PRESCRIPTION MEDICINES
CODE OF PRACTICE AUTHORITY

CODE OF PRACTICE REVIEW

NUMBER 57 AUGUST 2007

The Prescription Medicines Code of Practice Authority was established by The Association of the British Pharmaceutical Industry (ABPI) in 1993 to operate the ABPI Code of Practice for the Pharmaceutical Industry independently of the Association itself.

Code awareness campaign wins Communiqué award

The Code awareness campaign, 'It Takes Two to Tango', won the Communiqué award for Best Professional Campaign last month. Four other campaigns were short listed in the category.

The 'It Takes Two to Tango' campaign was run by Santé Communications on behalf of the ABPI and PMCPA in 2006. The aim of the campaign was to raise awareness of the Code amongst doctors and others. The first ever Code Awareness Day took place on 25 April 2006 as part of this campaign. On this day more than 8,000 sales representatives from 50 pharmaceutical companies across the UK talked to health professionals about the Code.

Highlights from the day included:

- 7,500 clinicians were exposed directly to Code Day messages at two major congresses.
- Over 22,000 doctors were sent personal e-alerts.
- A targeted media campaign resulted in more than 15 features.
- A Parliamentary Motion supporting Code Awareness Day and the Code was signed by 41 MPs.
- Many companies ran in-house events for staff.

The Communiqué judges said that this was a highly effective awareness-raising campaign that demonstrated the ethics and transparency of the industry and delivered outstanding results. The campaign was praised for handling a profoundly challenging topic with creativity and great thought.

The campaign to raise awareness of the Code is ongoing, and the second Code Awareness Day took place on 15 May 2007. Nurses and pharmacists are now also being targeted alongside doctors as part of this campaign

Annual Report for 2006

The Annual Report of the Prescription Medicines Code of Practice Authority for 2006 has now been published and copies have been sent to all who are on the mailing list for the Code of Practice Review. Further copies are available on request.

There were 134 complaints in 2006 as compared with 101 in 2005. There were 119 complaints in 2004.

The 134 complaints in 2006 gave rise to 128 cases. The number of cases generally differs from the number of complaints, the reason being that some complaints involve more than one respondent company and some complaints do not become cases at all, usually because no prima facie case is established.

Of the 272 rulings made by the Code of Practice Panel in 2006, 232 (85%) were accepted by the parties, 25 (9%) were unsuccessfully appealed and 15 (6%) were successfully appealed. This compares with the 4% of rulings which were successfully appealed in 2005.

The Code of Practice Panel met 63 times in 2006 (57 in 2005) and the Code of Practice Appeal Board met 11 times in 2006 (13 in 2005). The Appeal Board considered appeals in 22 cases as compared with 17 in 2005.

The number of complaints made by health professionals in 2006 exceeded the number made by pharmaceutical companies, there being 57 from health professionals and 23 from pharmaceutical companies. This has historically been the usual pattern although in 1996, 1999, 2001, 2002 and 2003 the reverse was true.
Under new provisions in the revised Constitution and Procedure, the Authority now advertises brief details of all cases where companies were ruled in breach of Clause 2 of the Code, were required to issue a corrective statement or were the subject of a public reprimand. These advertisements both act as a sanction and highlight what constitutes a serious breach of the Code.

Two such advertisements were placed in the BMJ and The Pharmaceutical Journal in 2006 and the remainder were published or to be published in 2007. Copies of the advertisements are on the PMCPA website.

CODE OF PRACTICE TRAINING

Training seminars on the Code of Practice, run by the Prescription Medicines Code of Practice Authority and open to all comers, are held on a regular basis in central London.

These seminars comprise a full day course offering lectures on the Code and the procedures under which complaints are considered, discussion of case studies in syndicate groups and the opportunity to put questions to the Code of Practice Authority.

The next Code of Practice seminar dates on which places remain available are:

Monday, 15 October
Monday, 19 November

Short training sessions on the Code or full all day seminars can be arranged for individual companies, including advertising and public relations agencies and member and non member companies of the ABPI. Training sessions can be tailored to the requirements of the individual company.

For further information regarding any of the above, please contact Lisa Matthews for details (020 7747 8885 or email lmatthews@pmcpa.org.uk).

How to contact the Authority

Our address is:

Prescription Medicines
Code of Practice Authority
12 Whitehall
London SW1A 2DY

www.pmcpa.org.uk

Telephone: 020 7747 8880
Facsimile: 020 7747 8881

Copies of the Code of Practice for the Pharmaceutical Industry and of this Review can be obtained from Lisa Matthews (020 7747 8885 or email lmatthews@pmcpa.org.uk).

Direct lines can be used to contact members of the Authority.

Heather Simmonds:	020 7747 1438
Etta Logan:	020 7747 1405
Jane Landles:	020 7747 1415

The above are available to give informal advice on the application of the Code of Practice.

The Authority rather than the ABPI is the contact point for information on the application of the Code.

Meeting venues

Companies are reminded that when organizing meetings which are subject to the Code, they must ensure, *inter alia*, that the venue is appropriate and conducive to the main purpose of the meeting. Responsibility in this regard should not be delegated to a third party.

It follows that venues must be approved on a case by case basis according to the type of meeting to be held and the target audience. For example a venue which is suitable for a two day meeting of international thought leaders might not be suitable for an evening meeting of local GPs. Similarly, successful use of a venue does not guarantee its suitability for future meetings. Venues can change over time with regard to the facilities and/or level of hospitality offered.

Cut your carbon footprint!

The Authority appreciates the efforts made by companies regarding the presentation of material submitted to it. Whilst it is helpful to have documents neatly labelled and separated into bundles, it is often the case that individual papers/appendices within the bundles are enclosed in plastic folders and the like. At the completion of a case only the papers are kept – we try to recycle as much of the 'packaging' (plastic folders and ring binders etc) as we can, but nonetheless a quite considerable volume has to be discarded as we have no further use for it. Whilst not wishing to discourage the careful presentation of papers, the Authority asks companies to think twice before providing them in excessive amounts of plastic!

CASE AUTH/1925/12/06

NOVARTIS v APOPHARMA

Breach of undertaking

Novartis alleged that a promotional piece for Ferriprox (deferiprone) was clearly in breach of the undertaking given in Case AUTH/1822/4/06. Novartis further alleged that a claim about survival data was unsubstantiated. As the complaint involved an alleged breach of undertaking the matter was taken up with ApoPharma by the Director as it was the Authority's responsibility to ensure compliance with undertakings. Novartis supplied Desferal (desferoxamine).

Novartis noted that an animated Ferriprox banner advertisement which appeared as a link on the website of the British Journal of Haematology, contained the claim 'New Cardioprotection and Survival Data Now Available'. The statement 'For reference or prescribing information please click here' linked to another website 'Ferriprox.com' and the landing page was headed with the claim 'Life is Getting Longer … in thalassaemia major patients'. There was a link to a summary of product characteristics and a link marked 'for information on Ferriprox and cardioprotection, please click here'. When this link was followed, it took the reader to the Pub Med listing for the abstract of Borgna-Pignatti et al (2006).

Novartis alleged that the claim 'Life is Getting Longer … in thalassaemia major patients' found in breach recently was a hanging comparison. As this was previously found to be in breach for exactly the same reasons it also represented a breach of undertaking.

Secondly, Borgna-Pignatti et al did not provide survival data of any form that could support this claim. The paper discussed cardiac events but there was no analysis of survival. This represented a failure to substantiate a claim and also, by directing the reader to this paper, it was also a misrepresentation of data.

The Panel noted that in Case AUTH/1822/4/06 a Ferriprox banner advertisement, in the electronic version of the British Journal of Haematology, which claimed that 'Life is Getting Longer' was ruled in breach of the Code because it was a hanging comparison. In error, as acknowledged by ApoPharma, the claim had been used again and in breach of the undertaking given in Case AUTH/1822/4/06. The Panel ruled breaches of the Code. The Panel further considered that ApoPharma, by not doing all that it could have done to comply with its undertaking had brought discredit upon, and reduced confidence in, the pharmaceutical industry. A breach of Clause 2 was ruled.

The Panel noted that the banner advertisement on the British Journal of Haematology website stated 'New Cardioprotection and Survival Data Now Available'. The data available was Borgna-Pignatti *et al*, an epidemiological, natural history study conducted in Italy which compared cardiac morbidity and mortality in deferoxamine- or deferiprone-treated patients with thalassemia major. The authors reported that deferiprone therapy was associated with significantly greater cardioprotection than desferoxamine. The authors, however, noted that the study was not randomized and so treatment groups might not have been comparable. Further, there might have been a bias against deferiprone because in the early stages of the 9 year study it was experimental and given to patients with a higher body iron load. Conversely, because deferiprone was not licensed in Italy until mid-way through the trial, some doctors might have been reluctant to prescribe it for their sicker patients thus introducing a bias in favour of the medicine. The authors commented that neither consideration appeared to have strongly biased the results. The authors further noted that the study had potential for length bias in that in order to have received deferiprone, patients would have had to survive long enough to receive it. Thus the sickest patients, possibly, who had cardiac events, were those who did not have the opportunity to receive deferiprone, and the observations on deferiprone might not have been long enough for cardiac events to occur. There were two deaths reported in the deferiprone group (1.3%) compared with 24 in the desferoxamine group (6.7%). Of the 24 deaths in the desferoxamine group, 15 were cardiac related; neither death in the deferiprone group was cardiac related. The authors calculated a hazard ratio of 0.38 (CI 0.9, 1.6) of death on deferiprone but given the small number of events the study did not have sufficient power to test this question.

The Panel considered that the claim 'New Cardioprotection and Survival Data Now Available' implied that there was positive data in this regard. The Panel considered that, in view of the limitations noted by Borgna-Pignatti et al, such a claim was too strong and could not be substantiated. A breach of the Code was ruled.

Upon appeal by ApoPharma the Appeal Board noted that the claim appeared as a banner on a specialist website – ie the website of the British Journal of Haematology. By clicking on the banner the reader was taken to Borgna-Pignatti et al as cited on Pub Med. The Appeal Board considered that, as presented, the claim 'New Cardioprotection and Survival Data Now Available' was a statement of fact and not a claim for positive data for Ferriprox in this regard. No breach of the Code was ruled.

Novartis Pharmaceuticals UK Ltd alleged that a promotional piece for Ferriprox (deferiprone) which appeared as a link on the website of the British Journal of Haematology was clearly in breach of the undertaking given in Case AUTH/1822/4/06. Novartis further alleged that a claim about survival data was unsubstantiated. As the complaint involved an alleged breach of undertaking the matter was taken up with ApoPharma Inc by the Director as it was the Authority's responsibility to ensure compliance with undertakings. Novartis supplied Desferal (desferoxamine).

COMPLAINT

Novartis noted that the material at issue, an animated Ferriprox banner advertisement, contained the claim 'New Cardioprotection and Survival Data Now Available'. The statement 'For reference or prescribing information please click here' linked to another website 'Ferriprox.com' and the landing page was headed with the claim 'Life is Getting Longer … in thalassaemia major patients'. There was a further link to a summary of product characteristics following a further link marked 'for information on Ferriprox and cardioprotection, please click here', the reader was taken to the Pub Med listing for the abstract of Borgna-Pignatti *et al* (2006).

Novartis did not believe that including the statement on the landing page that the website was intended for Hong Kong residents only made it any more acceptable under the Code given that UK readers of the journal had been directed to these pages from a UK journal site.

Novartis considered that the material breached the Code in several areas. The first was the retention of the claim 'Life is Getting Longer … in thalassaemia major patients' found in breach recently. This still remained a hanging comparison, in breach of Clause 7.2, as there was no explanation as to what Ferriprox was being compared with. As this was previously found to be in breach for exactly the same reasons it also represented a breach of undertaking (Clause 22).

Secondly, Borgna-Pignatti *et al* did not provide survival data of any form that could support this claim. The paper discussed cardiac events but there was no analysis of survival. This represented a failure to substantiate a claim and also, by directing the reader to this paper, it was also a misrepresentation of data. Novartis alleged a breach of Clause 7.4.

Novartis considered that ApoPharma had failed to comply with the Authority's previous ruling and the undertaking associated with it.

When writing to ApoPharma, the Authority asked it, in addition to those clauses cited by Novartis, to respond to Clauses 2 and 9.1.

RESPONSE

ApoPharma stated that as per its undertaking, it had stopped using the 'Life is Getting Longer' banner advertisement in the British Journal of Haematology on 25 August 2006. The advertisement was replaced with another that did not make any claims, but did provide a notification of published data pertaining to the effects of deferiprone on the heart ('Cardioprotection and Survival Data Now Available'). As noted by Novartis, a link in the banner advertisement allowed the reader to access prescribing information for Ferriprox.

However, this was not the Hong Kong website for Ferriprox as stated by Novartis. It was a link to enable readers to access information specified in the advertisement, and it also served as a portal for entry into the Hong Kong Ferriprox website for Hong Kong residents, if they so chose. A copy of the site was provided, demonstrating the need to follow another link to enter the Hong Kong website.

The page attached differed in one important aspect from that viewed by Novartis at the time of its complaint. While the current introductory line read, 'Life is waiting', the previous line stated 'Life is Getting Longer'. Removal of this statement from all European advertising had been executed, as stated. However, in error, it was not removed from this link, which UK physicians might access. In this regard, ApoPharma had failed through oversight, not defiance. This oversight did not appear in an advertisement in the UK.

Since the current advertisement in the British Journal of Haematology did not make a claim of increased survival, the complaint by Novartis regarding the adequacy of the references was irrelevant. However, the view expressed by Novartis regarding a lack of adequate data on survival in the reference was incorrect, as revealed by a review of the extensive data presented in the article, which was summarized unequivocally by Borgna-Pignatti *et al* as follows, 'The results of the current study demonstrate that patients with thalassemia major who switched to deferiprone therapy had a remarkably lower prevalence of cardiac disease and cardiac death than patients chelated with [deferoxamine] only'.

Now there was yet another publication which had also demonstrated a dramatic decline in cardiac deaths in thalassemia patients in the whole of Cyprus since the introduction of deferiprone, used primarily in combination therapy in that country (Telfer *et al* 2006).

ApoPharma hoped that this provided the information necessary to demonstrate that no further breach had occurred, but if additional information was required it would readily provide it.

ApoPharma noted that the Authority had asked it for details of the steps it had taken to comply with the undertaking given in Case AUTH/1822/4/06. With regards to the banner advertisement in the British Journal of Haematology: the phrase, 'Life is getting longer' was removed on 25 August 2006: a direct link to Ferriprox prescribing information was introduced; a replacement line, educational in nature, was used to inform clinicians of important information on studies relating to thalassemia, cardiac iron, cardiac disease

and survival ('Cardioprotection and Survival Data Now Available') and a link to Ferriprox prescribing information was provided for readers of the banner advertisement in the British Journal of Haematology.

ApoPharma confirmed that it would comply with the Authority's ruling and ensure that there was no further occurrences that breached the Code. Furthermore ApoPharma was committed to providing a first class service and enhancing the reputation of the pharmaceutical industry with its customers, both with the medical profession and with their patients.

PANEL RULING

The Panel considered that an undertaking was an important document. It included an assurance that all possible stops would be taken to avoid similar breaches of the Code in future. It was very important for the reputation of the industry that companies complied with undertakings.

