that the university was the study sponsor for the purposes of the clinical trial regulations and Pfizer provided the funding. The university undertook to keep Pfizer updated on progress at regular intervals and provide quarterly written reports. Pfizer Inc personnel were permitted to attend meetings of the Executive Committee and the Steering Committee as non voting observers. Pfizer's attendee's at these meetings had been epidemiologists. After January 2009, monthly teleconferences were also held with Pfizer.

The Appeal Board was concerned that the first time Pfizer UK heard about the meeting at issue was when it was contacted by a journalist who wished to attend the meeting which was held in the UK and thus potentially subject to the UK Code. UK health professionals had attended the meeting.

The Appeal Board noted that once it knew about the meeting in the hotel Pfizer had contacted the principal investigator and requested that the venue be changed as there was a high likelihood of Pfizer being associated with it. However, the university proceeded with the arrangements. Pfizer submitted that it was unable to prevent the meeting taking place and that it had no legal control over the meeting.

The Appeal Board noted from the study agreement that £170,000 was set aside for practice recruitment and initiation meetings for each of the first two years. The Appeal Board was concerned about Pfizer's lack of control or even guidance about how this money was to be used.

The Appeal Board acknowledged that investigator initiated studies made an important contribution to knowledge about medicines and their use. Whether or not they were subject to the Code would depend on the circumstances of each particular case. The fact that some of these studies might be subject to the Code did not, in itself, mean that they could not happen. Each case would be considered on its own particular merits.

The first matter to be decided in this case was whether Pfizer was responsible under the Code for a study it had funded and which was undertaken to satisfy regulatory requirements and maintain Celebrex's marketing authorization. The Appeal Board noted that given the regulatory requirement for the study funded by Pfizer the description used by Pfizer, 'investigator initiated' did not give a wholly accurate impression of the process by which the study was devised.

The Appeal Board noted that when approving protocols etc for company-funded studies regulators imposed certain obligations upon those companies particularly, for instance, with regard to the collection of adverse event data. The mere fact

that a company acted to fulfil its obligation in this regard in what was otherwise a wholly independent study did not necessarily mean that the study could not be considered to be conducted at arm's length. Taking all the circumstances into account the Appeal Board decided that although Pfizer funded the study there was a high degree of independence built into it. The Appeal Board decided that Pfizer was not responsible under the Code for the arrangements of the meeting in question; these were the responsibility of the university. The Code did not apply and thus there could be no breach of it. The appeal was successful.

Notwithstanding its ruling above that the arrangements at the investigator's meeting were not covered by the Code, the Appeal Board was very concerned about the perception of such meetings and their possible adverse effect upon the reputation of the pharmaceutical industry. The Appeal Board was also concerned that the materials circulated for the meeting, including invitations to potential investigators, did not mention Pfizer's funding role. It considered that, in their contracts with study sponsors, companies would be well advised to at least refer to the requirements of the Code in relation to meetings and to transparency in relation to the involvement of the company even if the arrangements, as here, were not subject to the Code.

The BMJ (5 September 2009) featured an article entitled 'In clear sight' which criticised a Celebrex (celecoxib) study and meeting. Celebrex was Pfizer Limited's product indicated for symptomatic relief in the treatment of osteoarthritis, rheumatoid arthritis and ankylosing spondylitis.

The meeting was held at a five star hotel resort in March 2009. The journalist had attended the meeting at the invitation of the university which acted as the sponsor for the study at issue. A similar meeting had been held in January 2009. Both meetings aimed to provide general practices with sufficient information about the study to enable GPs to decide whether to participate.

In accordance with Paragraph 6.1 of the Authority's Constitution and Procedure, the matter was taken up as a complaint by the Director. The author was asked whether she wished to be involved in the case and whether she had any additional information to submit. The journalist did not respond to this request.

COMPLAINT

The article was concerned about the meeting arrangements. The invitation did not mention Pfizer although it provided £26 million for the study. The study was described as an 'academic, investigator-initiated study, requested by the European Medicines Agency (EMEA) and sponsored by the [named university]'. The study application form submitted to the NHS research ethics committee indicated that Pfizer was the sole funder of the study.

The study compared the cardiovascular safety of the cyclo-oxygenase-2 (COX-2) inhibitor celecoxib with that of other non-steroidal anti-inflammatory drugs (NSAIDs) in patients over 60, already taking a non-selective NSAID regularly, and who did not have established cardiovascular or peripheral vascular disease or severe heart failure.

According to the article the journalist was invited to attend the meeting by the principal investigator via a public relations firm that listed Pfizer as one of its clients. The meeting started at 9am on Saturday and ended with a three course lunch. Attendees had complimentary drinks and dinner the night before, accommodation at the five star luxury hotel on the Friday night and their travel reimbursed.

The principal investigator stated that attendees received only 'standard set menus and no excessive hospitality was given'. He also stressed 'GPs had given up their Saturday without pay to be trained in trial methodology'. Further the meeting at the hotel was a cost cutting measure, 'We found that if we rented out a room somewhere during the week, doctors weren't coming. But they are coming if we set up meetings at the weekend at the hotel. This still works out better for us. The whole deal we get from the hotel is a lot less than £300. You could say the recession's helped us do the study'. His argument was that doctors had to be paid a locum fee of £350 a day if the meetings were held during the week and one partner had to leave the surgery.

The article stated that thirty five doctors attended the meeting from 25 practices. Up to four GPs attended from one practice. Some doctors said their practice had already signed up to the trial. One of them admitted coming along just for the hospitality. Another joked, 'If we don't sign up now, does that mean we get to come to [the hotel] again and again until we make our minds up?'.

Practices that signed up received £1,000 and a further £5 every two months for each patient reporting progress on a web portal. The principal investigator stated: 'Some practices have more than 50 patients. That's quite a lot of money, but it goes to the practice. The university does not sign any cheques for doctors'.

The principal investigator defended the study's independence and submitted that the trial created vital research capacity. It was entirely run by the sponsoring university with no pharmaceutical company involvement in any of its meetings. As such, mention of the Code was inappropriate. The article referred to the requirements of Clause 19.1 of the Code and advice that companies were asked 'would you and your company be willing to have these arrangements generally known?' when determining whether the arrangements for any meeting were acceptable.

A Pfizer spokesman supported the principal investigator's position that the ABPI Code did not

apply. The study was an investigator driven research project led by the principal investigator of the university which sponsored the study. Pfizer had financially supported the study, but it was managed and operated independently of Pfizer. This meeting was not organised by Pfizer or on Pfizer's behalf; it was solely the initiative and responsibility of the principal investigator and the sponsoring university.

The article quoted a doctor commenting that '…this is obviously not how patients for trials should be recruited. Doctors should be encouraged to recruit in a trial because they think it's a good thing and will be beneficial for the patient. There are loads of ways they could go about recruiting for trials – they could go to health centres, have lunch meetings, for example – the hotel would seem inappropriate to most people. I would also question whether the overnight stay is necessary. Most doctors could have driven to the meeting in the morning'.

A senior lecturer in clinical pharmacology, also had reservations: 'Like all academic research projects with external funding, Pfizer has agreed to provide a certain sum of money to pay for the trial, and this will include costs of recruitment and investigators' meetings – in the hotel for this particular study. The money has been given to the university, but the source is still commercial'.

The lecturer referred to a meeting he had held for 12 researchers which cost roughly £300 – sandwiches in a small hotel right next to a railway station. There were lavish meetings and frugal – usually tax payer funded – ones, he stated 'the principal investigator was only able to hold the meeting in question at the hotel because money was coming from Pfizer. There would be no chance of the university agreeing to pay for such a meeting from university funds'.

The lecturer, who specialised in developing methods for evaluating data on adverse effects, was also concerned about the design. Patients all underwent a run-in phase before randomisation where they took celecoxib for two weeks before being allowed to take full part in the trial. The lecturer questioned the effect of this run-in phase. In his opinion, all those who suffered side effects from celecoxib would drop out in the first two weeks, thus ensuring that only those who did well with celecoxib continued. He had strong concerns about the study design as the safety data would not be as valid as with other designs.

A professor of biostatistics and biomathematics, who specialised in clinical trials design and analysis, agreed stating that the run-in would remove patients with unfavourable cardiovascular or gastrointestinal response. Those with side effects to celecoxib would be out of the study. Using a run-in with so many completed studies on celecoxib was silly. The study should be revised and the run-in deleted.

A spokesman for Pfizer noted that: 'the study was an investigator driven research project and stated that the study sponsors should be contacted for a response to questions relating to the conduct of the study.

The sponsoring university declined to comment on the specific criticisms of the trial design but had released the full protocol after a request under the Freedom of Information Act. The document provided a rationale behind choices of study design: 'The trial identifies chronic NSAID users in the population who were not taking 'coxib' [COX-2] drugs. These subjects have demonstrated tolerance to NSAIDs. Switching of drug therapy to celecoxib as would happen to 50% of subjects if randomization occurred without an open label phase was thought to introduce a bias in that subjects would be more likely to tolerate their previous drug than the new one. For this reason the open label phase allows those who have relatively similar tolerability and efficacy to both therapies prior to randomization'.