The Panel noted that in Case AUTH/1822/4/06 a Ferriprox banner advertisement, in the electronic version of the British Journal of Haematology, which claimed that 'Life is Getting Longer' was ruled in breach of Clause 7.2 because it was a hanging comparison. In error, as acknowledged by ApoPharma, the claim had been used again. Although the claim did not appear on the British Journal of Haematology website it did appear on a direct link from the Ferriprox banner advertisement on that site. The Panel considered that the linked page was covered by the Code and thus the use of the claim 'Life is Getting Longer' was in breach of the undertaking given in Case AUTH/1822/4/06. The Panel ruled breaches of Clauses 7.2 and 22. High standards had not been maintained. A breach of Clause 9.1 was ruled. The Panel further considered that ApoPharma, by not doing all that it could have done to comply with its undertaking had brought discredit upon, and reduced confidence in, the pharmaceutical industry. A breach of Clause 2 was ruled. These rulings were not appealed.

The Panel noted that the banner advertisement on the British Journal of Haematology website stated 'New Cardioprotection and Survival Data Now Available'. The data available was Borgna-Pignatti *et al*, an epidemiological, natural history study conducted in Italy which compared cardiac morbidity and mortality in deferoxamine- or deferiprone-treated patients with thalassemia major. The authors reported that deferiprone therapy was associated with significantly greater cardioprotection than desferoxamine. The authors, however, noted that the study was not randomized and so treatment groups might not have been comparable. Further, there might have been a bias against deferiprone because in the early stages of the 9 year study it was experimental and given to patients with a higher body iron load. Conversely, because deferiprone was not licensed in Italy until mid-way through the trial, some doctors might have been reluctant to prescribe it for their sicker patients thus introducing a bias in favour of the medicine. The authors commented that neither consideration appeared to have strongly biased the results. The authors further noted that the study had potential for length bias in that in order to have received deferiprone, patients would have had to survive long enough to receive it. Thus the sickest patients, possibly, who had cardiac events, were those who did not have the opportunity to receive deferiprone, and the observations on deferiprone might not have been long enough for cardiac events to occur. There were two deaths reported in the deferiprone group (1.3%) compared with 24 in the desferoxamine group (6.7%). Of the 24 deaths in the desferoxamine group, 15 were cardiac related; neither death in the deferiprone group was cardiac related. The authors calculated a hazard ratio of 0.38 (CI 0.9, 1.6) of death on deferiprone but given the small number of events the study did not have sufficient power to test this question.

The Panel considered that the claim 'New Cardioprotection and Survival Data Now Available' implied that there was positive data in this regard. The Panel considered that, in view of the limitations noted by Borgna-Pignatti *et al*, such a claim was too strong and could not be substantiated. A breach of Clause 7.4 was ruled. This ruling was appealed.

APPEAL BY APOPHARMA

ApoPharma submitted that it was critical that it addressed a misconception of the Panel regarding the banner and one of the two studies listed in its links. Data on cardioprotection and survival relating to the use of deferiprone had appeared in the medical literature prior to the appearance of the new data to which the banner referred. The link associated with the new banner lead the reader to the abstracts of two studies published in Blood ie 'Randomized controlled trial of deferiprone or deferoxamine in beta-thalassemia major patients with asymptomatic myocardial siderosis' (Pennell *et al* 2006) and 'Cardiac morbidity and mortality in deferoxamine- or deferiprone-treated patients with thalasseamia major' (Borgna-Pignatti *et al*). It appeared that the Panel considered that the latter study did not substantiate the statement 'New Cardioprotection and Survival Data Available'. The study had contained new data relating to cardioprotection and survival.

ApoPharma noted that the Panel had considered that the limitations noted by Borgna-Pignatti *et al*, particularly that the sickest patients, who had cardiac events, were those who did not have the opportunity to receive deferiprone, would bias the results of this study in favour of deferiprone. The consideration was incorrect. In fact, to avoid this potential bias, the study enrolled only patients who had not had cardiac events at the start of the observation period: 'The analysis included all patients treated for thalassemia major at the 7 centers participating in this study who were born between 1970 and 1993 and who on January 31, 1995, were alive, on follow-up, had not undergone bone marrow transplantation, **and had not had a cardiac event'** (Borgna-Pignatti *et al*) (emphasis added by ApoPharma).

ApoPharma submitted that the assessment of potential biases in this study had been evaluated in the editorial that accompanied the publication of Borgna-Pignatti *et al*: 'Although potential bias could easily arise in a retrospective study of unmatched groups, the authors have examined possible biases in a comprehensive fashion, controlling for as many as possible, and explaining the rest with admirable clarity and near-perfect patient ascertainment' (Neufeld, 2006).

The Panel had concluded that Borgna-Pignatti *et al* was unable to show a significant difference between treatments by referring to the Cox regression analysis of total deaths between the two groups (p=0.19). However, ApoPharma noted that since the only two deaths that occurred in patients on deferiprone were neither cardiac- nor deferiprone-related, the authors conducted further analyses, which revealed a significant difference, as described in the publication: 'In addition, we performed a Cox regression that included the noncardiac deaths as failure events in addition to the cardiac events (ie, redefining the failure event as cardiac event or death, whichever occurred first). This analysis included the 2 deaths on deferiprone and provided an estimated hazard ratio of a cardiac event or death of .078 (CI .010, .56; P = .011) on deferiprone relative to [deferoxamine]'.

ApoPharma submitted that as described above, Novartis had claimed that Borgna-Pignatti *et al* did not provide survival data of any form that could support this claim. The paper discussed cardiac events but there was no analysis of survival, this was incorrect. Having considered the limitations of their study, Borgna-Pignatti *et al* concluded that '… this epidemiologic study demonstrated a **significant difference in cardiac morbidity and mortality between thalassemia patients treated with deferiprone and those treated with [deferoxamine]. In contrast to patients treated with [deferoxamine], the patients on this study treated with deferiprone did not have cardiac events'** (emphasis added by ApoPharma).

ApoPharma submitted that the editorial that accompanied the publication also concurred with the conclusion of the authors by stating 'This stunning finding, coupled with similar but less rigorous data from other sites, is hard to ignore. The results confirmed a smaller retrospective analysis of Piga *et al*' (Neufeld).

ApoPharma submitted that Borgna-Pignatti *et al* and Pennell *et al*, published in August 2006, were indeed new data on the role of deferiprone in protecting the heart; iron-related cardiac disease was responsible for approximately 70% of deaths in patients with thalassemia.

COMMENTS FROM NOVARTIS

Novartis continued to maintain that the website was in breach of Clause 7.4 because the reference cited to substantiate a claim of overall survival improvement did not substantiate the claim.

The website in its original form was clearly headed with the claim 'Life is getting longer … in thalassemia major patients'. This was clearly a claim for overall survival benefit from treatment with deferiprone irrespective of cause. This claim was a hanging comparison as ruled by the Panel as it was not clear to what treatment deferiprone was being compared. Below this claim appeared a series of options for the reader including a bullet point with the following direction: 'For information on Ferriprox and survival, please click here'. The link led the reader to the Pub Med citation for Borgna-Pignatti *et al*, which was then evidently intended to substantiate the key claim at the head of the website that 'Life is getting longer …' and the reader was led to believe that it contained robust data to demonstrate a survival benefit from treatment with deferiprone.

Novartis alleged, however, that the study did not demonstrate any such overall survival benefit. As the Panel noted in its ruling, the hazard ratio for death for patients on deferiprone was 0.38 (CI 0.9, 1.6) (p=0.19) which was not statistically significant and indeed the authors concluded that the study did not have sufficient power to test the question of survival.

It was incorrect and misleading to make such a bold claim for increased survival and only discuss cardiac causes of death. Thus, irrespective of the criticisms of the trial design which the Panel and ApoPharma had commented on, the fact remained that the results of the study were insufficient to substantiate an overall survival advantage of treatment with deferiprone over treatment with deferoxamine.

APPEAL BOARD RULING

The Appeal Board noted that the claim 'New Cardioprotection and Survival Data Now Available' appeared as a banner on a specialist website – ie the website of the British Journal of Haematology. By clicking on the banner the reader was taken to Borgna-Pignatti et al as cited on Pub Med. The Appeal Board considered that, as presented, the claim 'New Cardioprotection and Survival Data Now Available' was a statement of fact and not a claim for positive data for Ferriprox in this regard. No breach of Clause 7.4 was ruled. The appeal was successful.

Complaint received	**1 December 2006**
Case completed	**19 April 2007**

CASE AUTH/1941/1/07

ASTRAZENECA v ALTANA PHARMA

Promotion of Protium

AstraZeneca complained about the promotion of Protium (pantoprazole) by Altana Pharma. The items at issue were two mailings and a clinical paper summary which compared Protium with AstraZeneca's product Nexium (esomeprazole).

AstraZeneca noted that the claims 'Endoscopic healing rates equivalent to esomeprazole 40mg', 'Endoscopic healing rates comparable to esomeprazole 40mg' and '40 mg pantoprazole and 40mg esomeprazole are equivalent in the healing of esophageal lesions' were referenced to Gillessen *et al* (2004), which was a non-inferiority study, comparing the endoscopic healing rates of pantoprazole 40mg (n=113) and esomeprazole 40mg (n=114) in oesophagitis. The study utilised a hierarchical test procedure assessing a difference initially of 15% down to 5% between the two arms. The results contained no power calculations or 95% confidence intervals. Therefore this study could not prove its primary end point in order to substantiate these claims. Statistical equivalence could not be inferred from this type of study.

Conversely the more recent EXPO study had shown that esomeprazole 40mg was superior to pantoprazole 40mg in terms of healing rates in oesophagitis (Labenz *et al* 2005). This was a much larger (n=3151), well-powered study than Gillessen *et al*. Labenz *et al* showed esomeprazole had statistically superior healing rates in oesophagitis at four and eight weeks compared with pantoprazole. In addition two systematic reviews had shown that esomeprazole had superior healing rates compared with other proton pump inhibitors (including pantoprazole) (Edwards *et al* 2006, Isakov and Morozov 2006). The EXPO study and the systematic reviews supported the overall balance of evidence that esomeprazole had superior healing rates compared with pantoprazole. The Code, required promotion to be based on an up-to-date evaluation of all the available evidence; it must not mislead or make exaggerated claims.

AstraZeneca alleged that the claims were incorrect, misleading and incapable of substantiation.

The Panel noted that three head-to-head studies of pantoprazole vs esomeprazole had been submitted (Gillessen *et al*, Labenz *et al* and Bardhan *et al*). The claims at issue had been referenced to Gillessen *et al* which was a study set up to determine whether two treatments were equivalent. The overall endoscopically proven healing rates for both treatment groups were 88% in the intention to treat population. The corresponding values for the per protocol population were 95% (pantoprazole) and 90% (esomeprazole). The authors stated that these figures demonstrated that there existed 'at least equivalence' of pantoprazole and esomeprazole therapy. At ten weeks the healing rates were 91% in the pantoprazole group and 97% in the esomeprazole group. No significant differences between the pantoprazole and esomeprazole groups could be shown. The Panel did not accept that an inability to show a statistical difference between the groups proved that the two treatments were equivalent. Gillessen *et al* noted that prior to their study there existed no comparable clinical material that directly compared pantoprazole and esomeprazole.

The results of the EXPO study were published the year after Gillessen *et al*. This was a much larger study designed to compare esomeprazole 40mg (n=1562) with pantoprazole 40mg (n=1589) for healing in patients with erosive oesophagitis. After up to eight weeks significantly more esomeprazole-treated patients were healed (95.5%) compared with pantoprazole-treated patients (92%) ($p<0.001$).

The Panel noted the table of results from Bardhan *et al* given by Altana was stated to show the percentage of healing rates but the figures quoted were in fact the cumulative rates of complete remission as reported by the authors. (Complete remission was defined as both endoscopically confirmed healing and symptom relief as assessed by questionnaire.) Altana had shown for the last of these results (12 weeks) that Protium was statistically superior to Nexium; this was not so. At 12 weeks the authors had reported that pantoprazole was not inferior to esomeprazole. With regard to the healing of oesophageal lesions at 12 weeks, pantoprazole showed superior results compared with esomeprazole (98% v 94.4%) although the statistical significance of this result was not stated.

The Panel noted the sizes of the three studies cited and considered that the balance of evidence lay with the EXPO study ie that although in absolute terms the healing rates of both pantoprazole and esomeprazole were very similar there was a statistically significant difference in favour of esomeprazole.

The Panel thus considered that the claims that Protium 40mg was equivalent or comparable to esomeprazole in terms of healing were incorrect, misleading and not capable of substantiation as alleged. Breaches of the Code were ruled.

Upon appeal by Altana in relation to the claim 'Endoscopic healing rates comparable to esomeprazole 40mg', the Appeal Board considered that, in common parlance, if two medicines were described as comparable then prescribers and patients would generally not mind which one was used. The Code required material including comparisons to have a statistical foundation. Clinical relevance was an important consideration.

The Appeal Board noted how the parameters of Gilleson et al had changed as the study progressed and in that regard it considered that the results were not as robust as those from the EXPO study. The Appeal Board further noted that unlike the EXPO study, Gilleson *et al* had not included patients with Los Angeles grade D (ie more severe) oesophagitis. The EXPO study had shown that for both esomeprazole and pantoprazole there was a decline in healing rates with increasing baseline severity of oesophagitis. After 8 weeks of therapy the healing rates for esomeprazole 40mg were statistically superior to pantoprazole 40mg with LA grades B, C and D at baseline.

The Appeal Board considered that the claim 'Endoscopic healing rates comparable to esomeprazole 40mg' was too broad such that it was ambiguous. It implied that in patients with any grade of gastroesophageal reflux disease (GERD), healing rates observed with Protium had been shown to be statistically similar to those observed with Nexium which was not so. The claim was misleading in that regard. The Appeal Board upheld the Panel's ruling of a breach of the Code.

The Appeal Board noted that the EXPO study had shown that, overall, healing rates with Protium and Nexium were very similar in absolute terms. In that regard the Appeal Board thus considered that there was no breach.

AstraZeneca noted that the claim 'Once daily pantoprazole 40mg and esomeprazole 40mg have equivalent overall efficacy in relieving GERD-related symptoms' was referenced to Scholten *et al* (2003), a superiority study comparing the area under the curves (AUCs) for the symptom scores. There was no statistical difference (p>0.05) between the two treatment groups. From this non-significant value it was concluded that pantoprazole and esomeprazole were equivalent with respect to symptoms. This was an incorrect conclusion; a non-significant p value for superiority did not imply equivalence. In order to show equivalence, a pre-specified equivalence margin had to be stipulated with construction of confidence intervals for the treatment difference. Equivalence was inferred if the confidence intervals fell entirely within the equivalence margins.

AstraZeneca submitted that differences that did not reach statistical significance must not be presented in such a way as to mislead. Thus this claim was misleading and incapable of substantiation.

The Panel noted that Scholten *et al* was designed to compare the efficacy of pantoprazole (40mg) (n=112) and esomeprazole (40mg) (n=105) in the treatment of GERD-related symptoms. The primary criterion of the study was to evaluate symptom load of GERD-related symptoms, defined as AUC for the symptom score. Over the 28 day treatment period the AUCs for the six typical GERD-related symptoms (heartburn, acid regurgitation, gastric complaints, pressure in the epigastrum, feeling of satiety and flatulence) were similar and comparable in the two treatment groups (p>0.05). Thus the study was unable to show a statistically significant difference between the two medicines. The results did not mean that the study had proven the two were equivalent. The Panel thus considered that the claim 'Once-daily pantoprazole 40mg and esomeprazole 40mg have equivalent overall efficiency in relieving GERD-related symptoms' was misleading and could not be substantiated as alleged. Breaches of the Code were ruled.

AstraZeneca noted that the claims 'Fast symptom control- 2 days faster than esomeprazole 40mg', 'daytime symptom relief – 2 days faster' and '2 days faster than esomeprazole 40mg' were referenced to the secondary end points of Scholten *et al*. As stated above, this study did not reach statistical significance in terms of the primary outcome (AUC of the GERD symptoms scores between esomeprazole 40mg and pantoprazole 40mg).

AstraZeneca believed that if there was an inconsistency in terms of the interpretation of the study from a secondary endpoint alone, the primary endpoint should be given sufficient clarity, such that the claim could be immediately seen in the context of the primary endpoint. AstraZeneca considered that it was misleading to use a secondary endpoint alone if it would lead the reader to draw a different conclusion to that of the primary end point.

AstraZeneca submitted that in this case, the secondary endpoint claims did not inform the reader of the primary outcome of the study (AUC of symptoms scores between esomeprazole 40mg and pantoprazole 40mg) and were not consistent with the result of the primary end point. In addition, as a secondary endpoint, the study would not have been appropriately powered to examine this measure, and was therefore at risk from statistical error.

In addition, the EXPO study showed that esomeprazole 40mg provided faster and more effective resolution of heartburn than pantoprazole 40mg. This was based on the time to sustained resolution of symptoms (defined as a period of seven consecutive days without heartburn). This was in contrast to the assessment of symptoms in Scholten *et al* that assessed time to adequate relief. In Scholten *et al* patients did not have to reach complete resolution of symptoms. Time to sustain a resolution of symptoms as shown by esomeprazole 40mg was much more clinically relevant as it was a period of prolonged improvement in contrast to achieving a period of partial symptomatic relief. Thus, the claims were misleading and did not reflect the available evidence.

The Panel noted that in Scholten *et al* patients recorded the perceived intensity of GERD-related symptoms (heartburn, acid regurgitation, gastric complaints, pressure in the epigastrum, feeling of satiety and flatulence). A five-point Likert scale was used to assess the intensity of each symptom: none (0), mild (1), moderate (2), severe (3) and very severe (4). Each symptom was assessed and scored and if the sum score fell below 5 for the first time, the patient was characterized as having reached adequate relief from GERD-related symptoms. The patients did not have to

reach complete symptom relief. The results of the study showed that for daytime, the first time to reach adequate relief of GERD-related symptoms in the pantoprazole group was 3.73 days and 5.88 days for the esomeprazole group (p=0.034). This was the result upon which the claims in question were based. The Panel noted, however, that the claims only referred to 'symptom relief' or 'symptom control', not 'adequate symptom relief control'. In the Panel's view the claims implied total symptom relief/control which was not so. The Panel further noted that the claims did not refer to 'first time' relief and in that regard there was an implication that sustained relief of symptoms was achieved with pantoprazole after 3.7 days. There was no data to show this.

The Panel thus considered that the claims at issue were misleading and did not reflect the available evidence as alleged. Breaches of the Code were ruled.

Upon appeal, the Appeal Board considered that it was unacceptable to use secondary data to claim an advantage for Protium over Nexium when the primary endpoint had been unable to show such a difference. The Appeal Board considered that the claims were misleading in this regard and did not reflect the available evidence as alleged. The Appeal Board upheld the Panel's rulings of breaches of the Code.

AstraZeneca UK Limited complained about the promotion of Protium (pantoprazole) by Altana Pharma Limited. The items at issue were two mailings (ref PAN208/071205/P and PAN291/020806/P) and a clinical paper summary (PAN202/291105/P) which compared Protium with AstraZeneca's product Nexium (esomeprazole).

1 Claims 'Endoscopic healing rates equivalent to esomeprazole 40mg' (PAN208/071205/P), 'Endoscopic healing rates comparable to esomeprazole 40mg' (PAN291/020806/P) and '40 mg pantoprazole and 40mg esomeprazole are equivalent in the healing of esophageal lesions' (PAN202/291105/P)

COMPLAINT

AstraZeneca noted that all of these claims were referenced to Gillessen *et al* (2004), which was a non-inferiority study, comparing the endoscopic healing rates of pantoprazole 40mg (n=113) and esomeprazole 40mg (n=114) in oesophagitis. The study utilised a hierarchical test procedure assessing a difference initially of 15% down to 5% between the two arms of the study. The results in this study contained no power calculations or 95% confidence intervals, which were the accepted methods to assess statistical relevance of the findings. Therefore this study could not prove its primary end point in order to substantiate these claims. This was further supported by a published letter to the editor of the journal which re-iterated that the study had insufficient power and sample size to reach a conclusion (Madisch *et al* 2005). Furthermore, statistical equivalence could not be inferred from this type of study.

AstraZeneca noted that in contrast the more recent EXPO study had shown that esomeprazole 40mg was superior to pantoprazole 40mg in terms of healing rates in oesophagitis (Labenz et al 2005). This was a much larger (n=3151), well-powered study than Gillessen *et al*. Labenz *et al* showed esomeprazole had statistically superior healing rates in oesophagitis at four and eight weeks compared with pantoprazole. In addition two systematic reviews had shown that esomeprazole had superior healing rates compared with other proton pump inhibitors (including pantoprazole) (Edwards *et al* 2006, Isakov and Morozov 2006). The EXPO study and the systematic reviews supported the overall balance of evidence that esomeprazole had superior healing rates compared with pantoprazole. AstraZeneca noted that the Code required promotion to be based on an up-to-date evaluation of all the available evidence; it must not mislead or make exaggerated claims.

AstraZeneca stated that there should be a sound statistical basis for all statistical claims and comparisons in promotional material, and that care should be taken to ensure that the information was not presented in such a way as to mislead. Thus, AstraZeneca alleged that the claims at issue were incorrect, misleading and incapable of substantiation in breach of Clauses 7.2, 7.3 and 7.4 of the Code.

RESPONSE

Altana submitted that Gillessen *et al* was a peer-reviewed article published in the Journal of Gastroenterology and as such both the study methodology and the clinical paper had been independently peer reviewed before publication. Furthermore the study design and statistical methods were approved by ten independent local ethics committees before the study started. This clearly demonstrated that the study design was robust and that the results achieved were both meaningful and clinically relevant. The study was designed to show non-inferiority using a hierarchical test procedure, testing the non-inferiority margin initially at 15%, then at 10% and finally at 5%. Therefore a lower 95% confidence interval of less than 5% would indicate non-inferiority. Whilst it was regrettable that this lower 95% confidence interval was not included in the original publication, the clinical research department at Altana AG (study sponsors) had confirmed that this figure was 4.88%, thus confirming the authors' conclusion that '40mg pantoprazole (Protium) daily and 40mg daily esomeprazole (Nexium) were equally effective for the healing of esophageal lesions'.

Altana submitted that the power calculations were not relevant to the outcome of the study. The letter from Madisch *et al* to the editor of the journal suggesting that the trial was underpowered and lacking in sample size was adequately refuted (Gillessen 2005a).

Altana noted that AstraZeneca had stated that the EXPO study and two review papers supported its position that Nexium was superior to Protium in terms of healing rates in erosive oesophagitis. Altana noted, however, that Edwards et al compared Nexium to 'other proton pump

inhibitors' (PPIs) which included omeprazole, lansoprazole and Protium. Therefore the Nexium versus 'combined PPI' summary findings had no relevance to this complaint when the data required was head-to-head comparisons of Nexium and Protium in the healing of erosive oesophagitis. Further, Edwards *et al* only included one Nexium versus Protium study (the EXPO study) in the set of six studies that were included in the final analysis. Thus in citing Edwards *et al* AstraZeneca had offered no further support to its position as it was, in effect, a repeat citing of the EXPO study.

Altana submitted that the Isakov and Morozov meta-analysis was also a combined analysis in which Nexium was compared to omeprazole, lansoprazole and Protium. This meta-analysis considered eight clinical papers, only three of which were trials of Nexium versus Protium. As stated earlier, this type of combined endpoint was not relevant to this complaint when the data required was head-to-head comparisons of Nexium and Protium in the healing of erosive oesophagitis.

Altana submitted the EXPO study was the only study cited by AstraZeneca to support a claim that Nexium had statistically superior healing rates in oesophagitis at four and eight weeks. However the absolute difference between the two treatments was very small, 3.5%, and both showed healing rates greater than 90%. Disparities in the distribution of less severe patients between the trial groups, which might have materially affected this very small absolute difference in favour of Nexium had been raised (Gillessen 2005b).

Equally the relevance of the absolute difference, 3.5%, observed in healing rates was of little clinical significance when both products had a success rate of over 90%.

Altana submitted that the claims in question were fully supported by a full review of the available evidence looking at healing rates in erosive oesophagitis in clinical trials of 40mg Protium versus 40mg Nexium.

Altana submitted a table that summarised the clinical trial results from three studies considering this matter (Gillessen *et al*, Labenz *et al* and Bardhan *et al* 2005). Whilst it would always be the case that individual studies would have a unique design the three listed all looked at endoscopically proven healing of erosive oesophagitis over time.

Altana submitted that the table supported its position that, upon an up-to-date analysis of all the available evidence, there was minimal difference between the two products in clinical terms for oesophageal healing rates. In different studies both Protium and Nexium had been shown to be statistically superior at different time points. However this was of no clinical relevance when the entire data set was reviewed and it was recognised that despite small inter-study variation the healing rates in every study were very closely similar.

Altana submitted that claims made in promotional material must not mislead and should reflect both the statistical and clinical relevance. Therefore this table of data strongly supported the terms 'equivalent' and 'comparable' as used in the claims at issue.

The term 'equivalent' was taken directly from the title of Gillessen *et al* and Scholten *et al* (2003) also used the term 'equivalent' in its title. These publications were in peer-reviewed journals and reflected the average physician's interpretation of the term 'equivalent' through its common or everyday meaning. In this clinical context 'equivalent' was understood to mean 'as effective as', and was not interpreted in a pure statistical manner.

Altana submitted the term 'comparable' was entirely appropriate and fully substantiated given the minimal absolute difference between the products in oesophageal healing rates in every study.

Altana denied breaches of Clauses 7.2, 7.3 and 7.4.

PANEL RULING

The Panel noted that three head-to-head studies of pantoprazole versus esomeprazole had been submitted (Gillessen *et al*, Labenz et al and Bardhan *et al*). The claims at issue had been referenced to Gillessen *et al* which was a study set up to determine whether the two treatments were equivalent. The overall endoscopically proven healing rates for both treatment groups were 88% in the intention to treat population. The corresponding values for the per protocol population were 95% (pantoprazole) and 90% (esomeprazole). The authors stated that these figures demonstrated that there existed 'at least equivalence' of pantoprazole and esomeprazole therapy. At ten weeks the healing rates were 91% in the pantoprazole group and 97% in the esomeprazole group. No significant differences between the pantoprazole and esomeprazole groups could be shown. The Panel did not accept that an inability to show a statistical difference between the groups proved that the two treatments were equivalent. Gillessen et al noted that prior to their study there existed no comparable clinical material that directly compared pantoprazole and esomeprazole.

The results of the EXPO study were published the year after Gillessen *et al*. This was a much larger study designed to compare esomeprazole 40mg (n=1562) with pantoprazole 40mg (n=1589) for healing in patients with erosive oesophagitis. After up to eight weeks significantly more esomeprazole-treated patients were healed (95.5%) compared with pantoprazole-treated patients (92%) ($p<0.001$).

The Panel noted that Altana had cited Bardhan *et al*. The table of results given by Altana was stated to show the percentage of healing rates but the figures quoted for Bardhan *et al* were in fact the cumulative rates of complete remission as reported by the authors. (Complete remission was defined as both endoscopically confirmed healing and symptom relief as assessed by questionnaire.) Altana had shown for the last of these results (12 weeks) that Protium was statistically superior to Nexium; this was not so. At 12 weeks the authors had reported that pantoprazole was not inferior to esomeprazole. With regard to the healing of oesophageal lesions at 12 weeks, pantoprazole showed superior

results compared with esomeprazole (98% v 94.4%) although the statistical significance of this result was not stated.

The Panel noted the sizes of the three studies cited and considered that the balance of evidence lay with the EXPO study ie that although in absolute terms the healing rates of both pantoprazole and esomeprazole were very similar there was a statistically significant difference in favour of esomeprazole.

The Panel thus considered that the claims that Protium 40mg was equivalent or comparable to esomeprazole in terms of healing were incorrect, misleading and not capable of substantiation as alleged. Breaches of Clauses 7.2, 7.3 and 7.4 were ruled.

APPEAL BY ALTANA

Altana appealed the Panel's rulings of breaches of Clauses 7.2, 7.3 and 7.4 of the Code with regard to the claim 'Endoscopic healing rates comparable to esomeprazole 40mg'.

Altana considered that the Panel's ruling appeared to be entirely inconsistent with the wording used within the text of the ruling. Altana submitted that the word 'comparable' was not a defined term with respect to statistics or medicine. Therefore the accepted use of this word in English should be used in this case, this being 'similar in size, amount or quality to something else'.

The ruling stated that 'The Panel noted the sizes of the three studies cited and considered that the balance of evidence lay with the EXPO study ie that although in absolute terms the healing rates of both pantoprazole and esomeprazole were very similar there was a statistically significant difference in favour of esomeprazole' (emphasis added by Altana).

Altana submitted that in view of the meaning of 'comparable', deeming that the word was 'incorrect, misleading and not capable of substantiation' in this instance appeared to be an illogical conclusion given that the Panel had agreed that there was almost no difference in absolute healing rates between the two products. This closely similar absolute healing rate represented the success rate that any physician might expect to achieve when using either product.

Altana submitted that by the Panel's own words it was clear that this statement was not misleading to the intended audience of health professionals. The healing rates of the two products were, without doubt, comparable when all the studies in the pool of evidence were considered.

Altana submitted that the balance of evidence showed that there was no difference between the two products in absolute healing rates, their effect was very similar and therefore use of the term comparable was appropriate and correct.

Altana submitted that it was improper, and in itself misleading, for the Panel to determine that the minimal absolute difference in the EXPO study should be seen as a statistically superior advantage for Nexium given that two other well-powered studies showed contrary results. The balance of evidence strongly supported essential similarity between the products and justified use of the term 'comparable' in this context.

Altana submitted that large studies, such as the EXPO study might give rise to statistically significant results for clinically meaningless absolute differences. It was wrong to claim that the size of the study had any bearing on the balance of evidence. Studies were powered according to the study type (non-inferiority, superiority) and according to the magnitude of the difference between the treatments that was predicted to exist. Ethics committee review ensured patient enrolment into clinical studies was sufficient to demonstrate a real difference if the difference really existed. If the clinical difference between the products was predicted to be small many patients might be required as in the EXPO study.

Altana submitted that it was a flawed argument to suggest that the EXPO study should be given more credibility and weighting in the pool of available data than Gillessen *et al*, Achim *et al*, and Bardhan *et al* for the reasons given. A statistician would confirm that the size of a study did not relate to the relative merits of its outcome.

Altana submitted that there must be clinical relevance in the delivery of promotional claims or they were themselves misleading to the intended audience. For the Panel to express the opinion that the EXPO study carried more weight in the available evidence when Achim *et al* and Gillessen *et al* demonstrated non-inferiority and superiority for Protium over Nexium was not representative of the balance of evidence available.