The document explained that at the end of the run-in period, 'Subjects who have taken at least one dose of celecoxib and who do not express a strong preference for either their previous treatment or celecoxib will be eligible for randomization. Preference will be determined by the patient response to a questionnaire'.

The article stated that the trial had been registered on ClinicalTrials.gov which encouraged transparency in clinical research by providing free access to information about funding, sponsorship, methodology, intervention, and research question. Its policy was consistent with US law and did not require the listing of collaboration or funders if they were not considered the sponsor. There was no mention of Pfizer in the trial registration form.

A spokesperson for the International Committee of Medical Journal Editors (ICMJE) stated: 'As stated in the ICMJE policy, funding source or sponsor is a required field for registration. Without this information, the ICMJE would consider registration insufficient'.

A spokesperson for Pfizer stated: 'Pfizer considers investigator driven research to be important in advancing disease treatments and consequently improving the lives of patients. Pfizer encourages all investigators to disclose information on research they are conducting; however, there is no formal requirement for them to do so'.

The university had not commented on why it chose to leave out the funding source from the clinical register.

A professor of sociology, also raised concerns that the study website did not mention funding from Pfizer – a fact also missing from some news pieces announcing the study. 'Neglecting to mention the financial sponsor of the research is deceptive', he stated 'On the other hand the recruitment of doctors via entertainment in five star luxury also appears to be ethically questionable'.

The director of a university institute of medical

humanities who specialised in ethical issues in primary care and professional integrity in clinical research added: 'The purpose of the study in the trial register reads more like a press release promoting celecoxib than a statement of today's science. The notion that other NSAIDs pose a significant cardiovascular risk, comparable to that of COX-2 drugs, is a very dubious claim. This certainly makes me worried that the information to be presented to research subjects will sound more like a marketing ploy and less like an assessment of the science'.

The participant information sheet presented to potential research subjects stated that 'One NSAID which appears to be at least as safe as most NSAIDs and may be safer than some is celecoxib'. The document highlighted that 'there have also been a number of recent studies of this group of drugs [COX-2s] some of which have suggested there may be a link between these newer drugs and increased heart disease and strokes. For Celebrex [celecoxib], this evidence is not conclusive and there have been many studies that have shown no increased risk of heart disease and strokes'. It pointed to a recent meta-analysis suggesting that cardiovascular effects for celecoxib were similar to those of other NSAIDs and stated 'there is also evidence that older NSAIDs have cardiovascular effects'.

The article stated that the principal investigator insisted that 'This isn't a commercially viable trial for Pfizer. It's not going to help their business model. They're doing this because they have to fill a regulatory EMEA commitment'.

The health regulator had monitored COX-2 inhibitors since 2004, when rofecoxib was withdrawn because of a risk of thrombotic cardiovascular events and questions were raised regarding the cardiovascular safety of other COX-2 inhibitors. As part of the EMEA's December 2005 decision to keep celecoxib on the market, it recommended a long term study to investigate its safety relative to non-selective NSAIDs. An EMEA spokesperson stated: 'You cannot force anyone to conduct clinical trials, but if a company wants its product to stay on the market then we need to be convinced that it should be there. It is in Pfizer's commercial interest to do it'.

When writing to Pfizer the Authority asked it to respond in relation to Clauses 2, 9.1, 9.10, 12.2, 18.1, 18.6, 19.1 and 19.3 of the Code.

RESPONSE

Pfizer explained that as a result of the withdrawal of another COX-2 inhibitor, rofecoxib, in September 2004 due to safety concerns, the European Commission recommended that the cardiovascular safety of all COX-2 inhibitors should be re-examined. The CHMP subsequently required a commitment by Pfizer to undertake a global study to confirm the long term cardiovascular safety of celecoxib. Pfizer also agreed to discuss the design of such a study with EMEA/CHMP.

The study initially designed by Pfizer Inc and approved by the FDA was not acceptable to CHMP as in its view it did not reflect actual use of Celebrex in Europe. The principal investigator, a university professor, was one of Pfizer's external experts during this procedure and, when it became clear that the initial study design could not be modified to meet the CHMP's requirements, he proposed an alternative design, which was ultimately accepted by CHMP and became the study at issue. This study would be conducted in the EU, while the initial study design would be conducted in non-EU countries including the US.

The protocol was drafted by the principal investigator and his academic colleagues and, although it was reviewed and amended by Pfizer and by EMEA/CHMP, most of the study documentation was prepared by the principal investigator and his team and the study design remained essentially as those academics had envisaged. The final study protocol was agreed in July 2007. The study contract between Pfizer Inc and the sponsoring university, under which Pfizer Inc funded the study, was entered into in July 2007 and the study commenced in 2008. Pfizer's funding of the study was made clear in section 14.5 of the study protocol and the participant information sheet, which informed prospective study participants that 'Pfizer, the company who have developed celecoxib, is giving a grant to the [named university] to allow this study to be done'.

The study, a large streamlined safety study (with a prospective randomised open blinded end-point design) was developed to compare the cardiovascular safety of celecoxib with that of traditional NSAIDs. Inclusion criteria were patients sixty years of age or older with clinically diagnosed osteoarthritis or rheumatoid arthritis who were free from established cardiovascular disease and who required chronic NSAID therapy. Patients who signed informed consent and met inclusion and exclusion criteria were then entered into a two-week (14 +/- 7 days) open-label run-in of treatment with celecoxib. (The primary objective of the open-label run-in was to include subjects with relatively similar tolerability and efficacy to both therapies prior to randomisation). At the end of the run-in, patients who had taken at least one dose of celecoxib and who did not strongly prefer either their previous treatment or celecoxib were eligible for randomisation. Medication was taken by the patient consistent with clinical practice on an as required basis. At the time of the protocol completion, it was anticipated that participants would be followed up for an average of 2 years. The primary endpoint of the study was the first occurrence of hospitalisation or death for the Anti-Platelet Trialists' Collaboration (APTC) cardiovascular endpoint of non-fatal myocardial infarction, non-fatal stroke or cardiovascular death.

The study was designed to reflect real life use of medicines, and was a type of study that the principal investigator had advocated for many years. As

stated by a participating GP, in a 'rapid response' to the BMJ article, '[This] is an academic study, run to the protocol developed by [named professors] and managed jointly with other academics from [other universities]'. Two of the named professors, in response to the article stated that it was incorrect to describe the study as 'a Pfizer study' and further explained that: 'The European Medicines Agency (EMEA) obliged Pfizer to fund such a trial if it was feasibly [sic] to do so'. We responded by designing a study that EMEA regarded as feasible and required Pfizer to fund. The study was welcomed by the Chief Medical Officer, Chief Pharmacist and Chief Scientist in [a named country] in part because it tried to develop methodology to extend the ability to do outcomes studies to non-industry investigators …'.

Whilst Pfizer Inc funded the study, the study design was essentially the work of the principal investigator and his academic colleagues, and he was concerned that the study should be run independently of Pfizer and that the university would act as sponsor for the purposes of the clinical trial regulations.

The study protocol provided that the study would be overseen by an Executive Committee. According to the contract, two representatives of Pfizer could be present at meetings of the Executive Committee as observers, although they were not permitted to vote. In addition a Steering Committee would be established to oversee the conduct of the study. Pfizer had no contractual right to participate in or observe the Steering Committee, but had in practice been invited to attend all Steering Committee meetings in non-voting capacity. [A second university] supervised monitoring of the study and also undertook quality assurance, reporting its findings to the sponsoring university. Similarly, [a third university] would be responsible for the statistical analysis of the study data, similarly under contract to the sponsoring university. An independent data monitoring committee was also planned to be constituted to review unblinded data and recommend any necessary study modifications, to the Steering Committee.

The running of the study was therefore determined and conducted entirely independently of Pfizer, save for the fact that Pfizer representatives could contractually be present as observers at meetings of the Executive Committee and had attended meetings of the Steering Committee as non-voting members. In practice, however, Pfizer had rarely been invited to any meetings of the Executive Committee and had not been party to any decisions made by it.

As of January 2009, the team of relevant personnel based at Pfizer Inc in the US met by teleconference with the study sponsor's team, on a weekly and subsequently bi-weekly basis. The aim of these study team meetings was to share information on the progress of the study, particularly in relation to enrolment and, in view of Pfizer's regulatory commitment to the EMEA, for Pfizer to share with the sponsor's team, its skills or expertise relevant to improving enrolment of both GPs and patients.

Meeting at the hotel

Both Pfizer Inc and the sponsoring university recognised that the principal investigator needed to hold meetings with GPs to tell them about the study so that they could consider whether to take part. £170,000 per year for years 1 and 2 was allocated for the purposes of practice recruitment and initiation meetings with a further £10,000 in year 3. The recruitment strategy was not specified in the contract or the study protocol and the arrangements were matters to be determined by the principal investigator as he considered appropriate in all the circumstances, together with all the other arrangements for the study. The study payment schedule was provided.