Altana submitted that it had not claimed Protium superiority over Nexium because this would have misrepresented the entire data set and be misleading to health professionals. Equally the reverse was true. It could not be deemed by the Panel 'that although in absolute terms the healing rates of both pantoprazole and esomeprazole were very similar there was a statistically significant difference in favour of esomeprazole'. This was a misrepresentation of the entire data set available.

Altana submitted that the only possible outcome upon consideration of the whole data set, that would not mislead customers, was that Protium and Nexium had very similar or comparable healing rates. These considerations previously raised by Altana had not been adequately discussed in the Panel ruling to illustrate its reasoning and create a transparent response.

COMMENTS FROM ASTRAZENECA

AstraZeneca noted Gillessen *et al* used a hierarchical test procedure assessing a difference initially of 15% down to 5% between the two treatment arms. The study had several serious limitations due to poor statistical analysis

and inappropriate sample size in order to draw any meaningful conclusions.

- It did not follow the guidelines of the European Medicines Evaluation Agency in utilizing a pre-specified non-inferiority margin instead of shifting margins. Changing the non-inferiority margins would require a different sample size in order to prove the study hypothesis. The choice of the margin was critical in calculating the sample size and in the interpretation of the data.

- The authors did not describe any sample size and power calculations or 95% confidence intervals which was highly important for any non-inferiority study.

- If the study had planned a non-inferiority margin of 5% then more than 1000 patients would be required to test for non-inferiority at this level.

- Using a non-inferiority margin of up to -15%, was a difference too large to conclude that treatments were comparable in healing oesophagitis.

- Using the data presented, the 95% confidence interval (CI) for the intention to treat (ITT) difference might be calculated to -9 to +9%, clearly not significant at the non-inferiority limit of 5%. For the per protocol (PP) analysis the estimated difference was 4.4% and the 95% two-sided CI was -3 to +12%. Testing the PP treatment difference with Fisher's exact test gave p=0.29, which was clearly not statistically significant.

- The study was limited to patients with Los Angeles grade B and C oesophagitis and with treatment groups split into three strata, resulting in fewer than 40 patients per stratum. No results of this stratification were presented.

AstraZeneca alleged that Gillessen *et al* was unable to prove the primary endpoint of non-inferiority of pantoprazole 40mg to esomeprazole 40mg and thus the claim for comparable healing rates to esomeprazole 40mg could not be justified.

Statistical information should not be presented in a way to mislead the reader.

AstraZeneca alleged it had conclusively shown in a much larger (n=3151), well-designed study (EXPO) that was performed after Gillessen *et al*, that esomeprazole 40mg was indeed superior to pantoprazole 40mg for healing oesophagitis (Labenz *et al*).

AstraZeneca noted that Altana had claimed that the EXPO findings were not clinically important.

- Given the number of patients who were treated with PPIs, the statistically significant 3.5% improvement in healing rates with esomeprazole relative to pantoprazole was clinically important and represented a clear improvement over pantoprazole for patients with erosive oesophagitis.

- Moreover, the difference was substantially greater after 4 weeks of treatment and with increasing severity of oesophagitis respectively.

- In addition, logistic regression analysis of EXPO clearly identified choice of PPI (esomeprazole vs pantoprazole - odds ratio 1.3) as an independent predictor of success in healing (Labenz *et al* 2006) and heartburn resolution (Labenz *et al* 2005).

- Furthermore, the EXPO study also provided greater therapeutic relevance because it assessed not only the acute treatment of oesophagitis, but also, in the same patient population, maintenance therapy with esomeprazole 20mg or pantoprazole 20mg (Labenz *et al* 2005).

AstraZeneca noted that Altana had referred to a study that was not used to support this claim in its promotional material. The abstract on healing, Bardhan *et al* and the combined analysis, Achim *et al* had not been published in a peer reviewed journal in order to assess their validity in determining sample size and statistical analyses. The authors used an integrated approach combining both endoscopic healing and symptom status. As this methodology combined two variables it could not be used to support the claim of 'comparable healing'.

AstraZeneca noted that in Achim *et al* the non-inferiority margin had been set at -15%; pending statistical validity, again such a large treatment difference could not justify the term 'comparable healing'.

AstraZeneca alleged that the claim 'comparable healing rates to esomeprazole 40 mg' could not be substantiated when it had been shown that esomeprazole was superior to pantoprazole in the healing of oesophagitis. Such a claim did not represent the balance of evidence.

APPEAL BOARD RULING

The Appeal Board considered that, in common parlance, if two medicines were described as comparable then prescribers and patients would generally not mind which one was used. The Code required material including comparisons to have a statistical foundation. Clinical relevance was an important consideration.

The Appeal Board noted how the parameters of Gilleson *et al* had changed as the study progressed and in that regard it considered that the results were not as robust as those from the EXPO study. The Appeal Board further noted that unlike the EXPO study, Gilleson *et al* had not included patients with Los Angeles grade D (ie more severe) oesophagitis. The EXPO study had shown that for both esomeprazole and pantoprazole there was a decline in healing rates with increasing baseline severity of oesophagitis. After 8 weeks of therapy the healing rates for esomeprazole 40mg were statistically superior to pantoprazole 40mg with LA grades B, C and D at baseline.

The Appeal Board considered that the claim 'Endoscopic healing rates comparable to esomeprazole 40mg' was too broad such that it was ambiguous. It implied that in patients with any grade of gastroesophageal reflux

disease (GERD), healing rates observed with Protium had been shown to be statistically similar to those observed with Nexium which was not so. The claim was misleading in that regard. The Appeal Board upheld the Panel's ruling of a breach of Clause 7.2. The appeal on this point was unsuccessful.

The Appeal Board noted that the EXPO study had shown that, overall, healing rates with Protium and Nexium were very similar in absolute terms. In that regard the Appeal Board thus considered that there was no breach of either Clause 7.3 or 7.4 and ruled accordingly. The appeal on these points was successful.

2 Claim 'Once daily pantoprazole 40mg and esomeprazole 40mg have equivalent overall efficacy in relieving GERD-related symptoms' (PAN202/291105/P)

COMPLAINT

AstraZeneca noted that the claim was referenced to Scholten *et al* (2003), which was designed as a superiority study comparing the area under the curves (AUCs) for the symptom scores of pantoprazole and esomeprazole. There was no statistical difference (p>0.05) between the two treatment groups. It was incorrect to conclude from this non-significant value that pantoprazole and esomeprazole were equivalent with respect to symptoms; a non-significant p value for superiority did not imply equivalence. In order to show equivalence, a pre-specified equivalence margin had to be stipulated with construction of confidence intervals for the treatment difference. Equivalence was inferred if the confidence intervals fell entirely within the equivalence margins.

AstraZeneca submitted that differences that did not reach statistical significance must not be presented in such a way as to mislead. Thus this claim was misleading, incapable of substantiation in breach of Clauses 7.2, 7.3 and 7.4

RESPONSE

Altana submitted that Scholten *et al* was designed as a non-inferiority study and not as a superiority study as stated by AstraZeneca. The study received prior independent ethics committee approval and was subsequently published in a peer-reviewed journal. The primary criterion of Scholten *et al* was to evaluate Protium and Nexium in terms of symptom load of GERD-related symptoms, defined AUC for the symptom score. The between group comparisons for the AUC was done by Wilcoxon rank-sum test (5% level, two-sided). The AUCs for the GERD-related symptoms were similar and comparable between the two treatment groups (p>0.05). This claim did not misrepresent the statistical outcome from this study.

Altana submitted that as in point 1 above, 'equivalent' was taken directly from the title of Scholten *et al*. Publication was in a peer-reviewed journal and reflected the average physician's interpretation of the term 'equivalent' through its common or everyday meaning. In this clinical context 'equivalent' was understood to mean 'as effective as', and was not interpreted in a pure statistical manner. This claim was not in breach of Clauses 7.2, 7.3 and 7.4.

PANEL RULING

The Panel noted that Scholten *et al* compared the efficacy of pantoprazole (40mg) (n=112) and esomeprazole (40mg) (n=105) in the treatment of GERD-related symptoms. The primary criterion of the study was to evaluate symptom load of GERD-related symptoms, defined as AUC for the symptom score. Over the 28 day treatment period the AUCs for the six typical GERD-related symptoms (heartburn, acid regurgitation, gastric complaints, pressure in the epigastrum, feeling of satiety and flatulence) were similar and comparable in the two treatment groups (p>0.05). Thus the study was unable to show a statistically significant difference between the two medicines. The results did not mean that the study had proven the two were equivalent. The Panel thus considered that the claim 'Once-daily pantoprazole 40mg and esomeprazole 40mg have equivalent overall efficiency in relieving GERD-related symptoms' was misleading and could not be substantiated as alleged. Breaches of Clauses 7.2, 7.3 and 7.4 were ruled.

3 Claims 'Fast symptom control - 2 days faster than esomeprazole 40mg' (PAN208/071205/P), 'daytime symptom relief - 2 days faster' (PAN202/291105/P) and '2 days faster than esomeprazole 40mg' (PAN291/020806/P)

COMPLAINT

AstraZeneca noted that the claims were referenced to the secondary end points of Scholten *et al* (time to adequate relief of GERD-related symptoms). As stated at point 2 above, this study did not reach statistical significance in terms of the primary outcome (AUC of the GERD symptoms scores between esomeprazole 40mg and pantoprazole 40mg).

AstraZeneca believed that it was appropriate to use secondary endpoints without the primary end point when the analysis of the secondary end point was consistent with the primary endpoint of the study. If there was an inconsistency in terms of the interpretation of the study from a secondary endpoint alone, the primary endpoint should be given sufficient clarity, such that the claim could be immediately seen in the context of the primary endpoint. AstraZeneca considered that it was misleading to use a secondary endpoint alone if it would lead the reader to draw a different conclusion to that of the primary end point.

AstraZeneca submitted that in this case, the secondary endpoint claims did not inform the reader of the primary outcome of the study (AUC of symptoms scores between esomeprazole 40mg and pantoprazole 40mg) and were not consistent with the result of the primary end point. In addition, as a secondary endpoint, the study would not have been appropriately powered to examine this

measure, and was therefore at risk from statistical error.

AstraZeneca considered that the Panel's ruling on a similar case, Case AUTH/1579/4/04, was relevant.

AstraZeneca stated that in addition, the EXPO study showed that esomeprazole 40mg provided faster and more effective resolution of heartburn than pantoprazole 40mg. This was based on the time to sustained resolution of symptoms (defined as a period of seven consecutive days without heartburn). This was in contrast to the assessment of symptoms in Scholten *et al* that assessed time to adequate relief. In Scholten *et al* patients did not have to reach complete resolution of symptoms. Time to sustain a resolution of symptoms as shown by esomeprazole 40mg was much more clinically relevant as it was a period of prolonged improvement in contrast to achieving a period of partial symptomatic relief. Thus, the claims were misleading, did not reflect the available evidence and were in breach of Clauses 7.2, 7.3 and 7.4.

RESPONSE

Altana submitted these claims were derived from a secondary endpoint stated in Scholten *et al*. With demonstration of the primary endpoint (as detailed in point 2 above), secondary endpoints that illustrated a meaningful clinical benefit to patients might be used without misleading the reader. Here a statistically superior and clinically relevant reduction in the time required to achieve pre-defined symptom relief was seen between the products, with Protium being superior to Nexium. No claims of superiority with regards to the primary endpoint had been made.

Altana stated that AstraZeneca's submission that 'as a secondary endpoint, the study would not have been powered appropriately to examine this measure, and was therefore at risk from statistical error' was incorrect. Power was defined as the probability to reject the null hypothesis in the case that a real difference existed. Therefore a statistically significant test result was not influenced by this parameter. In short, the power of Scholten et al had no influence on the conclusions drawn from the statistically significant difference seen in this secondary objective.

Altana noted that furthermore AstraZeneca alleged that as the EXPO study showed that esomeprazole 40mg provided faster and more effective resolution of heartburn than pantoprazole 40mg the claims were misleading and did not reflect the available evidence.

Altana submitted that Scholten *et al* focused on the treatment of GERD. Multiple definitions of GERD from wide-ranging parties existed (Vakil *et al* 2006, AstraZeneca website, NICE website). Although the precise definitions varied there was a common consensus that GERD was caused by the reflux of acidic contents from the stomach into the oesophagus leading to a variety of symptoms. Although heartburn was one of the most common symptoms there was growing evidence and consensus that many patients presented with a wide variety of GERD-related symptoms (regurgitation of gastric contents, chest pain, difficulty in swallowing, wheezing, hoarseness etc) that were clinically significant and meaningful. This was also reflected in a very recent consensus publication, done by some of the leading experts in the field (Vakil *et al*). The approach taken by Scholten *et al* was in line with this and therefore reflected clinical reality. It attempted to gain a wide-ranging measure of GERD symptom relief on PPI therapy. This study looked at adequate symptom relief but did not require complete symptom resolution, reflecting that many patients might have mild intermittent symptoms during therapy but could be dramatically improved from their original symptoms. This was further supported by recent studies in individuals without GERD where it could be shown that they might also experience some mild symptoms that were commonly ascribed to GERD. This led to the introduction of a symptom threshold in contrast to a 'complete' symptom relief concept (Stanghellini et al 2005 and Stanghellini *et al* 2006.

Altana submitted that the EXPO study focused on heartburn only in terms of complete symptom control. Heartburn, although a symptom of GERD, did not represent the spectrum of symptoms associated with this disease. The EXPO study was based upon the time to sustained complete resolution of heartburn over a period of seven consecutive days.

Altana submitted that in summary;

- the EXPO study looked at oesophageal erosion healing rates and the absolute resolution of heartburn over time.

- Scholten *et al* studied the reduction in GERD symptom load over time (six different symptoms).

Altana submitted that these studies had thus considered different parameters measured by different methodologies. They could not be considered as similar and could not be compared. The concept as purported by AstraZeneca that the EXPO study might in some way negate or counter the claims made on the findings of Scholten *et al* was illogical on this basis. Altana denied that the claims were in breach of Clauses 7.2, 7.3 and 7.4.

PANEL RULING

The Panel noted that in Scholten *et al* patients recorded the perceived intensity of GERD-related symptoms (heartburn, acid regurgitation, gastric complaints, pressure in the epigastrum, feeling of satiety and flatulence). A five-point Likert scale was used to assess the intensity of each symptom: none (0), mild (1), moderate (2), severe (3) and very severe (4). Each symptom was assessed and scored and if the sum score fell below 5 for the first time, the patient was characterized as having reached adequate relief from GERD-related symptoms. The patients did not have to reach complete symptom relief. The results of the study showed that for daytime, the first time to reach adequate relief of GERD-related symptoms in the pantoprazole group was 3.73 days and 5.88 days for the esomeprazole group (p=0.034). This was the result upon which the claims in question were based. The

Panel noted, however, that the claims only referred to 'symptom relief' or 'symptom control', not 'adequate symptom relief control'. In the Panel's view the claims implied total symptom relief/control which was not so. The Panel further noted that the claims did not refer to 'first time' relief and in that regard there was an implication that sustained relief of symptoms was achieved with pantoprazole after 3.7 days. There was no data to show this. In that regard the Panel noted the results of the EXPO study which had shown that time to sustained resolution of heartburn, the most common GERD-related symptom, (defined as a period of seven consecutive days without heartburn) was statistically significantly shorter for patients treated with esomeprazole than for those receiving pantoprazole (6 days versus 8 days; $p<0.001$).

The Panel thus considered that the claims at issue were misleading and did not reflect the available evidence as alleged. Breaches of Clauses 7.2, 7.3 and 7.4 were ruled.

APPEAL BY ALTANA

Altana appealed the ruling that the claims 'Fast symptom control - 2 days faster than esomeprazole 40mg', 'daytime symptom relief - 2 days faster' and '2 days faster than esomeprazole' were in breach of Clauses 7.2, 7.3 and 7.4.

Altana rejected the Panel's decision that Scholten *et al* and the EXPO study were suitable for direct comparison as they were based upon entirely different study designs, in different populations and with entirely different endpoints.

Altana submitted that as previously stated, the EXPO study looked at oesophageal erosion healing rates and the absolute resolution of heartburn over time. Scholten *et al* looked at the reduction in GERD symptom load over time - six different symptoms typical of GERD including acid regurgitation, gastric complaints, pressure in the epigastrium, feeling of satiety, flatulence and heartburn. Altana submitted the following as further supporting material reflecting the latest thinking in GERD, which made a comparison of these studies misleading in the extreme.

Altana submitted that an understanding of current medical thinking on GERD was vital in considering why the two studies were radically different in design and therefore could not be compared.

These studies considered different medical conditions and used different methodologies. They could not be considered as studying the same endpoint and thus could not be directly compared. Indeed the area under the curve (AUC) symptom load table (Scholten *et al*) illustrated that in endoscopically proven GERD, heartburn contributed less than 25% of the symptom load during the study.

Amongst others the Montreal Definition and Classification of Gastroesophageal Reflux Disease published in 2006 (supported by AstraZeneca) confirmed that GERD was considered to be a disease with a wide range of both oesophageal and extra-oesophageal symptoms not just a disease of heartburn. Modlin *et al* (2007) (in press) reiterated the movement away from studying heartburn as a single symptom of GERD and the importance of considering the broad range of oesophageal and extra-oesophageal symptoms that patients experienced.

Altana submitted that the design of Scholten *et al* reflected this modern clinical interpretation of GERD. It looked for improvement in a range of six GERD related symptoms and did not focus entirely on heartburn. It defined a successful clinical outcome as a reduction in total symptom score to below a pre-defined level. This did not require complete symptom resolution.

Altana submitted that Stanghellini *et al* (2005 and 2006) discussed this concept of GERD symptom reduction to a lower threshold but not to zero. Individuals without evidence of GERD experienced low levels of symptoms commonly ascribed to GERD. The background incidence of GERD-type symptoms in a healthy population was not zero although a few individuals within the broader population might experience zero symptoms. This had been confirmed by two clinical studies with more than 1500 healthy volunteers. Stanghellini *et al* (2005) (national German study) eligible for analysis, n=385 and Stanghellini *et al* (2006) (international study) eligible for analysis, n=1,167.

Altana submitted that therefore, it followed that a study designed to illustrate complete symptom resolution (zero symptoms) in GERD would expect to fail. Thus at best one might hope to reduce the symptoms of GERD within a study population to reach the expected background incidence. However a pre-determined clinically meaningful benefit might be defined. This benefit would reduce the burden of symptoms to a clinically relevant threshold above the background level. This was what Scholten *et al* achieved.

Altana submitted that however, it was possible to achieve complete resolution of heartburn, as illustrated by the EXPO study, if only heartburn was considered.

Altana submitted that thus what was claimed to be 'complete symptom resolution' (zero heartburn) seen with the EXPO study could not be logically compared with the symptom load reduction seen in Scholten *et al*, which because of the applied threshold concept could never achieve complete symptom resolution. The study designs logically did not allow for comparison. Indeed the claim of complete symptom resolution made for the EXPO study was in itself misleading.

Altana thus disagreed with the Panel's ruling that the terms 'symptom control' and 'symptom relief' were misleading. For studies looking at symptom load reduction in GERD these phrases were entirely appropriate – symptom control/relief could not reach zero for the reasons stated above.

Furthermore Altana contested the Panel's assertion that 'there was an implication that sustained relief of symptoms was achieved with pantoprazole after 3.7 days'.

Altana submitted that an understanding of modern GERD clinical study design should have invalidated AstraZeneca's claim in its complaint that 'Time to sustain a resolution of symptoms as shown by esomeprazole 40mg was much more clinically relevant as it was a period of prolonged improvement in contrast to a achieving a period of partial symptom control'. AstraZeneca was factually incorrect as the EXPO study measured treatment of heartburn not resolution of symptoms as previously shown.

Altana concluded that Scholten *et al* represented the more modern methodology and more clinically relevant interpretation of GERD, assessing the broad spectrum of GERD symptoms. It could not be compared with older methodologies, such as the EXPO study measuring heartburn only. To this end the assertions in the complaint should carry no weight with the Panel nor influence the interpretation of Altana's claims, which should be viewed in isolation from any argument derived from the non-comparable EXPO study.

Altana submitted that its claims only referred to the time of onset of symptom relief in the Scholten *et al* head-to-head comparator study measuring GERD symptom load. A statistically significant difference between the two products was seen for this parameter in favour of Protium. This was stated. There was no claim of prolonged relief. The claims were entirely in line with the time to event analysis used to determine this outcome and suitably referenced.

COMMENTS FROM ASTRAZENECA

AstraZeneca noted that Scholten *et al*, a direct comparison study, evaluated the primary outcomes (AUCs for GERD symptom scores) between esomeprazole 40mg and pantoprazole 40mg. As stated in the results section there was no statistical difference ($p>0.05$) between the two treatment groups, ie the study did not meet its primary endpoint and was thus inconclusive.

The claims at issue 'Faster symptom control - 2 days faster than esomeprazole 40mg', 'daytime symptom relief - 2 days faster' and '2 days faster than esomeprazole' related to the secondary end points of Scholten *et al*. AstraZeneca alleged that as this study did not meet its primary endpoint it was not appropriate to use secondary endpoints that were inconsistent with the primary outcome of the study. This point was addressed in the European Medicines Evaluation Agency guidance.

AstraZeneca alleged that differences that did not reach statistical significance must not be presented in such a way as to mislead. Non-significant p values across the primary parameters equated with the negative results in the study irrespective of the results from secondary parameters. Secondary endpoints could not be used to 'salvage' an otherwise non-supported study. Results from secondary parameters might suggest new parameters that need to be explored as primary outcomes in a trial.

AstraZeneca therefore alleged these claims to be misleading, as the use of the secondary endpoints alone would lead the reader to draw a different conclusion if they were unaware of the primary outcome of the study. In addition there was no indication what type of symptoms were controlled/ improved and that partial symptom resolution was needed to be achieved in the study. These matters were addressed in the Panel's rulings.

AstraZeneca alleged furthermore, that the '2 day difference' was based on calculating the mean, which was a biased estimate for Kaplan-Meier analysis due to censored observations. The standard summary statistic should be the median, which was two days for both treatment groups.

In addressing the issue raised by Altana relating to a broader definition of GERD-related symptoms' which also included gastric complaints, feeling of satiety, and flatulence, AstraZeneca was concerned that these were not generally accepted as specifically related to GERD. The most important and predominant symptoms were heartburn and acid regurgitation as discussed in the Montreal definition (Vakil *et al*). In Scholten *et al* these symptoms were experienced by 77% of the patients.

AstraZeneca alleged that utilizing a much broader spectrum of GERD symptoms, that included elements of irritable bowel syndrome, raised uncertainty as an improvement in a patient's overall symptom score (eg driven by improvements in symptoms such as flatulence) could mask deterioration in a more troublesome symptom such as heartburn. The EXPO study showed that esomeprazole 40mg provided faster resolution of heartburn than pantoprazole 40mg. This was based on the time to sustained resolution of heartburn (defined as a period of seven consecutive days without heartburn). This was also addressed in the Panel's rulings.

APPEAL BOARD RULING

The Appeal Board noted the claims at issue relied upon secondary end point data from Scholten *et al*, a study which had failed to show a statistically significant difference between Protium and Nexium with regard to the primary endpoint. The failure to satisfy the primary end point was not made clear in the material. In such circumstances the Appeal Board considered that it was unacceptable to use secondary data to claim an advantage for Protium over Nexium when the primary endpoint had been unable to show such a difference. The Appeal Board considered that the claims were misleading in this regard and did not reflect the available evidence as alleged. The Appeal Board upheld the Panel's rulings of breaches of Clauses 7.2, 7.3 and 7.4. The appeal on this point was unsuccessful.

Complaint received	**4 January 2007**
Case completed	**8 June 2007**

CASE AUTH/1950/1/07

FORMER EMPLOYEE v ASTRAZENECA

Promotion of Casodex 150

A former employee of AstraZeneca complained about misleading claims for Casodex 150 (bicalutamide), call rates for representatives and advice on staying within the Code.

The complainant felt that he was being asked to break the law by delivering misleading promotional claims for Casodex and that AstraZeneca was bringing the industry into disrepute which might be a breach of Clause 2 of the Code. Only when the complainant raised his concerns via a formal grievance procedure did AstraZeneca take action in February 2006. AstraZeneca changed the claim for Casodex from 'equivalent to castration' to 'no different to castration in overall survival'. Casodex 150 was, however, up to 36% worse than castration for survival.

Casodex 150mg was indicated for the management of patients with locally advanced, non-metastatic prostate cancer for whom surgical castration or other medical intervention was not considered appropriate or acceptable, ie a second line treatment after a leutinizing hormone releasing hormone (LHRH) analogue; surgical castration was not widely used.

The point about an 'equivalent efficacy to castration' campaign was that if the medicines were equally effective then a decision could be made on first line treatment based on the preferred side effect profile of the treatment. This was a much bigger group of patients and was outside the marketing authorization. AstraZeneca did not consider that patient safety was compromised by the use of the equivalence campaign.

In Iversen *et al* (2000) at a median follow up of 6.3 years, mortality was 56%. The median survival was 63.5 months in the Casodex 150 group and 69.9 months in the castration group. If patients were not informed that Casodex 150 could be up to 36% worse for survival than castration their safety was compromised.

If AstraZeneca was allowed to use the revised claim 'No different to castration in overall survival' it would continue a first line campaign and public health would not be safe guarded.

The Panel considered that the claim 'Equivalent efficacy to castration' was misleading given the statement in the summary of product characteristics (SPC) that 'equivalence of the two treatments [Casodex 150 and castration] could not be concluded statistically'. Thus the Panel ruled a breach of the Code as acknowledged by AstraZeneca.

The Panel noted the complainant's concerns about the revised claim 'No different to castration in overall survival' based on Iversen *et al*. The results from this study were reported in the Casodex 150mg SPC and supported the statement 'At 56% mortality and a mean follow-up of 6.3 years, there was no significant difference between Casodex and castration in survival (hazard ratio = 1.05 [CI 0.81 to 1.36]); however equivalence of the two treatments could not be concluded statistically'. The complainant was concerned that the claim 'No different to castration in overall survival' failed to alert prescribers that patients' survival might be compromised by up to 36%. Equally, however, survival might be improved by up to 19%. The Panel considered that the target audience would appreciate that there were always confidence intervals in statistics. Readers would understand the claim in question to mean that, overall, no meaningful or clinically significant difference in survival had been reported between Casodex 150 and castration which was so. No breach of the Code was ruled. This ruling was upheld on appeal by the complainant.

With regard to call rates, the complainant stated that if a carrot in the form of the AZpiration scheme failed to induce representatives into breaching the Code (Case AUTH/1899/10/06) then a stick in the form of short-term performance measures was threatened.

This was viewed as the first step in a disciplinary process and was a threat which was used, formally and informally, to bully and harass representatives into achieving the frequency of 12 face to face calls. This amounted to harassment to breach the Code.

The complainant noted that the findings in Case AUTH/1899/10/06 regarding frequency of calling referred to this campaign in terms of incentivisation to break the Code. The complainant requested a response concerning the fact that representatives could be put on short-term performance procedures for failing to be incentivised to break the Code in terms of frequency of visits.

The Panel noted that in the previous case, Case AUTH/1899/10/06, it had been ruled that representatives' call rates and incentivisation were in breach of the Code as alleged. In the present case, Case AUTH/1950/1/07, the complainant had asked the Panel to consider the specific allegation that placing representatives on short-term objectives for failing 'to be incentivised to break the Code' in terms of frequency targets was in breach of the Code. This had not been addressed as a discrete issue previously.

The Panel noted the points raised by the complainant and AstraZeneca's comments about the number of representatives on short-term objectives and reasons

given by those leavers who attended exit interviews. In 2004 two members of the entire oncology sales force of 80-85 were on short-term objectives. AstraZeneca's submission that less than 70% of the oncology team had left during 2004/05 was also noted. Taking all the evidence into account the Panel decided that on the balance of probabilities there was insufficient evidence to show a breach of the Code as alleged. The Panel therefore ruled no breach of the Code. This ruling was not appealed.

The complainant stated that during 2004 and the first 6 months of 2005 the oncology team were under extreme pressure to achieve metrics which included (in 2004) 12 face to face calls a year on the main group of target customers. The complainant and others tried to raise their concerns about achieving these metrics and staying within the Code via the union representative.

Concern was raised at all levels of management including hospital area sales manager, national sales manager, human resources, UK director level, the whistleblowing line and the chief executive. Most of this was documented via the union representative; no advice was received.

The complainant provided farewell emails and two witness reports from hospital area managers which might give insight into this fear culture which prevented concerns being raised. ABPI complaints forced a change of culture and the medical director had to acknowledge this with an email in November 2005 entitled 'Embracing our People'. The complainant alleged that AstraZeneca ignored the concerns about the Code effectively demeaning the Code and this brought discredit to the pharmaceutical industry in breach of Clause 2.

The Panel noted that in the previous cases breaches of the Code had been ruled. The Panel noted that the allegation now to be considered was wider than that in Case AUTH/1714/5/05 which related specifically to references to the Code in the campaign notes. The Panel considered that the briefing material had been inadequate in relation to the general allegation now before it. The Panel therefore ruled a breach of the Code as acknowledged by AstraZeneca.

The Panel was concerned that AstraZeneca's promotional material was inconsistent with information in the Casodex SPC. It noted that the complaint about call rates and call frequency had been dealt with in previous cases but the complainant had now alleged that those rulings together with those in the above amounted to a breach of Clause 2 of the Code.

Taking all the circumstances into account and bearing in mind its rulings in the previous case, Case AUTH/1899/10/06, the Panel did not accept that the cumulative effect of the Panel's rulings in the above and the previous case were, on balance, sufficient to warrant a breach of Clause 2 which was a sign of particular censure and reserved for such use. The Panel ruled no breach of Clause 2 and this ruling was upheld on appeal by the complainant.

The Medicines and Healthcare products Regulatory Agency (MHRA) forwarded part of a complaint which it had received from an ex-employee of AstraZeneca UK Limited. The complaint, Case AUTH/1899/10/06, concerned, *inter alia*, representative call frequency targets in relation to the promotion of Casodex 150 (bicalutamide). An AstraZeneca oncology sales and marketing booklet showing activity targets was provided together with a company email explaining the call frequency targets for employees. The Panel ruled breaches of the Code (Clauses 9.1, 15.4 and 15.9) and no breach of Clause 2. The complainant appealed the no breach ruling and in the appeal referred to matters in his complaint to the MHRA that had not been referred to the Authority and thus not considered by the Panel. Thus the additional matters in the appeal could not be considered as part of the appeal. The complainant was so informed and subsequently decided to withdrew the appeal and sent a new complaint (Case AUTH/1950/1/07).

1 Misleading claims

COMPLAINT

The complainant alleged that from January 2004 to February 2006 AstraZeneca used a misleading claim when promoting Casodex 150 to urologists, oncologists and their teams (eg detail aid ref 05/15791). AstraZeneca claimed equivalent efficacy to castration whereas the summary of product characteristics (SPC) stated that 'equivalence of the two treatments could not be concluded statistically'.