On 28 January 2009, at meeting of the study team, reference was made to a recruitment meeting to be held on 30/31 January for GP practices which were not yet participating in the study. The meeting was informed that 40 GPs would attend this recruitment meeting to learn about the study and consider taking part. According to the minutes of the meeting and the recollection of the Pfizer team, no information was provided about the location for the meeting or the arrangements.

At the next meeting of the study team, 4 February 2009, Pfizer Inc personnel requested feedback from the recruitment meeting on 30/31 January and were told, for the first time, that the meeting had been held at the five star hotel in question. In the circumstances of this investigator led study, the Pfizer Inc US personnel did not view the choice of hotel as a cause for concern.

On 24 March Pfizer UK received an enquiry from a freelance journalist about the 30/31 January meeting. This was the first time the UK organisation knew that a meeting related to the study had been held at the hotel, and the US team was alerted to the UK perspective on the use of such venues, in the context of the principles of the Code, albeit that this was an event organised and controlled by the study sponsor, independently of Pfizer. Pfizer's response to the journalist's questions were shared with the principal investigator in advance. He agreed with the responses; in his view he was fully responsible for the meeting and would defend his choice of venue publicly.

On 25 March 2009, at a further meeting of the study team, Pfizer Inc discovered that another meeting had been arranged at the hotel on 27/28 March and that 34 GPs were expected to attend. Pfizer Inc personnel expressed concern about the venue in the context of the principles of the Code. The principal investigator explained that the meeting was educational and wholly independent of Pfizer and therefore unobjectionable. He maintained that the hotel was more cost-effective than other venues as a result of the favourable terms negotiated and the fact that, because the meeting would be on a Saturday, the cost of locum cover for attending GPs was avoided. Finally he advised the study team that he had invited

the freelance reporter who had previously contacted Pfizer, to attend the meeting, so that she could see for herself that the meeting was educational and that there was nothing untoward about the arrangements.

After the study team meeting, Pfizer discussed internally the proposed meeting at the hotel and the principal investigator's comments. While the study was investigator designed and driven and the meeting arrangements were wholly the responsibility of the investigator, Pfizer was concerned that, as Pfizer Inc had funded the study, Pfizer would be linked with the meeting and that such association might be viewed as inconsistent with the principles of the Code. Pfizer was unable to compel the principal investigator to rearrange the meeting, in accordance with the contractual arrangements between Pfizer and the university, or otherwise. Accordingly, after several unsuccessful attempts to telephone him, Pfizer emailed him, in the strongest terms, to ask him to change the arrangements for the meeting, in particular to ensure that it was held at an alternative venue to mirror the principles of the Code, in order to guard against potential reputational damage to Pfizer or the university. A copy of the email was provided. Nonetheless the meeting proceeded as originally planned and Pfizer received no reply to the concerns expressed in its email or to its request that the meeting be rearranged at a different venue.

The meeting at the hotel was discussed at the next meeting of the study team on 1 April 2009. The principal investigator reported that he had contacted the PMCPA and had established that the sponsor university was not subject to the Code. It was unclear whether he had contacted the PMCPA before or after the meeting and what information he had provided during that discussion. He commented that it was difficult to find any other appropriate meeting venue nationally and reiterated his view that the hotel was cost-effective and appropriate. He strongly objected to Pfizer's email.

However, at the end of April, the university's team asked Pfizer to suggest appropriate alternative venues for the meetings in question. On May 7 Pfizer sent to the sponsor an article entitled '10 Ways to Run an Event Within the ABPI Guidelines', a practical guide. To Pfizer's knowledge, since the March recruitment meeting, no further meetings had been held at the hotel at issue or any similar venue that might be viewed as inconsistent with the principles of the Code.

While the study was investigator initiated, and Pfizer had no wish to prejudice the independence of the investigator/sponsor in its organisation or arrangements, the company was concerned that the meeting at the hotel could result in adverse reputational consequences for Pfizer and for the university principal investigator. Therefore, when on 8 June 2009 Pfizer sent a proposed contract amendment to the university, this included, inter alia, an amendment seeking to strengthen the existing wording in the contract on the governance of the study such that Pfizer would require the university to conduct the study in accordance with 'all applicable laws, regulations, and codes of practice', in an attempt to reinforce the points made to the university in March concerning the principles of the Code. The university had not formally responded to this amendment request.

In summary, Pfizer had no involvement whatsoever in either of the two meetings held at the hotel in January and March 2009. Pfizer only knew about the January meeting after it had taken place and about the March meeting two days beforehand. Pfizer was not involved in the initiation or running of the meetings and no-one from Pfizer attended either meeting. The meeting materials prepared by the principal investigator and his team were not discussed with or shown to Pfizer. While it seemed likely that Pfizer Inc's funding for practice recruitment and initiation meetings during the study would have paid for the meetings in question, such expenditure was not discussed with, specifically invoiced to or approved by Pfizer, and Pfizer did not know how much was spent on the meetings. As it was not present at or involved in the meetings, Pfizer had no first hand knowledge of these matters, however some further information had been published by the doctors who submitted rapid responses to the article published in the online version of the BMJ (see below).

The principal investigator advised Pfizer Inc that 40 GPs attended the meeting in January 2009 and that 34 were due to attend the meeting in March. The BMJ article stated that 35 GPs attended the meeting on 27/28 March. Pfizer could not confirm the accuracy of these figures. Pfizer had not seen any of the material used by the principal investigator during the meetings at the hotel. No agency was involved on behalf of the company in relation to such meetings. As Pfizer had had either no advance knowledge (January) or minimal advance knowledge (March) of the meeting there was no opportunity for the company to ensure that materials used had included a declaration that funding had been provided by Pfizer.

Pfizer had no specific knowledge of the role of the public relations agency in respect of the study or the meetings at the hotel. Pfizer assumed that the university had hired the agency to assist with the meeting arrangements and/or communications. The BMJ article stated that the public relations agency claimed that Pfizer was a client - however any relationship between Pfizer and the agency was unrelated to the study.

Immediately following the publication of the article in the BMJ, a rapid response letter from a GP and trial physician, involved with running the study at the sponsor university, was published on the BMJ website. A copy of this response was provided.

- The GP justified the use of the hotel to recruit doctors and indicated that other presentations

had been given at smaller locations. He confirmed that 'there was no golf, spa treatments or any other luxurious indulgence going on' during the meeting. He concluded 'in exchange for giving up this Saturday morning to hear about and decide whether to take part in one the largest academic NSAID safety studies ever attempted, GPs were provided with free dinner, B&B and/or lunch. Concerning the venue they expressed a preference for a hotel without sticky carpets'.

- The GP also stated that Pfizer's funding had never been secret. He said 'it is irrelevant because [the study] is an academic study run to the protocol developed by [named professors] and managed jointly also with other academics.

- He confirmed his view that the money offered to practices to take part in the study was appropriate and 'money has not been an incentive as most practices have fewer than 20 eligible patients and the sums involved are nominal'.

- Finally, he justified the design of the study stating 'patients who do a lot better, as well as those who do worse, on celecoxib compared with their usual NSAID are both excluded from randomisation. This is because we need to observe patients for a considerable time to detect differences between all NSAIDs in their cardiovascular risk effects and during that time they need to stay on their randomised therapy. Therefore we select patients who don't care if they are randomised to celecoxib or their old NSAID. That is not what you do if you are trying to bias the results in favour of celecoxib'.

A second rapid response letter, from the two professors who were co-authors of the study protocol, was subsequently published on the BMJ website. A copy of this letter was provided.

- The two professors corrected the characterisation of the study as 'a Pfizer study', explaining its academic origins and design and Pfizer's obligation to fund it, in light of the company's obligation to the EMEA.
- They explained the necessity of the 'run-in period' and denied that the purpose of the study was marketing-related.
- With regard to the meeting venue, they suggested that the cost was likely to be no more and possibly less than other less famous venues and stated that the Comprehensive Research Networks established by the UK government encouraged 'similarly-costed away days to increase awareness and interest and which pay trial participants comparable amounts for their activity'. Finally they underlined the importance and challenge of encouraging individuals to take on research responsibilities 'in a target-driven clinical world'.

Responses to the clauses from the Code

The BMJ article referred only to the hotel meeting in March 2009 attended by the journalist. Nevertheless in circumstances where, as explained above, Pfizer understood that two meetings were held, it addressed both of these in its response.

Clauses 9.1 and 9.10

Clause 9.1 of the Code provided that high standards must be maintained at all times and Clause 9.10 stated that material relating to medicines and their uses, sponsored by a pharmaceutical company must clearly indicate that it had been sponsored by that company. In this context, the BMJ article stated that the invitation to the March meeting did not mention the provision of funding by Pfizer.