This situation probably arose as a 'Dear Doctor' letter had been sent to advise of the change to the licence in 2003 when treatment of localised prostate cancer was removed.

Using a study (which failed to demonstrate equivalence between bicalutamide monotherapy and castration with respect to death, progression and treatment failure by rejecting the hypothesis that bicalutamide was at least 25% worse than castration) to say that Casodex 150mg demonstrated equivalent efficacy to castration was misleading. Statistical significance between treatment groups was not demonstrated (Iversen *et al* 2000).

This study was based on the results of combining trials 306 and 307. The Food and Drug Administration (FDA) in the US decided that these trials could not be combined because of positive results in one and negative results in the other. The negative trial (307) was more than twice the size. When put together there was a wash. A non-approvable letter was issued. Did the UK have different statistical methods?

The complainant felt that he was being asked to break the law by delivering misleading promotional claims and that AstraZeneca was bringing the industry into disrepute which might be a breach of Clause 2 of the Code.

Zoladex was £84.14 per 28 days and Casodex 150 was £240 per 28 days. The equivalent efficacy claim from January 2004 to February 2006 could have resulted in patients being inappropriately prescribed Casodex 150.

The study became a basis of Jenkins *et al* (2005).

The complainant noted UK law and MHRA guidance. The complainant alleged a breach of Clause 7.2 of the Code.

The complainant stated that AstraZeneca said no to the following: In the interests of Winning the Right Way do you intend to send out a 'Dear Doctor' letter to counteract over two years of misleading promotional claims?

Only when the complainant raised his concerns via a formal grievance procedure did AstraZeneca take action in February 2006. AstraZeneca changed the efficacy key message 'Equivalent to castration' to 'No different to castration in overall survival'. Although Casodex 150 was up to 36% worse than castration for survival.

Casodex 150mg was indicated for the management of patients with locally advanced, non-metastatic prostate cancer for whom surgical castration or other medical intervention was not considered appropriate or acceptable. Effectively this relegated Casodex 150 to second line treatment after a leutinizing hormone releasing hormone (LHRH) analogue; surgical castration was not widely used.

The point about an 'Equivalent efficacy to castration' campaign was that if the medicines were equally effective then a decision could be made on first line treatment based on the preferred side effect profile of the treatment. This was a much bigger group of patients and was outside the marketing authorization.

AstraZeneca did not consider that patient safety was compromised by the use of the equivalence campaign.

In Iversen *et al*, quoted by AstraZeneca, at a median follow up of 6.3 years, mortality was 56%. The median survival was 63.5 months in the Casodex 150 group and 69.9 months in the castration group. If patients were not informed that Casodex 150 could be up to 36% worse for survival than castration their safety was compromised.

The complainant stated that if AstraZeneca was allowed to use the revised claim 'No different to castration in overall survival' it would continue a first line campaign and the MHRA and ABPI would not be safeguarding public health.

The equivalence campaign (with the might of AstraZeneca's resources behind it) ran for over two years and many patients were inappropriately on Casodex 150. It should now be made clear to urologists, oncologists and their teams that their patients' survival could be compromised by up to 36%. If patients were not informed that Casodex 150 could be worse for survival than castration their safety was compromised.

RESPONSE

AstraZeneca submitted that the matter had been dealt with appropriately in correspondence with the MHRA.

It was first raised internally with AstraZeneca by the complainant with the medical director at the end of 2005 and formed the basis of his grievance. At a grievance hearing in January 2006 the complainant was able to expand on the points raised and to provide evidence to support his claims. This specific point (the promotional claim that survival with Casodex was equivalent to that with castration) of the formal grievance procedure was upheld and the complainant was thanked for bringing it to AstraZeneca's attention. On 17 February 2006 AstraZeneca initiated a recall of all promotional material that bore the claim and new material was produced to more accurately reflect the reference publication and the Casodex 150 SPC.

The grievance procedure was concluded in January 2006 and the complainant left AstraZeneca in summer 2006. AstraZeneca received a complaint via the MHRA on the same issue relating to claims for Casodex 150 on 5 October 2006. AstraZeneca informed the MHRA of the corrective action taken as well as the justification for not issuing a 'Dear Doctor' letter. The MHRA was also given a copy of a Casodex 150 sales aid prepared in March 2006 that bore a revised claim. The assertion that Casodex was up to 36% worse than castration for survival was not an accurate reflection of the data and was based on an inaccurate interpretation of the 95% confidence interval associated with the result. The hazard ratio for survival was 1.05 (95% CI of 0.81-1.36). The 95% confidence limit indicated that the range in which the true value might lie was somewhere between Casodex being up to 19% better or up to 36% worse than castration. Overall, AstraZeneca concluded only that no statistically significant difference was found between the two treatments.

The MHRA upheld the complaint but determined that no further action would be taken against AstraZeneca. The outcome was published on the MHRA website.

As an indication of AstraZeneca's commitment to the Code and the Medicines Act it restated that this matter was dealt with immediately after the complainant brought it to AstraZeneca's attention. AstraZeneca accepted a breach of Clause 7.2.

AstraZeneca noted that the promotion of Casodex 150 for a first line indication for prostate cancer was consistent with the SPC. Casodex 150 was indicated for immediate use alone or as adjuvant to surgery or radiotherapy for the treatment of locally advanced prostate cancer, in addition to being indicated for the management of patients with locally advanced, non-metastatic prostate cancer for whom surgical castration or other medical intervention was not considered appropriate or acceptable.

PANEL RULING

The Panel noted that its role related to matters covered

by the Code. The complaint had been considered by the MHRA which was responsible for administering UK law on behalf of the health ministers.

The Panel considered that the claim 'Equivalent efficacy to castration' was misleading given the statement in the SPC that 'equivalence of the two treatments [Casodex 150 and castration] could not be concluded statistically'. Thus the Panel ruled a breach of Clause 7.2 as acknowledged by AstraZeneca.

The Panel noted the complainant's concerns about the revised claim 'No different to castration in overall survival' based on Iversen *et al*. The results from this study were reported in the Casodex 150mg SPC and supported the statement 'At 56% mortality and a mean follow-up of 6.3 years, there was no significant difference between Casodex and castration in survival (hazard ratio = 1.05 [CI 0.81 to 1.36]); however equivalence of the two treatments could not be concluded statistically'. The complainant was concerned that the claim 'No different to castration in overall survival' failed to alert prescribers that patients' survival might be compromised by up to 36%. Equally, however, survival might be improved by up to 19%. The Panel considered that the target audience would appreciate that there were always confidence intervals in statistics. Readers would understand the claim in question to mean that, overall, no meaningful or clinically significant difference in survival had been reported between Casodex 150 and castration which was so. No breach of Clause 7.2 was ruled. This ruling was appealed by the complainant.

The Panel noted that Casodex 150 was indicated first line either alone or as adjuvant therapy in patients with locally advanced prostate cancer. In patients with locally advanced, non-metastatic prostate cancer it could be used in those for whom surgical castration or other medical intervention was not considered appropriate or acceptable.

AstraZeneca needed to be clear when promoting Casodex first line but such promotion was not necessarily outside the marketing authorization.

APPEAL BY THE COMPLAINANT

The complainant appealed the ruling of no breach of Clause 7.2 with regard to the revised claim 'No different to castration in overall survival' bearing in mind the statistical design of Iversen *et al*. The trials were designed to demonstrate equivalence between bicalutimide monotherapy and castration with respect to death, progression and treatment failure by rejecting the hypothesis that bicalutimide was at least 25% worse than castration.

The complainant noted the Panel's ruling that 'AstraZeneca needed to be clear when promoting Casodex 150 first line but such promotion was not necessarily outside the marketing authorization'. The complainant alleged that it was very clearly outside the marketing authorization. Where was the first line licence? There was not a first line licence. From the SPC: 'Casodex 150mg is also indicated for the management of patients with locally advanced, non-metastatic prostate cancer for whom surgical castration or other medical intervention is not considered appropriate or acceptable'. Effectively the above statement relegated Casodex 150 to second line treatment after an LHRH analogue (surgical castration was not widely used).The complainant noted 'In patients with locally advanced prostate cancer Casodex 150 is indicated as immediate therapy either alone or as adjuvant to treatment by radical prostatectomy or radiotherapy' and stated that in this adjuvant trial patients were randomly allocated to Casodex 150 or placebo in addition to receiving standard care (watchful waiting, radical prostatectomy or radiotherapy). Watchful waiting (or active monitoring): many patients with locally advanced disease were elderly, and thus would have a relatively short life expectancy. Watchful waiting might be a valid treatment option in these patients who would often succumb to other co-morbid conditions. This was the group of patients where 'Casodex 150 is indicated as immediate therapy (either) alone or as adjuvant to treatment by radical prostatectomy or radiotherapy'.

The complainant alleged that giving a group of patients active therapy who were considered not to need it categorically did not constitute a first line licence. There was no first line licence.

The complainant noted that this adjuvant trial (also known as the AstraZeneca Early Prostate Cancer (EPC) trial programme) was the subject of the 'Dear Doctor' letters referred to in AstraZeneca's response. In those patients with localised prostate cancer, who would otherwise have been managed only by watchful waiting, there was an increase in the number of deaths for Casodex 150mg patients when compared with patients who received placebo. Presumably if there was some background adverse metabolic effect it could also be in the locally advanced group. It would be purely speculation to consider that this was one possible reason why Casodex 150 was not equivalent to castration. Survival was the ultimate aim of all patients with incurable cancer.

The complainant noted that in Iversen *et al*, at a median follow up of 6.3 years, mortality was 56%. The median survival was 63.5 months in the Casodex 150 group and 69.9 months in the castration group. The complainant alleged that if patients were not informed that Casodex 150 could decrease survival compared with castration their safety was compromised.

As there was no first line licence AstraZeneca should not be allowed to promote it in this fashion. Both Iversen et al trial and the EPC data were considered to have too many faults by the FDA and non-approvable letters were issued. The therapeutic indications were misleading and a corrective statement should be required.

COMMENTS FROM ASTRAZENECA

AstraZeneca noted that the claims at issue related to

the promotion of Casodex 150, in particular the statement 'No different to castration in overall survival' and the positioning of Casodex 150 to include first line use either alone or as adjuvant therapy in patients with locally advanced prostate cancer.

AstraZeneca submitted that the claim, 'No different to castration in overall survival' was supported by Iversen et al. The complainant's view that this study showed that patients did 36% worse than castration in overall survival was an inaccurate interpretation of the 95% confidence intervals associated with the actual result. The hazard ratio for survival was 1.05 (95% CI of 0.81-1.36). The 95% confidence limit indicated the range in which the true value might lie was somewhere between Casodex being up to 19% superior or up to 36% inferior to castration. Overall, no statistically significant difference was found between the two treatments. While this study did not achieve the required threshold for the demonstration of equivalence, it did demonstrate that there was no significant difference between Casodex 150mg and castration. This flowed from the fact that the 95% confidence interval for the difference between Casodex 150mg and castration included unity and hence, by statistical definition and without exception, the difference between the treatments being compared was 'not statistically significant'.

AstraZeneca maintained that this claim was in keeping with the scientific evidence and not in breach of Clause 7.2.

In summary the claim that Casodex 150 was 'No different to castration in overall survival' was accurate and not misleading and therefore not in breach of Clause 7.2. The licensed indication included use in the first line setting and promotion in this context was within the licensed indication and not in breach of Clause 7.2.

FURTHER COMMENTS FROM THE COMPLAINANT

The complainant referred to the Casodex 150 Sales Campaign June 2005 (Date of prep: May 2005 Ref: 16127) for use with Casodex 150/Zoladex Sales Aid (ref 15790):

> 'Key Message
>
> Casodex 150mg has equivalent efficacy to castration.
>
> Make the page live
>
> Use this page to demonstrate that Casodex 150 has equivalent efficacy to castration (138 medical (i.e. Zoladex), 22 surgical).
>
> Whilst survival is the ultimate aim for incurable cancer, such as locally advanced prostate cancer, ensure the customer knows that randomised controlled trial data is regarded as the most valuable type of evidence for demonstrating the efficacy of therapies.
>
> Ensure that the customer knows that this is a robust study (a randomised controlled trial) in 480 patients. After a median follow up of 6.3 years when 56% of patients had died and the trial was mature, Casodex 150 and castration therapy were shown to be equivalent in terms of time to disease progression and overall survival. Can the customer think of any data that contradict this result?
>
> Consider the benefit of equivalent efficacy to both the customer and the patient; now there is a real and alternative choice of treatments that provide equivalent efficacy in treating locally advanced disease. How will this make the clinician and customer feel? Again, can the customer think of any data that contradict this result?
>
> Ask the customer how confident and comfortable they feel about the efficacy of Casodex 150 for patients with locally advanced disease - ask whether they would be willing to use Casodex 150 in place of Zoladex with these new active patients with locally advanced disease.'

The complainant alleged that this did not fit with the licensed indication from the SPC: 'Casodex 150mg is also indicated for the management of patients with locally advanced, non-metastatic prostate cancer for whom surgical castration or other medical intervention is not considered appropriate or acceptable'. Effectively the above statement relegated Casodex 150 to second line treatment after an LHRH analogue (surgical castration was not widely used).

The complainant noted that according to the Casodex 150mg SPC 'In patients with locally advanced prostate cancer Casodex 150 is indicated as immediate therapy either alone or as adjuvant to treatment by radical prostatectomy or radiotherapy'. In this adjuvant trial patients were randomly allocated to Casodex 150 or placebo in addition to receiving standard care (watchful waiting, radical prostatectomy or radiotherapy). Watchful waiting (or active monitoring). Many patients with locally advanced disease were elderly, and thus would have a relatively short life expectancy. Watchful waiting might be a valid treatment option in these patients who would often succumb to other co-morbid conditions. This was the group of patients where 'Casodex 150 is indicated as immediate therapy (either) alone or as adjuvant to treatment by radical prostatectomy or radiotherapy'.

The complainant alleged that giving a group of patients active therapy who were considered not to need it categorically did not constitute a first line licence. There was no first line licence.

The complainant alleged that the misleading and unlawful campaign ran for over two years and a corrective statement should be published. If patients were not informed that Casodex 150 could decrease survival compared with castration their safety was compromised.

APPEAL BOARD RULING

The Appeal Board noted that according to its SPC Casodex 150 was indicated first line either alone or as adjuvant therapy in patients with locally advanced prostate cancer. In patients with locally advanced, non-metastatic prostate cancer it could be used in those for whom surgical castration or other medical intervention was not considered appropriate or acceptable.

The Appeal Board considered that AstraZeneca needed to be clear when promoting Casodex first line but such promotion was not necessarily outside the marketing authorization.

The Appeal Board noted that data from IversEn *et al* was reflected in Section 5.1 of the Casodex 150mg SPC which stated 'At 56% mortality and a median follow-up of 6.3 years, there was no significant difference between Casodex and castration in survival (hazard ratio = 1.05 [CI 0.81 to 1.36]); however equivalence of the two treatments could not be concluded statistically'. The Appeal Board noted AstraZeneca's explanation that the 95% confidence interval indicated that the range in which the true value might lie was somewhere between Casodex being up to 19% superior or up to 36% inferior to castration. Whilst the study did not achieve the required threshold to demonstrate equivalence, as the 95% confidence interval included unity, it did demonstrate that there was no statistically significant difference between Casodex 150 and castration. The Appeal Board considered that the target audience would understand the claim in question to mean that, overall, no meaningful or clinically significant difference in survival had been reported between Casodex 150 and castration which was not an unfair reflection of the data and SPC on this point. The Appeal Board upheld the Panel's ruling of no breach of Clause 7.2 in relation to the revised claim 'No different to castration'. The appeal on this point was unsuccessful.