As indicated above, the trial was an investigator initiated study, run independently of Pfizer. The organisation of the study was carried out at arm's-length from Pfizer and without reference to the company. While Pfizer funded the study, a requirement that it be responsible for every action by the investigator and every document generated by the investigator would be inconsistent with fact that the study was an investigator initiated study and with the status and responsibilities of the investigator in this case, as sponsor in accordance with the clinical trial regulations. Furthermore, it was not clear from the wording of the Code that Clause 9 was directed towards material generated by an investigator in an investigator initiated study or that, in the circumstances of the study at issue, Pfizer was obliged to supervise all arrangements by the sponsor or to certify all materials generated by the sponsor in connection with the study.

In the context of the BMJ article Pfizer did not know about the January meeting at the hotel until after it had been held and received two days' notice of the meeting in March. Pfizer was not invited to the meeting nor provided with the agenda or any of the materials prepared by the sponsoring university for the meetings either before they took place or afterwards. It therefore had no knowledge of the materials used by the principal investigator or whether they referred to Pfizer's funding of the study. The contractual arrangements between Pfizer and the sponsoring university did not require the university to disclose such materials to Pfizer or to agree them with the company, as was appropriate given the university's position as study sponsor, being solely responsible for the conduct and operation of the study.

In relation to the assertion that announcements and press statements had not referred to Pfizer funding, to the extent that any had been made by Pfizer (such as the comments given to the journalist), Pfizer had always made this clear. Pfizer had not been consulted on or involved in announcements made by the university, but noted that one recent article concerning the study, published in the lay press on 19 August and extensively quoting the principal investigator, referred to the study being funded by Pfizer.

Clause 12.2 – Disguised promotion

The study at issue was an investigator initiated study set up at the request of the EMEA/CHMP. The study was designed by the principal investigator and his academic colleagues, and while the original draft protocol was amended following input from both Pfizer and the EMEA/CHMP, the final protocol was essentially his work. The protocol was considered in detail with the EMEA/CHMP and approved by them before recruitment commenced.

Pfizer funded the study in order to satisfy a regulatory obligation imposed by the EMEA/CHMP. The company vigorously refuted any suggestion that the study was disguised promotion.

Clauses 18.1 and 18.6 - Gifts, inducements, promotional aids and the provision of medical and educational goods and services

The BMJ article referred to the fact that practices that agreed to take part in the study would receive £1,000 and a further £5 every two months for each patient reporting progress on a web portal. As was appropriate in an investigator driven study of which the university was the sponsor, Pfizer had not been involved in determining these sums or making these arrangements. However, Clause 8 the GP template contract supplied by the university to Pfizer (solely for information) in January 2009 read: 'The Practice shall receive the sum of £5.00 per month for each Study Participant recruited to the Study by the Practice, plus £1.00 per month per Study Participant for the provision of prescribing data in relation to each Study Participant which sums will be paid by the University quarterly in arrears based on the Study data records held by the University detailing recruitment/retention at the Practice. In addition a one off payment of £1000.00 shall be paid to the Practice in relation to searching records and writing to patients required in relation to the Study'.

Although not involved in determining these figures, Pfizer considered that they represented a fair payment for the time spent by a GP in considering the study materials and identifying patients who appeared to be potential study subjects as well as providing the required follow-up information. Certainly they seemed well below the level customarily paid in industry sponsored clinical trials. In this regard, according to the relevant section of the British Medical Association website which set out suggested payment rates for various types of work for pharmaceutical companies, the rate suggested for clinical trial work was £223 per hour. £1,000 payment therefore represented a little over four hours' work at this rate, which seemed entirely reasonable for the work required. These payments thus did not incentivise doctors to take part in the study.

With respect to Clause 18.6, as indicated in the response to Clause 12.2 above, the study was a genuine scientific study, designed with substantial input from the EMEA/CHMP and approved by them. The study was not organised or run by Pfizer: Pfizer had funded the study in order to satisfy a regulatory obligation. The study constituted genuine research and not an inducement to prescribe, supply, administer, recommend, buy or sell any medicine.

Clauses 19.1 and 19.3 - Meetings and hospitality

The BMJ article criticised the meeting at the hotel in relation to the level of hospitality provided (explicit reference to Clause 19.1 was included in the article) and because the invitation did not state that funding had been made available by Pfizer.

The principal investigator's position was that he arranged for the hotel meetings independently of Pfizer and that they were not objectionable. The principal investigator was not subject to the Code and had confirmed the position with the PMCPA. He believed that the hotel represented a cost-effective use of resources and that GPs who were willing to give up a Saturday morning in order to learn about the trial, in reasonably comfortable surroundings. Finally, Pfizer knew of no evidence that any of the GPs who attended the meeting used any of the hotel's sporting facilities. The journalist was invited to the meeting by the principal investigator without reference to Pfizer.

As Pfizer had explained, it was not involved in the arrangements for either meeting held at the hotel, as was appropriate given that the university was the sponsor and entirely responsible for its conduct and operational arrangements. While the principal investigator maintained strenuously that the Code was not applicable to meetings organised by the sponsoring university, Pfizer was nevertheless concerned that it would be linked with the meeting. Pfizer therefore strongly requested the principal investigator to change the venue, but the university proceeded with the arrangements and Pfizer was unable to prevent the meeting taking place. While Pfizer's funding was intended to include support for meetings for the study it would have been inappropriate for Pfizer to request involvement in the operational arrangements. In any event, from the description of the meeting provided by a GP in his response to the article, the actual meeting arrangements and hospitality were not lavish.

As indicated above, the BMJ article stated that the invitation to the meeting did not state that the study was sponsored by Pfizer. Pfizer had explained that it had had no prior knowledge of the meeting and was not provided with the agenda or any of the meeting materials. The company was thus unable to confirm the accuracy of the BMJ article in this regard.

Clause 2 - Discredit to, and reduction of confidence in, the industry

While Pfizer would have preferred the meeting to have been held at a different venue, thereby avoiding any controversy, it believed that a finding of a breach of Clause 2, in the circumstances, would be unfair and disproportionate. The study was a

genuine, major scientific study, established at the request of the EMEA/CHMP, designed and run by the principal investigator and his academic colleagues, and approved by EMEA/CHMP following detailed consideration of the study protocol. As explained above, the sponsor of the study was a university.

As such, the meeting at the hotel was organised and held without Pfizer's input or its knowledge as was appropriate in the circumstances where, as study sponsor, the university was entirely responsible for the conduct of the study and its operational arrangements. Nevertheless, as soon as it knew about the matter the company strenuously tried to persuade the principal investigator to hold the March meeting elsewhere, in order to guard against any reputational damage to Pfizer (and therefore the wider pharmaceutical industry), or the university itself. Despite its efforts Pfizer was unable to prevent the meeting taking place. There were no other measures which Pfizer could reasonably have taken in order to change these meeting arrangements.

While it could not confirm the content of the materials distributed at the hotel meetings, in circumstances where Pfizer had no knowledge of the meetings and was given no opportunity to review the documents, it was unable to require that a statement regarding Pfizer funding of the study was included.

The circumstances described did not warrant the level of censure that should be reserved for a breach of Clause 2.

Further Information

In response to a request for further information Pfizer provided additional comment and documentation.

Pfizer noted that it had not previously asked the sponsoring university for the detailed information requested by the Authority about the meeting on 27/28 March 2009, believing it inappropriate in the context of an investigator run study where the university as sponsor was solely responsible for such organisational matters, and given that the university had no obligation to disclose such information to Pfizer under the study contract. However, following the Authority's request for further information Pfizer requested this information from the principal investigator. The principal investigator declined to provide this information directly to Pfizer but had offered to provide it directly to the Authority. Pfizer did not object to him doing so, and was aware that the Authority had now informed him that he must either copy Pfizer so that it received the same information, or send it directly to Pfizer as originally requested. Pfizer had no preference as to either route.

The study was a matter of international importance for all of the companies in the Pfizer group, The global medical and clinical teams for Celebrex, based in the US, drove the arrangements for the study and were the contact points with the sponsoring university for the purposes of the study. All relevant affiliates of Pfizer, including Pfizer Limited, as marketing authorization holders for Celebrex in the EU (and elsewhere), knew about the CHMP opinion and the commitment to the EMEA, and the design, objectives and progress of the study. European regional medical colleagues for Celebrex based in the UK would have been similarly well informed about the medical aspects of the study. European regulatory and European legal colleagues based in the UK were closely involved in the regulatory procedures and regulatory/legal aspects. However the Pfizer UK organisation was not involved in the operational, regulatory or contractual arrangements for the study. No advice was requested from the Pfizer UK organisation in this regard. Pfizer Limited UK first knew about the study meeting at the hotel on 24 March, when it received the enquiry from the journalist. It was then that the UK organisation advised the global team with respect to this matter.

Further material was received from the principal investigator including details of the meeting costs and a copy of the presentations. Pfizer confirmed on 26 November that the principal investigator's submission could be treated as part of its response.

The principal investigator accepted the PMCPA's role as a regulator of the marketing practices of pharmaceutical companies, but could not understand why a research meeting organised and run by a university, which was the legal sponsor of the trial protocol written and owned by university investigators, could be construed as within the PMCPA's remit. The investigators had agreed to provide the data requested but only because Pfizer asked them to do this.

PANEL RULING

The Panel noted Pfizer's submission and the comments of the principal investigator about their respective roles and responsibilities in relation to the study. The Panel considered that it was important to note the regulatory requirement for the study. The position was set out in the CHMP opinion dated 23 June 2005 which recommended the maintenance of the marketing authorization and, inter alia, also recommended that Pfizer initiated a long term study to investigate the safety of celecoxib relative to non-selective NSAIDs. Subsequent correspondence with the EMEA referred to Pfizer committing to perform a global cardiovascular (CV) study to confirm long term CV safety and to Pfizer's commitment to dialogue about the study design with EMEA/CHMP. The Panel noted that the BMJ article commented on the role of the principal investigator. The Panel noted Pfizer's submission that he acted as a global medical consultant on celecoxib for its parent company, Pfizer Inc, including attending the Oral Explanation before the CHMP. Pfizer explained that a protocol was drafted by the principal investigator and his academic colleagues, although it was reviewed and amended

by Pfizer and EMEA/CHMP. The university was the study sponsor for the purposes of the clinical trial regulations.

The Panel noted that the BMJ article criticised three key matters: the level of hospitality provided to potential clinical investigators and the acceptability of the venue; whether the SCOT study was promotional including the acceptability of the level of payments to investigators; and whether Pfizer's role in funding the study had been declared.

The Panel noted in relation to the study itself the relevant provision in the Code was Clause 12.2 which required that clinical assessments, post-authorization studies and the like must not be disguised promotion and must be conducted with a primarily scientific or educational purpose. In addition the supplementary information to Clause 19, Meetings and Hospitality, made it clear that, inter alia, investigator meetings for clinical trials were covered by the Code.

The first issue to be considered was the extent to which Pfizer was responsible, if at all, under the Code for any of the activities at issue. The Panel noted the regulatory requirement for the study. The Panel noted Pfizer's submission that 'The trial was an interventional, investigator initiated study, run independently of Pfizer. The organisation of the study was carried out at arm's-length from Pfizer and without reference to the company'.

The Panel considered that, in general terms, the extent to which a company was responsible for study arrangements had to be decided on a case by case basis on the individual facts of each case. The Panel noted that the arrangements between Pfizer and the university at which the principal investigator was based were set out in the study agreement to which the study protocol was annexed. The agreement described the parties as independent contractors. The university undertook to keep Pfizer updated on progress at regular intervals and to provide quarterly written reports on the study progress in terms of enrolment, study centre rollout and other material issues arising in relation to the study. Monthly teleconferences were also held with Pfizer. Under the study contract Pfizer undertook to provide two representatives to attend as obververs to the Executive Committee and Steering Committee. The Panel noted that Pfizer, by invitation, had attended meetings of the Steering Committee as non voting observers but had rarely been invited to attend any meetings of the Executive Committee.

The Panel noted that the position was complicated as Pfizer UK had little involvement in the matters subject to the complaint as its parent company Pfizer Inc led on this matter. The Panel was concerned that the first time Pfizer UK heard about the meeting at issue was when it was contacted by a journalist who wished to attend the meeting which was held in the UK and thus potentially subject to the UK Code (as set out in the supplementary information to Clause 1.7). UK health professionals had attended the meeting. It was an established principle under the Code that UK companies were responsible for the acts and omissions of their overseas affiliates that came within the scope of the Code.

Taking all the circumstances into account, the Panel did not accept that Pfizer had absolutely no responsibility under the Code for any aspect of the arrangements. It was not a strictly arm's length arrangement. Pfizer was obliged to initiate a long term study to investigate the safety of celecoxib vs non-selective NSAIDs to satisfy regulatory requirements and chose to do so via the study. On the evidence before the Panel, Pfizer Inc had not included a provision about Code compliance as part of the contract. The Panel noted Pfizer UK's proposal to subsequently amend the contract by adding a relevant provision that the university conduct the study in accordance with 'all applicable laws, regulations and codes of practice'. The Panel noted that on finding out about the meeting Pfizer UK had advised the principal investigator that there was a very high likelihood of Pfizer being associated with it and that it could not allow study funds to be used to hold meetings at a venue such as that proposed. The Panel also noted that, at the university's request, Pfizer had provided it with guidance on how to run an event within the ABPI guidelines. The Panel noted that there might be certain activities which fell solely within the investigator's remit on which the company quite properly had absolutely no influence. However, in the particular circumstances of this case, the Panel considered that it was beholden on Pfizer to use its best endeavours to ensure the contract provided that certain activities such as arrangements for meetings complied with the Code, otherwise the omission of such provisions would be a means of circumventing the relevant Code requirements. This would be unacceptable.

Taking all the circumstances into account the Panel considered that Pfizer UK was responsible under the Code for the matters raised in the article at issue.

The Panel noted that the supplementary information to Clause 19.1 stated, inter alia, that a meeting venue must be appropriate and conducive to the main purpose of the meeting; lavish, extravagant or deluxe venues must not be used. Venues renowned for their entertainment should be avoided. It should be the programme that attracted delegates and not the associated hospitality or venue. The impression created by the arrangements must be borne in mind.

The Panel noted that the meeting was designed to educate UK potential trial investigators about the study. The meeting started at 8.30am with registration followed by the first presentation on the study at 9am. This was followed by presentations on the role of nurses, data collection for research nurses, and monitoring and good clinical practice (GCP) training finishing at 1pm for lunch. Overnight accommodation and dinner had been provided for 34 doctors plus one journalist and 6 study staff. Three GPs, 4 study staff and 1 public relations person attended but did not stay overnight. The

overall cost was £215.63 per attendee, including study staff and investigators or £278.01 for delegates. The Panel considered that irrespective of the content, the impression given by holding a half day meeting at the hotel which was a renowned, deluxe venue, including an overnight stay for most delegates, was inappropriate. A breach of Clause 19.1 was ruled. High standards had not been maintained. A breach of Clause 9.1 was ruled. The impression given by the arrangements was such that they brought discredit upon and reduced confidence in the pharmaceutical industry. A breach of Clause 2 was ruled.

A declaration of Pfizer's role in relation to funding the study did not appear on the invitation or agenda or other meeting papers as required by Clause 19.3. Pfizer Inc's observer status was referred to on a slide which discussed the organisation of the study but not the company's financial role. A breach of Clause 19.3 was ruled. The Panel noted that other study material should have similarly contained a clear indication of Pfizer's role. The Panel noted that the only other relevant piece of material before the Panel was the GP template contract which referred to the Pfizer's funding role in the first paragraph. The Panel ruled no breach of Clause 9.10 in relation to the GP template contract.

The only issue to be considered by the Panel in relation to the study was whether it was disguised promotion contrary to Clause 12.2. In this regard particular reference was made in the article at issue to the run-in period. The study was run independently of Pfizer by the university investigators. Nonetheless the Panel considered that in the particular circumstances of this study it was beholden on Pfizer, before it provided the finance, to satisfy itself that the study was not a disguised promotional activity. The protocol stated that the study was powered to demonstrate that celecoxib was not inferior to standard NSAID therapy in relation to CV safety. Eligible patients were subject to a 2 week open-label run-in of treatment with celecoxib. At the end of this period subjects who had taken at least one dose and who did not express a strong preference for either their previous treatment or celecoxib were eligible for randomisation. Appendix 1 to the protocol explained some of the rationale behind the study design and explained that chronic NSAID users who were not taking 'coxib' medicines had demonstrated tolerance to NSAIDs and randomisation without an open phase was thought to introduce a bias in that such subjects would be more likely to tolerate their old medicine than a new one. For this reason the open label phase allowed those who had relatively similar tolerability and efficacy to both therapies prior to randomisation to be included. The Panel noted that the protocol was considered in detail with EMEA and CHMP and was approved by them before recruitment commenced. The Panel did not consider that the points of concern raised in the article at issue were sufficient to demonstrate that the study was disguised promotion. A reasonable explanation appeared in an appendix to the protocol. No breach of Clause 12.2 was ruled.

The Panel noted that given its ruling of no breach of Clause 12.2 it thus followed that given the narrow nature of the allegation in the article that there could be no breach of Clause 18.6 in that Pfizer had funded the study for research purposes and the funding to the university did not constitute an inducement to prescribe, supply, administer, recommend, buy or sell any medicine. No breach of Clause 18.6 was thus ruled.

The Panel noted Pfizer's submission about the modest nature of the payments to practices participating in the study. The practice received a one-off payment of £1,000 to search records and contact patients followed by £5 per month for each participant recruited by the practice and £1 per month for the provision of data in relation to each participant. Given its finding of no breach of Clause 12.2 and noting the level of the payments the Panel considered that the payments were not unreasonable and thus no breach of Clause 18.1 was ruled.