During its consideration of this case the Appeal Board queried AstraZeneca's submission that it took 'swift and positive action' with regards to the claim 'equivalent efficacy to castration'. The company had been notified of concerns about the claim at the end of November 2005 and accepted that it was not in accordance with the SPC in January and the brand manager advised sales teams of the change on 17 February 2006. At the appeal hearing the representatives accepted that the way the matter had been dealt with was convoluted particularly given the statement in the SPC. The company had not acted swiftly to withdraw the claim in question.

2 Call rates

COMPLAINT

The complainant stated that if the carrot in the form of the AZpiration scheme failed to induce representatives into breaching the Code (Case AUTH/1899/10/06) then a stick in the form of short-term performance measures was threatened.

This was viewed as the first step in a disciplinary process and was a threat which was used, formally and informally, to bully and harass representatives into achieving the frequency of 12 face to face calls. This amounted to harassment to breach the Code.

During 2004 and 2005 over 70% of the oncology team left AstraZeneca as they thought they were no longer working for an ethical company and bringing the industry into disrepute. In 2004/05 37 people left. In 2004 only 2 exit interviews were conducted.

Many customers complained. Oncologists specialising in breast and prostate cancer would be targeted 36 times a year by the company (12 x Faslodex, 12 x Arimidex, 12 x Casodex/Zoladex).

The complainant noted that the findings in Case AUTH/1899/10/06 regarding frequency of calling referred to this campaign in terms of incentivisation to break the Code. The complainant requested a response concerning the fact that representatives could be put on short-term performance procedures for failing to be incentivised to break the Code in terms of frequency of visits. In the complainant's area, 2 out of 6 representatives were on these procedures (33%) which were viewed as the first step in a disciplinary process.

When writing to AstraZeneca the Authority asked it to respond in relation to Clause 9.1.

RESPONSE

AstraZeneca stated that the complainant referred to both call rate and to call frequency which were defined as follows:

- The call rate was the number of calls made by a representative against specified customers in a given period of time. A call rate of 4 per day meant that a representative had seen 4 of their customers in a day
- The call frequency was the number of times a specified customer was seen by an individual representative over a given period of time

This complaint concerned matters closely similar to ones which had been the subject of previous adjudications. Case AUTH/1737/7/05 was based on statements made at two divisional meetings held by AstraZeneca in September 2002. Case AUTH/1714/5/05 related to materials used and activities of AstraZeneca during 2004.

The specific area AstraZeneca was asked to consider was the allegation of placing representatives on short-term performance procedures for 'failing to be incentivised to break the Code' in relation to call frequency.

The allegation of incentivising representatives to break the Code had already been addressed by AstraZeneca in Case AUTH/1737/7/05. Prior to Case AUTH/1714/05/05, representative incentive (which represented on average less than 20% of their base salary) was based on Cash Creator and AZpiration.

Cash Creator accounted for 80% of the incentive and was based on sales and market share performance. The AZpiration scheme that accounted for the other 20% and which was historically based on call frequency and call rates, was revised following Case AUTH/1714/05/05 to ensure that call frequency was no longer incentivised.

In the response to Case AUTH/1737/7/05 AstraZeneca clearly described its processes for managing poor performance. It was also pointed out that during the first half of 2005 (the latter part of the period in question) only 2 representatives out of an oncology sales force of 80-85 were placed on short-term objectives with specific action plans to improve performance.

Disciplinary action was only used if the individuals were not meeting their objectives and performance was at an unacceptable standard; it was a last resort in this situation. All managers received extensive training in the use of various coaching techniques and performance action planning. There was no evidence to support the allegation that disciplinary action was used as a threat either formally or informally, however all employees were fully aware of their targets and objectives as set out in their performance plans. The complainant's assertion was contradicted by the fact that in 2004 only 2 members of the entire oncology sales force were placed on short-term objectives yet continued to work for AstraZeneca.

In response to the allegation that 2 out of 6 representatives in the complainant's team were on short-term performance measures, AstraZeneca submitted that only 1 representative was placed on short-term objectives.

AstraZeneca noted that the complainant had asserted that 37 representatives left the company during 2004/05 but only 2 exit interviews were performed in 2004. The complainant had been given full details of the number of leavers and the number of exit interviews for the oncology sales force as part of his grievance procedure and so it was disappointing that he now selectively used that information. It was true that 2 exit interviews out of 14 leavers were performed in 2004. However, in 2005, 19 of 23 leavers had an exit interview. As leavers were not obligated to attend or take part in an exit interview, a response rate of over 50% was very reasonable.

AstraZeneca submitted that the allegation that during 2004/05 over 70% of the oncology team left the company as they thought they were no longer working for an ethical company and bringing the industry into disrepute had already been addressed in Case AUTH/1899/10/06. In 2004 attrition rates were similar across the business while in 2005 the rate of attrition was higher but far less than 70% and followed on from a significant reorganisation of the team. Only 4 of the 21 leavers who had an exit interview cited 'unhappy with the environment' as their reason for leaving; none of them cited 'no longer working for an ethical company and bringing the industry into disrepute' as a reason for leaving.

AstraZeneca noted that the complainant had not provided any evidence to support his claim that many customers complained. Similarly AstraZeneca did not have any record of customers complaining.

On the basis of the above, AstraZeneca firmly denied a breach of Clause 9.1.

PANEL RULING

The Panel noted that in the previous case, Case AUTH/1899/10/06, it had been ruled that representatives' call rates and incentivisation were in breach of the Code as alleged. In the present case, Case AUTH/1950/1/07, the complainant had asked the Panel to consider the specific allegation that placing representatives on short-term objectives for failing 'to be incentivised to break the Code' in terms of frequency targets was in breach of the Code. This had not been addressed as a discrete issue previously.

The Panel noted the points raised by the complainant and AstraZeneca's comments about the number of representatives on short-term objectives and reasons given by those leavers who attended exit interviews. In 2004 two members of the entire oncology sales force of 80-85 were on short-term objectives. AstraZeneca's submission that less than 70% of the oncology team had left during 2004/05 was also noted.

Taking all the evidence into account the Panel decided that on the balance of probabilities there was insufficient evidence to show a breach of the Code as alleged. The Panel therefore ruled no breach of Clause 9.1. This ruling was not appealed.

3 Advice on staying within the Code

COMPLAINT

The complainant stated that during 2004 and the first 6 months of 2005 the oncology team were under extreme pressure to achieve metrics which included (in 2004) 12 face to face calls a year on the main group of target customers. The complainant and others tried to raise their concerns about achieving these metrics and staying within the Code via the union representative.

Concern was raised at all levels of management including hospital area sales manager, national sales manager, human resources, UK director level, the whistleblowing line and the chief executive. Most of this was documented via the union representative; no advice was received.

The complainant noted a hospital area sales manager witness report which stated 'It was mentioned at a management group, [a named individual] kept saying that we were breaching the ABPI'. The concerns were not escalated as a management team because 'we were all in fear of losing our jobs'.

The complainant provided farewell emails and two witness reports from hospital area managers which might give insight into this fear culture which prevented concerns being raised. ABPI complaints forced a change of culture and the medical director had to acknowledge this with an email in November 2005 entitled 'Embracing our People'. The complainant alleged that AstraZeneca ignored the concerns about the Code effectively demeaning the Code and this brought discredit to the pharmaceutical industry in breach of Clause 2.

When writing to AstraZeneca the Authority asked it to respond in relation to Clause 15.9 and in addition, to Clause 2 in relation to the cumulative effect of points 1, 2 and 3.

RESPONSE

AstraZeneca stated that this specific complaint was not raised under Case AUTH/1899/10/06. However, this part of the complaint concerned matters closely similar to those that were the subject of previous adjudications and related solely to past activities within the company.

Whilst AstraZeneca sought to promote a culture of open communication, it acknowledged that at the time in question there was a failure to provide clarity and guidance on staying within the Code and promptly address certain concerns, in relation to call frequency. On this basis, AstraZeneca accepted a retrospective breach of Clause 15.9 but noted that significant measures had been put in place to address past shortcomings.

In response to the ruling in Case AUTH/1714/05/05 AstraZeneca put in place strengthened measures to ensure that all employees understood the requirements of the Code. Full details were provided in AstraZeneca's response to Case AUTH/1737/7/05. The measures previously taken were relevant to the current complaint and included the following:

1 Sales force briefing regarding call frequency and Code requirements
2 Establishment of field force discussion group
3 Company-wide email communication of coverage and frequency requirements
4 Senior managers conference
5 Company-wide cascades of information
6 Availability of call frequency Q&A document on corporate website

In addition, all internal meetings involving representatives included five mandatory slides summarising key aspects of the requirements of the Code. The requirement that no more than 3 unsolicited calls per representative per customer per year were allowed was explicitly highlighted.

In the response to Case AUTH/1737/7/05 AstraZeneca outlined the mechanisms and structures that enabled employees to raise concerns and ensured that this was done fairly. In addition to these general fora, AstraZeneca had established a corporate reputation team that reported into the legal function. Within this team, a compliance officer had the primary responsibility of ensuring business compliance as well as being responsible for running the compliance hotline

that enabled the confidential reporting of compliance issues.

In addition to the above three complaints, the complainant alleged a breach of Clause 2 of the Code. In relation to all of these complaints there was no dispute that they related to historical materials and activities at AstraZeneca. There was even recognition in the complaint that it was solely concerned with issues arising in 2004 and the first half of 2005.

The aim of the Code was to ensure that the promotion of medicines was carried out within a robust framework to support high quality patient care. In each case where a breach of the Code was ruled, the company concerned must give an undertaking that the practice in question had ceased forthwith and that all possible steps had been taken to avoid a similar breach in the future. There was no complaint that AstraZeneca had not complied with the undertaking given in the previous cases and details of the company's comprehensive action plan had already been provided. Additionally, there was no suggestion that there was an ongoing cultural issue within AstraZeneca, indeed it was recognized in some of the papers submitted by the complainant that significant steps had been taken.

The only element to consider here that could lead to a potential ruling of a breach of Clause 2 was that there were multiple/cumulative breaches of a similar and serious nature in the same therapeutic area within a short period of time.

AstraZeneca noted that the three previous cases essentially dealt with 7 breaches (3 breaches of Clause 9.1 (failure to maintain high standards); 2 breaches of Clause 15.4 (call activity out of line with the supplementary information) and 2 breaches of Clause 15.9 (failure to provide suitable briefing material for representatives)) in neurology and oncology over more than three years. In Cases AUTH/1714/5/05 and Case AUTH/1899/10/06, AstraZeneca was found in breach of Clauses 15.4 and 9.1. In Case AUTH/1737/7/05, AstraZeneca was found in breach of Clauses 15.9 and 9.1. In addition, in each of these cases AstraZeneca was asked to respond in relation to Clause 2 and in each case no breach of Clause 2 was ruled.

There was nothing therefore in the current case that justified a ruling of a breach of Clause 2. In light of this complaint, AstraZeneca requested that the broader policy issue of whether the Code was best served by being used in this way to allow previous rulings to be re-opened as part of employment disputes, should be considered.

In addition, AstraZeneca believed it was not appropriate for the complainant to use witness statements, that were provided under strict terms of

confidentiality, for these purposes. However, in the interests of transparency AstraZeneca dealt with the inaccuracies contained within those reports.

Furthermore, AstraZeneca asked the Authority to consider whether it was appropriate and in accordance with the spirit of the Code, to allow different complaints based on the same facts to proceed, particularly when the company had taken very significant corrective action in response to a previous ruling.

In summary, AstraZeneca had responded comprehensively through internal procedures to the concerns raised by the complainant and was disappointed that, subsequently, the same issues had formed the basis of complaints to the MHRA and the Authority. Nevertheless, AstraZeneca had responded fully to these latter complaints. AstraZeneca accepted historical breaches of Clauses 7.2 and 15.9 and did not accept a breach of Clause 2 for the reasons stated.

PANEL RULING

The Panel noted AstraZeneca's response to this allegation and its general points about the complaint.

The Panel noted that in the previous cases breaches of Clauses 15.4 and 15.9 had been ruled. The Panel noted that the allegation now to be considered was wider than that in Case AUTH/1714/5/05 which related specifically to references to the Code in the campaign notes. The Panel considered that the briefing material had been inadequate in relation to the general allegation now before it. The Panel therefore ruled a breach of Clause 15.9 as acknowledged by AstraZeneca.

The Panel was concerned that AstraZeneca's promotional material was inconsistent with information in the Casodex SPC (point 1 above). It noted that the complaint about call rates and call frequency had been dealt with in previous cases but the complainant had now alleged that those rulings together with points 1, 2 and 3 above amounted to a breach of Clause 2.

Taking all the circumstances into account and bearing in mind its rulings in the previous case, Case AUTH/1899/10/06, the Panel did not accept that the cumulative effect of the Panel's rulings at points 1, 2 and 3 above and the previous case were, on balance, sufficient to warrant a ruling of a breach of Clause 2 which was a sign of particular censure and reserved for such use.

APPEAL BY COMPLAINANT

The complainant was surprised that Clause 2 was not ruled. The complainant was interested in the Appeal Board's opinion of the House of Commons Health Committee report on The Influence of the Pharmaceutical Industry which stated:

'373. The PMCPA and MHRA do not effectively co-ordinate their work in the assessment and approval of medicines advertising and promotional material. The defences in place against the inappropriate or misleading promotion of medicines are weak. The MHRA, which has admitted it cannot vet all such material, seems reluctant to punish companies that commit offences in the promotion of medicines in a swift and effective manner. Publishing upheld complaints on the MHRA website is an inadequate response; so is forcing companies to make minor changes to their advertising catchphrases. We recommend that the MHRA and the PMCPA better co-ordinate their work relating to the promotion of medicines to avoid duplication. Complaints should be investigated swiftly, particularly when claims for new drugs are involved. When the PMCPA has evidence that a company has breached the regulations it should inform the MHRA of their findings. When companies are found to be in breach of advertising or marketing regulations by the MHRA, we recommend that corrective statements always be required and that such statements are given as much prominence as the original promotional piece. The publication of misleading promotional material is a criminal offence and the punishment should befit such a status.'

The complainant noted AstraZeneca's response to the original complaint enclosed a leavepiece (ref 05/15791). The complainant noted that he had quoted this merely as an example, and alleged that all the items associated with this campaign were misleading. The campaign ran for over two years and was refreshed every quarter. A further detail aid (ref 05/15790, 04/15075) and a representative briefing document dated May 2005 (ref 16127) being further examples. If the Authority had asked for all the materials associated with this misleading campaign a hefty postbag would result. Lots of law breaking. Surely this was much more serious than wining and dining wives and girlfriends in a sporting environment? So if this law breaking did not justify a breach of Clause 2 what would?

COMMENTS FROM ASTRAZENECA

AstraZeneca noted in response to the complaint that Casodex 150 was promoted in a first line indication for prostate cancer, that this was consistent with the SPC. Casodex 150 was indicated for immediate use alone or as adjuvant to surgery or radiotherapy for the treatment of locally advanced prostate cancer, in addition to being indicated for the management of patients with locally advanced, non-metastatic prostate cancer for whom surgical castration or other medical intervention was not considered appropriate or acceptable.