APPEAL BY PFIZER

Pfizer submitted that the study arose from the EMEA's review of the safety of the COX-2 inhibitors, including Celebrex in 2004/5. In June 2005, the CHMP adopted an opinion which required a commitment by Pfizer to undertake a global study to confirm the long term cardiovascular safety of celecoxib. The principal investigator was one of Pfizer's external experts during the review and therefore knew about the CHMP requirement. He subsequently presented a proposed study design which was ultimately accepted by CHMP as suitable in order to meet Pfizer's commitment. It was a large simple trial designed to reflect the real life use of medicines, devised by the principal investigator and his academic colleagues, of a type that he had advocated for many years.

The protocol was drafted by the principal investigator and his academic colleagues and, although it was reviewed and amended by Pfizer and by the CHMP, most of the study documentation was prepared by the principal investigator and his team and the study design remained essentially as those academics had envisaged. The final study protocol was agreed in July 2007. Therefore, whilst Pfizer Inc funded the study, its design was essentially the work of the principal investigator and his academic colleagues, and he was particularly concerned that it should be run independently of Pfizer and that his university would act as sponsor for the purposes of the clinical trials regulations. Pfizer agreed to that arrangement and informed the CHMP accordingly. Pfizer noted that the UK had a particularly strong tradition of clinical research being led, conducted and sponsored by academic institutions and other non-commercial bodies. The study was regarded by the medical and academic community as particularly significant in terms of clinical research nationally and Pfizer's funding as a notable achievement in this regard.

The study contract between Pfizer Inc and the sponsoring university was entered into on 26 July 2007, and the study commenced in January 2008. Under the contract it was clear that the university was the sponsor of the study for the purposes of the clinical trial regulations, and was therefore responsible for the study in regulatory terms, most notably towards the MHRA. The university therefore made the Clinical Trial Application to the MHRA, and received approval to conduct of the study in the UK on 12 April 2007. The university's sponsorship of the study, and Pfizer's funding of it, was made clear in both the study protocol and the participant information sheet, which informed prospective participants that Pfizer, the company which had developed celecoxib, was giving a grant to the sponsoring university to allow this study to be done.

Pfizer submitted that the university and its sub-contractors (mainly other academic institutions) were wholly responsible for the conduct and operation of the study. The contract thus did not require the university or the principal investigator to discuss the study organisation or arrangements with Pfizer, or to obtain Pfizer's approval for the arrangements. The imposition of such requirements would have been inconsistent with the fact that the study was to be conducted independently of Pfizer and with the university's status as sponsor for the purposes of the clinical trials regulations. The running of the study was therefore determined and conducted entirely independently of Pfizer, except that Pfizer representatives might under the contract be invited as observers at meetings of the Executive Committee and had also attended meetings of the Steering Committee as non-voting members. In practice, however, Pfizer was rarely invited to any meetings of the Executive Committee and had not been party to any decisions made by it. However, Pfizer was entitled under the contract to regular updates on the progress of the study via quarterly written reports and, after January 2009, monthly teleconferences. It was important for Pfizer to track the progress of the study given that the conduct of the study was a binding commitment to the CHMP and Pfizer was in turn required to provide updates on the progress of the study to the CHMP.

Pfizer submitted that the meeting on 27/28 March 2009 (and the similar one held on 30/31 January 2009) was initiated and organised by the principal investigator and his team, to inform GPs about the study, with a view to recruit them into it. The study budget set out in the contract with Pfizer allocated funding for all aspects of running the study, including a portion for practice recruitment and initiation meetings. However, the recruitment strategy and arrangements (including the choice of venue) were solely determined and implemented by the principal investigator and the university, as the sponsor of the study. Thus no Pfizer entity knew of the proposals or arrangements for the particular meetings, prior to the meeting held in January 2009. When in February the meeting and venue were first mentioned to the Pfizer Inc study team in the US, they were not familiar with the hotel and it did not therefore trigger any concern. However, once Pfizer UK knew about the March meeting and the planned venue, very shortly before it took place, the concern was raised and Pfizer immediately sought to persuade the principal investigator that the meeting should be held at a different venue. In Pfizer's view the Code did not apply to the university or its meeting, but it was mindful of the view taken of such venues under the Code and the risk that the circumstances of the meeting could be misinterpreted, particularly if the factual background to the study was not known, with consequent potential for reputational damage to Pfizer and the university. The principal investigator strongly objected to Pfizer's communication in this regard and its perceived interference in the logistical arrangements for the study, being entirely outside the company's remit. He declined to change the venue. In the week following the meeting the principal investigator told Pfizer that he before booking the venue he had telephoned the PMCPA, asking whether the Code applied to a meeting held to inform and recruit doctors to a university-sponsored study. He was told that the Code regulated the activities of the pharmaceutical industry and since the university was not the industry and not involved in marketing then the Code did not apply to the university. Pfizer had not been able to obtain any further information about this call; however, it was clear that the principal investigator was satisfied that the Code would not preclude him holding the planned meeting at the hotel.

According to the information provided by the principal investigator to the PMCPA the meeting itself ran from 8.30/9am for a half day on Saturday, 28 March. Thirty seven GPs attended, of which 34 were provided with dinner and accommodation the night before (3 lived locally to the venue). The overall cost was £215.63 per attendee (including study staff and investigators) or £278.01 per delegate (if calculated for GP delegates only). The principal investigator also provided the PMCPA with copies of the invitations, agenda, GCP documents and detailed slide presentations used at the meeting. There was no suggestion in the BMJ article, the Panel's rulings or otherwise that the meeting content was inappropriate or lacked scientific or clinical merit or relevance, or that the costs were excessive. Immediately following the March meeting the principal investigator had made clear to Pfizer his view that it was very difficult to find any other appropriate venue nationally and that the hotel was a cost effective, appropriate option. According to the BMJ article and subsequent correspondence on the topic in the BMJ, it appeared that the university had negotiated a favourable arrangement with the hotel in view of the adverse economic climate, and there was no suggestion or evidence that the hospitality provided was lavish. No leisure/sporting activity or entertainment was provided.

The principal investigator was reported in the article as stating that in his experience doctors were more likely to attend a meeting held on a Saturday than during the week, and it was more cost effective to do

so than to provide attendees with a locum fee of about £350 per day if they had to leave the practice on a working day. In his letter to the BMJ responding to the article he also stated that an evening meeting would not provide sufficient time to thoroughly brief and train GPs on all of the required issues relating to the study. In addition, he explained that since GPs from practices from a wide area were invited, a central venue was necessary, and at the time all other hotel options were more expensive or offered inadequate meeting room facilities or accommodation.

Pfizer submitted that following a number of enquiries from the journalist about the study, the principal investigator invited her to the March meeting at the hotel. His intention (as told to Pfizer when the company queried and objected to his proposals just before it took place) was to demonstrate the scientific value of the study and therefore to fully answer and negate the criticism inherent in her enquiries. The result however (some 5 months after the meeting took place) was the critical article published in the BMJ, which was the subject of this complaint.

The journalist declined the PMCPA's invitation to participate in the complaint procedure. As a result, save to the extent that the matters raised in her article were supported by documentation provided by the principal investigator or were accepted by Pfizer, the journalist's criticisms were unsupported by evidence. In particular the prejudicial comments attributed to unnamed doctors attending the meeting were unsubstantiated and, while the identity of other commentators had been provided, it was unclear what information was provided to them or whether their views were reported in their proper context. Certainly, much of the commentary provided by academics and doctors participating in the study in subsequent correspondence in the BMJ strongly refuted these criticisms. Subsequently, the principal investigator responded to the article in a letter published by the BMJ on 21 October 2009. In his letter he strongly countered the criticisms made in the article.

Pfizer noted that no complaint in relation to the meeting or article was received by the PMCPA or by Pfizer from any health professional attending the meeting or from any other source.

Pfizer submitted that the Panel's ruling was predicated upon its conclusion that the meeting at the hotel to discuss the study was subject to the Code. This, in turn, appeared to be based on its assessment that the study 'was not a strictly arm's length arrangement'. Pfizer disagreed with the Panel for the following reasons:

- While Pfizer was obliged to initiate a long term study to investigate the safety of celecoxib to satisfy regulatory requirements, this did not alter the position that the study was proposed and designed by the investigator/sponsor, that the sponsor was the university and not the company, and that it was agreed by all concerned that the study should be carried out independently of Pfizer. Naturally Pfizer would not have funded this large and expensive study if the company had not wished to obtain the results. However, the fact that Pfizer required the results did not mean it should be viewed as initiating and conducting a study when it was clear that this was not the position.

- As the principal investigator explained in his response to the BMJ article, sponsor had a precise meaning in EU legislation and did not simply mean the funder of the study. Sponsor was defined in the Clinical Trials Directive as 'an individual, company, institution or organisation which takes responsibility for the initiation, management and/or financing of a clinical trial'. UK academic institutions commonly initiated, led and managed industry funded clinical research. Such research made a vital contribution to the UK science base. In such situations, as in this case, the academic institution might properly be regarded by the regulatory authorities as the sponsor of the study. The university in question had one of the UK's leading medical schools and a particularly strong reputation, worldwide, for medical research.

- Pfizer noted that in relation to any such research of this kind, which was initiated, led and sponsored by an investigator/academic institution, and funded by industry, the investigator's proposed study protocol was commonly, and understandably, reviewed and commented on by the pharmaceutical company concerned. If this was sufficient for the arrangement to be regarded as 'not at arm's length', then this implied that all such research fell within the scope of the Code.

- The Panel's ruling specifically cited the supplementary information to Clause 19.1 of the Code as a reason why the meeting was within the scope of the Code. The third paragraph of the supplementary information referred, inter alia, to training and investigator meetings for clinical trials and non-interventional studies held or sponsored by companies. Pfizer's submitted that this paragraph was not applicable to the arrangements made solely by the principal investigator/the university in relation to the study. The meeting should not therefore be regarded as one to which this paragraph of the supplementary information, and therefore the Code, applied. If the company's funding of the study was sufficient to bring it within the scope of Clause 19.1, then again that would potentially bring into the scope of the Code all meetings for investigator led studies in which the funding companies had, properly, no actual involvement. In Pfizer's view that would have far-reaching and negative consequences for these arrangements between industry and academic institutions.

- The contract between Pfizer Inc. and the

sponsoring university did not require the investigator to comply with the Code, to obtain approval from Pfizer for the arrangements for the study or to permit Pfizer to comment on or contribute to the study documentation. Such control over the investigator and sponsor was inconsistent with the fact that the study was conducted independent of Pfizer and with the role of the university as sponsor of the study. The principal investigator also made clear, when Pfizer sought to persuade him to rearrange the meeting, that control by Pfizer over the organisation of the study was not acceptable to him. As confirmed by the PMCPA in its discussion with the principal investigator, investigators such as himself were not viewed as subject to the Code and while the principal investigator reassured Pfizer that he would comply with applicable laws and regulations, it was not envisaged that the Code could or should control his activities.

- The subsequent action by Pfizer UK in firstly seeking to persuade the principal investigator not to proceed with the meeting at the hotel and subsequently to amend the contract, reflected Pfizer UK's concern (justified by subsequent events) that the meeting could be misinterpreted in view of Pfizer's funding of the study, particularly in circumstances where the full background to the study and its organisation was not available. Pfizer knew about the view taken in relation to such venues under the Code, with the associated possibility of reputational damage to Pfizer and the sponsoring university. When Pfizer UK knew about the meeting and made every effort to persuade the principal investigator to change the venue, he declined to do so believing that the Code did not apply to his meeting and that Pfizer's interference was unwarranted and inappropriate. He told Pfizer at the study team meeting in the week following the meeting that he had considered resigning from the study, such was his objection to Pfizer's stance.

Overall, Pfizer submitted it was incorrect to conclude that Pfizer UK should be responsible under the Code for the meeting held by the principal investigator at the hotel in circumstances where:

a) it was intended by all parties that the study should be conducted at arm's length from Pfizer, the principal investigator insisted that the study should be sponsored by the university and conducted independently of the company and held a strong view, confirmed by his discussion with the PMCPA, that his activities, including the arrangements he made in connection with the study and meetings arranged by him in that context, were not subject to the Code; and

b) the hotel meeting was organised entirely by the principal investigator without reference to or knowledge of the company; Pfizer had no involvement whatsoever in the arrangements or choice of venue and no Pfizer personnel attended.

Pfizer noted that the Panel, in its ruling, recognised uncertainty in relation to the application of the Code to studies such as the one at issue. The Panel accepted that there might be certain activities which fell solely within the investigator's remit on which the company quite properly had absolutely no influence, although it then considered that it was beholden on Pfizer to use its best endeavours to ensure the contract provided that certain activities such as arrangements for meetings, complied with the Code. Pfizer did not understand the distinction suggested by the Panel and suggested that the inference that, in some ways (save for meetings, unspecified) studies such as that at issue might fall within the Code, although in other respects the Code did not apply, was unhelpful. Pfizer and the principal investigator submitted that studies such as the one at issue, where the funding pharmaceutical company had no involvement in the arrangements for the study, should fall outside the provisions of the Code. The Panel's concerns that this would, in some way, permit companies to circumvent the Code were not valid: in circumstances where a company sought to introduce practices contrary to the Code it could not be said that the company had no involvement in the organisation and arrangements for the study and/or meeting. Pfizer submitted that the hotel meeting fell outside the scope of the Code; in these circumstances, the provisions of Clause 19.1 which required that Pfizer certify the materials for meetings attended by health professionals were inapplicable and inappropriate.

However, if the Appeal Board considered that the hotel meeting was subject to the Code, Pfizer made the following submission in relation to the Panel's ruling of a breach of Clause 19.1.

1 The hospitality provided was not, on its facts, lavish or excessive. The amount spent per attendee was reasonable and the Panel did not suggest otherwise. The Panel had expressed the view that an overnight stay for most delegates was inappropriate; however no evidence was available as to the distance travelled by delegates who attended the meeting or whether it would have been difficult for them to get to the venue by 8.30am, without an overnight stay. Such information was not available to Pfizer and the evidence relied upon by the Panel had not been identified. Pfizer noted that some local GPs did not stay overnight, confirming that, in some cases where this was unnecessary, overnight accommodation was not provided. It seemed to Pfizer that delegates would also be more likely to attend a half day meeting on a Saturday than lose a full day of their weekend, and that a relatively early start was therefore necessary. This would be made more convenient and feasible for delegates from outside the immediate area by providing overnight accommodation.

2 The Panel had also criticised the impression given by holding a half day meeting at the hotel which a renowned, deluxe venue. However, the Code provided no absolute prohibition on the use of

five star hotel accommodation and the response to the BMJ article provided by a physician who attended the meeting was that 'there was no golf, spa treatments or any other luxurious indulgence going on'. The Panel's conclusion therefore appeared to be based solely on the impression created by the name of the hotel irrespective of the level of hospitality actually provided. In circumstances where the principal investigator, who chose the venue, expressed the view (which had not been challenged) that a suitable alternative was not available nationally, the arrangements for the meeting should not be viewed as inappropriate.

3 Pfizer was also concerned that the Panel's conclusions regarding the meeting were based on unsubstantiated quotations in the BMJ article. A journalist naturally had an interest in creating a 'story'. In this case, the journalist declined to participate in the complaints process and therefore much of her article was unsubstantiated and should not have been relied upon by the Panel. As indicated above, the accuracy of the quotations referenced in the article was uncertain and it was also unclear what information was provided to the commentators or whether the proper context for the quotations set out in the article had been provided. Such evidence might not properly form the basis for an adverse decision under a fair procedure.

4 A finding that a study such as that at issue was subject to the Code and that the arrangements for a meeting such as that held at the hotel were inconsistent with Clause 19.1 had substantial implications for future similar research in the UK. Large scale studies such as that at issue represented an important means of developing knowledge on use of medicines in a 'real life' context. It was also often viewed as desirable that studies were conducted at arm's length from industry. If, however, industry must control how such studies were organised, scrutinise the associated study material and remove discretion from the study investigators, then in practice this might make it impossible to conduct such research, at least in the UK. It was not a necessary or proportionate response to the requirement to achieve high standards.

Pfizer submitted that as explained above, the hotel meeting and the associated materials provided in the context of that meeting, fell outside the scope of the Code. In these circumstances, the fact that a declaration of Pfizer's role in relation to the funding of the study did not appear on the invitation or certain other meeting papers, as required by Clause 19.3, was not relevant.

The materials prepared for the meeting were not shown to Pfizer at any time. It would not have expected to see such materials as this would have demonstrated company control over the arrangements for the study, inconsistent with this being an investigator initiated study, conducted independently of Pfizer and in circumstances where the sponsor was the university, rather than the company.

Finally, whilst in Pfizer's view the materials for the meeting fell outside the scope of the Code, it was relevant to consider that the purpose underlying Clause 19.3 was to ensure that the industry's involvement in meetings attended by health professionals was transparent. In this case, there was no suggestion in the BMJ article that attendees were unaware of Pfizer's involvement. In fact the article stated that the meeting materials indicated clearly that the study had been requested by the EMEA and that an obligation to conduct such research had been placed on the Celebrex marketing authorization holder. Subsequent correspondence to the BMJ also supported that the participants were well aware of Pfizer's funding of the study, including the principal investigator's statement that 'The financial support of Pfizer for the study was clearly communicated in meeting slides, press releases, and published articles'.

The Panel's ruling of a breach of Clause 9.1 of the Code related to the ruling of a breach of Clause 19.1. The Panel concluded that 'high standards had not been maintained', although no specific explanation for this finding was provided. Pfizer's appeal in respect of the finding of a breach of Clause 19.1 was repeated here. Given that the meeting was not arranged by Pfizer, it had no knowledge of the arrangements and the meeting was, in any event, not lavish, a finding of a breach of Clause 9.1 was, inappropriate. The wording of the Panel ruling made clear that the only criticism of Pfizer was limited to the Panel's view that it was beholden on Pfizer to use its best endeavours to ensure the contract provided that certain activities complied with the Code. Even if, contrary to Pfizer's view, such a criticism had any merit, it did not warrant a finding of a breach of Clause 9.1. That view was given further support by the fact that the PMCPA itself reassured the principal investigator that the Code had no application to his activities.

The ruling of a breach of Clause 2 of the Code related to the Panel's earlier ruling of a breach of Clauses 19.1 and 9.1 arising from the impression created by the meeting held at the hotel, even though the hospitality provided was not lavish. Pfizer submitted that it was significant that the journalist who had written the article, which formed the basis for this complaint, did not view her 'story' as of sufficient interest or urgency to seek early publication and her allegations were followed by correspondence refuting her criticisms. The journalist declined to participate in the PMCPA investigation, to support the allegations made in the BMJ article. No other complaints from the health professionals attending the meeting or otherwise, or from any other source, had been received arising from this event. In these circumstances, it was simply incorrect to conclude that the meeting resulted in any genuine concern or criticism from anyone who knew the full facts.

Pfizer strongly believed that this case did not fall within the scope of Clause 2. The study was and continued to be run independently of Pfizer and the company had no involvement in the arrangements. In circumstances where Pfizer, concerned that the meeting could be misinterpreted, urged the principal investigator to rearrange the venue, but could not prevent the meeting proceeding and the PMCPA itself advised the investigator that his activities were not subject to the Code, a finding that particular censure of Pfizer's actions was required was wholly inappropriate. Pfizer referred to three other cases since 2006 which had included rulings of a breach of Clauses 2, 9.1 and 19.1 but were readily distinguished from the meeting at issue (Cases AUTH/1827/4/06, AUTH/1848/6/06 and AUTH/1745/7/05). Pfizer submitted that the ruling of a breach of Clause 2 related to certain of the meetings, namely a visit to a lap-dancing club and an event at Wimbledon. In all cases, hospitality/payments to journalists were offered by or on behalf of a company in respect of matters that were clearly subject to the Code and which constituted obvious breaches of its provisions.

Whilst Pfizer maintained that the hotel meeting should not be viewed as subject to the Code, it was significant that other cases where comparable levels of hospitality had been provided (eg Case AUTH/2068/11/07) did not result in a ruling of a breach of Clause 2 even though the hospitality was clearly subject to the Code, was arranged with the full knowledge of the relevant company and was comparable or more lavish than that provided in this case and where there was no indication that the company made the efforts recorded in this case to alter the arrangements.

In summary, Pfizer submitted that the Panel's rulings appeared to be based on allegations or comments contained in the BMJ article, in circumstances where the journalist had an interest in writing a 'story' and declined to participate in the complaints procedure. Save to the extent that matters of fact in relation to the hotel meeting had been substantiated, the article should not be regarded as determinant. Reliance upon unsupported allegations/comments by third parties to form the basis of an adverse decision was inconsistent with a fair procedure. The case raised important points of principle in relation to the extent to which a company should control the arrangements for independent, investigator initiated trials in the UK where the company only provided funding and was not the sponsor. The fact that this case represented new ground for the PMCPA was demonstrated by the lack of previous cases with comparable facts. Pfizer sought only arm's length involvement in the study and did not wish to influence arrangements made by the investigator - an approach viewed by the investigator, and the university sponsor, as critical. Pfizer played no part whatsoever in the arrangements for the meeting. In these circumstances, the study and the meeting should not be viewed as subject to the Code. That view was confirmed by the PMCPA in a discussion with the principal investigator, which he stated took place before he confirmed the arrangements for the meeting.

Pfizer alleged that the arrangements for a meeting such as that held at the hotel should be a matter for the investigator/sponsor of the study and that it was inappropriate for a company such as Pfizer to seek to influence the conduct of a study conducted independently of industry. Furthermore, in this case it was relevant that the investigator strongly defended his choice of venue and that it was, on the facts, not lavish or inappropriate in any way. The sole criticisms of the venue appeared to relate to the name of the hotel and in considering whether it was appropriate to hold the meeting at this site, and no account appeared to have been taken of the limited alternatives available.

In summary, Pfizer submitted that on the particular facts of this case, the meeting at the hotel should not be viewed as falling within the Code and therefore all of the Panel's rulings fell away. If, contrary to Pfizer's position, the meeting was subject to the Code, Pfizer's conduct, specifically its lack of any involvement in the arrangements for the meeting and its efforts to persuade the investigator to change the venue, meant that breaches of Clause 9.1 and 2 should not be found. Such findings would dilute the significance of breaches of those clauses to an extent that prejudiced their value as a deterrent.

APPEAL BOARD RULING

The Appeal Board noted Pfizer's submission and the comments of the principal investigator about their respective roles and responsibilities in relation to the study. The Appeal Board considered that it was important to note the regulatory requirement for the study. The EMEA had reviewed the safety of the COX-2s, including Celebrex in 2004/5. In June 2005 the CHMP recommended the maintenance of the marketing authorization for Celebrex on the basis that Pfizer initiated a global study to investigate the long term cardiovascular safety of celecoxib relative to non-selective NSAIDs. The Appeal Board noted that the BMJ article commented on the role of the principal investigator. The Appeal Board noted Pfizer's submission that he acted as an external medical consultant on celecoxib for Pfizer Inc including attending the Oral Explanation before the CHMP on Pfizer's behalf and it was in this capacity that he was aware of the CHMP requirement for a study and became involved. Pfizer had initially planned to sponsor the study which it submitted was the more usual approach. However, the principal investigator presented a proposed study design which was ultimately accepted by CHMP as suitable in order to meet Pfizer's regulatory commitment. The protocol was reviewed and amended by Pfizer and the CHMP.

The study agreement stated that the university was the study sponsor for the purposes of the clinical trial regulations and Pfizer provided the funding. The university undertook to keep Pfizer updated on progress at regular intervals and provide quarterly

written reports on the study progress in terms of enrolment, study centre rollout and other material issues arising in relation to the study. Pfizer Inc personnel were permitted to attend meetings of the Executive Committee and the Steering Committee as non voting observers. Pfizer's attendee's at these meetings had been epidemiologists. After January 2009, monthly teleconferences were also held with Pfizer.

The Appeal Board was concerned that the first time Pfizer UK heard about the meeting at issue was when it was contacted by a journalist who wished to attend the meeting which was held in the UK and thus potentially subject to the UK Code (as set out in the supplementary information to Clause 1.7). UK health professionals had attended the meeting.

The Appeal Board noted that once it knew about the meeting in the hotel Pfizer had contacted the principal investigator and requested that the venue be changed as there was a high likelihood of Pfizer being associated with it. However, the university proceeded with the arrangements. Pfizer submitted that it was unable to prevent the meeting taking place and that it had no legal control over the meeting.

The Appeal Board noted from the study agreement that £170,000 was set aside for practice recruitment and initiation meetings for each of the first two years. The Appeal Board was concerned about Pfizer's lack of control or even guidance about how this money was to be used.

The Appeal Board acknowledged that investigator initiated studies made an important contribution to knowledge about medicines and their use. Whether or not they were subject to the Code would depend on the circumstances of each particular case. The fact that some of these studies might be subject to the Code did not, in itself, mean that they could not happen. Each case would be considered on its own particular merits.

The first matter to be decided in this case was whether Pfizer was responsible under the Code for a study it had funded and which was undertaken to satisfy regulatory requirements and maintain Celebrex's marketing authorization. The Appeal Board noted that given the regulatory requirement for the study funded by Pfizer the description used by Pfizer, 'investigator initiated' did not give a wholly accurate impression of the process by which the study was devised.

Pfizer's representatives at the appeal hearing advised that as of July 2009 the regulators released Pfizer from its regulatory commitment to complete the study. Nonetheless, the study was currently continuing. Although of interest this was not relevant to the Appeal Board's consideration as when the meeting in question took place, the regulatory requirement was still in force.

The Appeal Board noted that when approving protocols etc for company-funded studies regulators imposed certain obligations upon those companies particularly, for instance, with regard to the collection of adverse event data. The mere fact that a company acted to fulfil its obligation in this regard in what was otherwise a wholly independent study did not necessarily mean that the study could not be considered to be conducted at arm's length. Taking all the circumstances into account the Appeal Board decided that although Pfizer funded the study there was a high degree of independence built into it. The Appeal Board decided that Pfizer was not responsible under the Code for the arrangements at the investigator's meeting in the hotel. These were the responsibility of the university. The Code did not apply and thus there could be no breach of it. The appeal was successful.

Notwithstanding its ruling above that the arrangements at the investigator's meeting in the hotel were not covered by the Code, the Appeal Board was very concerned about the perception of such meetings and their possible adverse effect upon the reputation of the pharmaceutical industry. The Appeal Board was also concerned that the materials circulated for the meeting, including invitations to potential investigators, did not mention Pfizer's role as funder of the study. It considered that, in their contracts with study sponsors, companies would be well advised to at least refer to the requirements of Clause 19 in relation to meetings and to transparency in relation to the involvement of the company even if the arrangements, as here, were not subject to the Code.

Proceedings commenced	**9 September 2009**
Case completed	**24 March 2010**