AstraZeneca noted the complainant had cited the Health Select Committee Report on the Influence of the Pharmaceutical Industry as a cause for ruling a breach of Clause 2 in this matter. The current Code followed the publication of this report and the more measured Government response to it (provided) and took into account the subsequent views of the MHRA. A ruling solely in accordance with the current Code was

therefore up-to-date and appropriate.

AstraZeneca submitted the above claims were not misleading, were not in breach of any clause of the Code and certainly not Clause 2.

AstraZeneca submitted the earlier claim of 'equivalent efficacy to castration' was accepted as misleading and had been promptly withdrawn in February 2006 after it was brought to its attention, as described in the response to this complaint. It was subsequently the subject of a complaint to the MHRA brought by the complainant and was accepted by AstraZeneca as a breach of Clause 7.2 in this case, ahead of the Panel ruling. AstraZeneca was committed to the Code and had acted promptly and appropriately in regard to this claim from the point at which the issue was raised. The materials were withdrawn promptly before any external complaint and the MHRA upheld the subsequent complaint made to it but determined that 'no further action will be taken' against AstraZeneca. This prompt action and assessment by the MHRA of no further action required suggested that there were no grounds for any complaint under Clause 2. AstraZeneca restated that it had introduced a number of measures to ensure that employees understood the requirements of the Code. These measures included the following:

1 Sales force briefing regarding call frequency and ABPI Code requirements.
2 Establishment of field force discussion group.
3 Company-wide email communication of coverage and frequency requirements.
4 Senior managers conference.
5 Company-wide cascades of information.
6 Availability of call frequency Q&A document on corporate website.

In addition, all internal meetings involving representatives included five mandatory slides summarising key aspects of the requirements of the Code (provided). The requirement that no more than 3 unsolicited calls per representative, per customer per year were allowed was explicitly highlighted.

AstraZeneca now had clear mechanisms and structures in place to enable employees to raise concerns and to ensure that this was done fairly. In addition, AstraZeneca had established a corporate reputation team that reported into the legal function. Within this team, a compliance officer had the primary responsibility of ensuring business compliance; the compliance officer was also responsible for running the compliance hotline that enabled the confidential reporting of any compliance issues. AstraZeneca's action in response to this issue was prompt, comprehensive and robust.

AstraZeneca noted that in this case, the Panel had considered the failure to refer to the Code in the campaign notes. This of itself could not be considered a breach of Clause 2 and the subsequent action suggested an approach that was consistent with upholding the reputation of the industry.

AstraZeneca noted that as described in its response to this complaint, the only reason a breach of Clause 2 might be considered was in regard to similar and cumulative serious breaches of the Code in the same therapy area within a short period of time. There had been two previous breaches ruled of Clause 15.9, in different therapy areas over a period of some three years. Similarly, with regard to call rates and breaches of Clause 15.4, there were two such rulings, similarly distributed over time and therapy area. None of the individual cases were considered to be serious enough to warrant a breach of Clause 2.

AstraZeneca noted that in the case of both call rates and advice on staying within the Code in campaign roll-outs it could not be claimed that there were multiple/cumulative breaches of a similar and serious nature in the same therapeutic area within a short period of time.

FURTHER COMMENTS FROM THE COMPLAINANT

Further comments as set out in point 1 above.

APPEAL BOARD RULING

The Appeal Board noted the supplementary information to Clause 2 listed activities likely to be in breach of Clause 2 and referred, inter alia, to multiple and cumulative breaches of a similar and serious nature in the same therapeutic area within a short period of time.

The Appeal Board noted the previous cases referred to by the complainant; Cases AUTH/1714/5/05, AUTH/1737/7/05 and AUTH/1899/10/06. Two therapeutic areas were involved: psychiatry and oncology. Case AUTH/1899/10/06 was closely similar to the present case but concluded at Panel level. Rulings of breaches of the Code had been made in relation to call rates and incentivisation (Cases AUTH/1714/5/05 and AUTH/1899/10/06) and also in relation to comments made by a senior executive at a national sales conference (Case AUTH/1737/7/05). Rulings of no breaches of the Code were also made. The Appeal Board also noted the rulings in the present case.

Taking all the circumstances into account the Appeal Board did not consider that the cumulative effect of previous cases and the Panel and Appeal Board rulings in the present case were, on balance, sufficient to warrant a breach of Clause 2 of the Code which was a sign of particular censure and reserved for such use. The Appeal Board upheld the Panel's ruling of no breach of Clause 2 of the Code. The appeal on this point was unsuccessful.

Complaint received **22 January 2007**

Case Completed **14 June 2007**

CASES AUTH/1951/2/07 to AUTH/1955/2/07

MEDIA/DIRECTOR v ASTRAZENECA

Insert on statins in The Pharmaceutical Journal

Five letters published in The Pharmaceutical Journal on 3 February criticised a twelve page supplement entitled 'The new NICE [National Institute for Health and Clinical Excellence] guidance on the use of statins in practice - Considerations for implementation' which had been distributed with the journal two weeks previously. The supplement, financially supported by AstraZeneca, had been written by a general practitioner and a pharmacist and it detailed the NICE guidance on the use of statins and charted the evolving guidance on statin use from 2000 until 2005. Optimization of statin treatment strategies was discussed as was the cost of implementing the NICE guidance across a primary care trust population. A cost effectiveness model was presented wherein either atorvastatin or rosuvastatin (AstraZeneca's product Crestor) was used when patients had failed to reach cholesterol targets on simvastatin (the medicine with the lowest acquisition cost). Finally the role of the pharmacist in helping to tackle cardiovascular disease was discussed.

In accordance with established procedure, the letters were taken up by the Director as complaints under the Code.

In Case AUTH/1951/2/07 the complainant stated that she found the inclusion of the AstraZeneca document masquerading as NICE guidance within The Pharmaceutical Journal profoundly depressing. When pharmacists and others were striving to improve the cost-effectiveness and evidence base of statin prescribing here was the pharmacists' own professional journal distributing a document which advocated JBS (Joint British Societies: British Cardiac Society; British Hypertension Society; Diabetes UK; HEART UK; Primary Care Cardiovascular Society; the Stroke Association) targets which were not national policy and were usually unachievable for the average patient, and the use of a statin [Crestor] for which there was no evidence to demonstrate that it saved lives or reduced cardiovascular events, and which was not even licensed as such.

The NHS statin of first choice for most patients was simvastatin based on a wealth of evidence, as detailed in the NICE guidance, and the targets to reach were those of the National Service Framework for coronary heart disease, affirmed by the cardiovascular disease 'tsar' in December 2006.

In Case AUTH/1952/2/07 the complainant stated that rather than being a useful publication covering the evidence base for the use of statins and practical issues on cost-effective implementation of national guidance, the supplement appeared to be a promotional brochure for Crestor.

The brochure appeared to support the JBS-2 lipid targets of 4 and 2mmol/L although these were not evidence based as recognised by the JBS itself in the statement 'There are no clinical trials which have evaluated the relative and absolute benefits of cholesterol lowering to different total and LDL-cholesterol targets in relation to clinical events' (JBS 2005).

The complainant stated that the Heart Protection Study had provided strong evidence that treating high-risk individuals with simvastatin 40mg/day for five years significantly reduced their chance of having a serious vascular event, irrespective of their lipid level (MRC/BHF Heart Protection Study 2002). The complainant noted that Crestor did not have this sort of patient-oriented evidence to support its use.

The complainant noted that the NICE guidance referred to in the supplement deemed it cost effective to extend access to statins on the NHS. Its cost-effectiveness analysis assumed that half of the prescriptions for statins would be simvastatin 20mg/day and half simvastatin 40mg/day. Arguably, more expensive statins would not be cost-effective and would waste scarce resources.

The complainant submitted that a policy of simvastatin 40mg/day for all those at high risk, irrespective of lipid level, was simple to implement, evidence based and cost effective.

The complainant stated that the bottom line was find the high risk patients, offer them simvastatin 40mg/day, strongly encourage them to take it, and do not worry too much about non-evidence based targets.

In Case AUTH/1953/2/07 the complainant stated that two points were of particular concern. The first was that the supplement, although purporting to be a summary of the NICE guidance, was in fact a marketing case for Crestor and argued heavily for lipid goals of 4 and 2mmol/L. Yet nowhere in the supplement was it stated that confirmed national health policy was for targets of 5 and 3mmol/L. The second was that AstraZeneca's own health economic data showed that if lipid goals of 4 and 2mmol/L were aimed for, nearly 40% of patients would require Crestor 40mg/day, a dose which, due to safety concerns, was restricted to specialist use only (Medicines and Healthcare products Regulatory Agency (MHRA) 2004).

The complainant queried if the requirements for specialist care had been factored into the economic analysis, never mind whether patients would actually want to use this therapy option if presented with the balanced data.

The complainant was concerned that distribution of the supplement via The Pharmaceutical Journal, might have lent it an air of credibility it did not deserve.

This complainant subsequently wrote separately to the Authority and noted that despite the title of the supplement 'The new NICE guidance on the use of statins in practice' the NICE technology appraisal it related to barely featured. Instead the supplement presented a health economic argument for using rosuvastatin (Crestor) in preference to atorvastatin (Lipitor) as it would be more cost effective. The case for lipid goals of 4 and 2mmol/L (as opposed to 5 and 3mmol/L) was heavily featured despite this not being discussed at all in the NICE appraisal. No mention was made that confirmed national health policy was for targets of 5 and 3mmol/L, which had been made absolutely clear by the Department of Health just weeks previously.

The complainant stated that in his view the supplement was essentially an advertisement for rosuvastatin, yet it did not contain appropriate prescribing information. Further despite the fact that the health economic case being strongly argued would end up with nearly 40% of the eligible population (or approximately 5% of the entire population) being treated with the 40mg dose, no mention was made of the MHRA warnings about this dose. Indeed, the supplement stated '… whether all currently marketed statins have a very similar low risk of serious adverse events. Based on the data thus far available, the answer is yes'. The complainant found this hard to reconcile with the MHRA advice and was concerned about the implications it could have for safe prescribing practice.

In Case AUTH/1954/2/07 the complainant was, *inter alia*, disappointed to see that the supplement was included with The Pharmaceutical Journal. Whilst industry supported documents were distributed with journals which relied heavily on advertising revenue, they were promotional and should be declared as such.

This complainant subsequently wrote separately to the Authority. The complainant stated that in his view the supplement was promotional and breached the Code in at least two areas:

- **It took the form of a discussion paper but made claims for the superior cost-effectiveness of rosuvastatin/simvastatin combinations compared to atrovastatin/simvastatin combinations. The evidence to support the claim was referenced as 'Data on File'. The insert was clearly promotional material but was not declared as such.**
- **Prescribing information on rosuvastatin was absent.**

In Case AUTH/1955/2/07 the complainant considered that the supplement was disguised promotion for Crestor, but no prescribing information was included.

The Panel noted that it was acceptable for companies to sponsor material. It had previously been decided, in relation to material aimed at health professionals, that the content would be subject to the Code if it was promotional in nature or if the company had used the material for a promotional purpose. Even if neither of these applied, the company would be liable if it had been able to influence the content of the material in a manner favourable to its own interests. It was possible for a company to sponsor material which mentioned its own products and not be liable under the Code for its contents, but only if it had been a strictly arm's length arrangement with no input by the company and no use by the company of the material for promotional purposes.

The supplement in question, sponsored/financially supported by AstraZeneca, had been initiated by the company and its communications agency had contacted the two authors. AstraZeneca was aware of the outline of the supplement and had, on request of one of the authors, provided cost-effectiveness tables for rosuvastatin vs simvastatin as well as data on file. The supplement was reviewed by AstraZeneca to ensure that it was factually correct. The two authors had full editorial control.

The Panel considered that AstraZeneca was inextricably linked to the production of the supplement. There was no arm's length arrangement between the provision of the sponsorship and the generation of the supplement. Given the company's involvement and content, the Panel considered that the supplement was, in effect, promotional material for Crestor. The supplement should have included Crestor prescribing information. Given that allegations were made in that regard in Cases AUTH/1953/2/07 to AUTH/1955/2/07, breaches of the Code were ruled in those cases. The Panel considered that the supplement was disguised promotion; it appeared to be independently written which was not so, the authors had, in effect, been chosen by AstraZeneca. The statement on the front cover 'Supported by AstraZeneca' added to the impression of independence. A breach of the Code was ruled in all five cases.

The Code required that material relating to medicines and their uses, whether promotional in nature or not, which is sponsored by a pharmaceutical company must clearly indicate that it has been sponsored by that company. The Panel concluded that although the phrase 'supported by AstraZeneca' did not give details about the company's role, AstraZeneca's support was clearly stated on the front cover of the supplement. No breach of the Code was ruled in all five cases.

The Panel considered that although the supplement was about the NICE guidance on the use of statins for the prevention of cardiovascular events, the document did not masquerade as NICE guidance as alleged in Case AUTH/1951/3/06. It was clear from the title on the front cover that the supplement discussed the implementation of the guidance. The Panel considered that the supplement was not misleading in that regard and no breach of the Code was ruled.

In its consideration of Cases AUTH/1951/2/07 and AUTH/1952/2/07 the Panel noted that the NICE guidance on statins recognised the body of evidence for reduction in cardiovascular morbidity and overall mortality associated with statin use across a broad spectrum of the population. It did not give targets for cholesterol levels, stating this was outside its remit. With respect to the choice of statin NICE recommended that therapy should usually be initiated with a medicine with a low acquisition cost (taking into account required daily dose and product price per dose). For many patients, the least expensive statin would be simvastatin. The supplement recognised this but put forward arguments for the use of rosuvastatin which was more expensive. By implication, therefore, the supplement advocated the use of rosuvastatin to reduce cardiovascular morbidity. Crestor, however, was not so licensed. Whereas simvastatin (Merck Sharp & Dohme's product, Zocor) was licensed for reduction of cardiovascular mortality and morbidity in certain patients, Crestor was only licensed for primary hypercholesterolaemia or homozygous familial hypercholesterolaemia. There would of course be benefits in lowering cholesterol but there was a difference between promoting a product for a licensed indication and promoting the benefits of treating a condition. The differences between the licensed indications was not made clear. Thus the Panel considered that by implication the supplement was misleading as to the licensed indication of Crestor. A breach of the Code was ruled in Cases AUTH/1951/2/07 and AUTH/1952/2/07.

The Panel noted in Case AUTH/1951/2/07 that it was stated on the supplement that the date of preparation was December 2006. In November 2006, the national director for heart disease and stroke had issued guidance confirming the current national policy on statin prescribing. This stated that national policy currently accepted 5mmol/L for total cholesterol and 3mmol/L for LDL cholesterol as targets for therapy as per the NSF for CHD and that the JBS-2 guidance was not national policy. This guidance had not been included in the supplement. The Panel noted AstraZeneca's submission that the supplement had been developed before the guidance was written. Nonetheless, the date of preparation of the supplement was a month after the November guidance was issued and the supplement was not distributed until 20 January 2007. Given the time frame involved the Panel considered that it was misleading to distribute the supplement which did not refer to important national guidance and was thus not up-to-date. A breach of the Code was ruled in Case AUTH/1951/2/07. A breach of the Code was similarly ruled in Case AUTH/1953/2/07.

With regard to the allegation in Cases AUTH/1951/2/06 and AUTH/1952/2/07 about unachievable JBS targets, the Panel noted that in the discussion on optimizing statin treatment strategies the supplement asked 'Are more challenging targets such as JBS-2, really achievable - and, more importantly, can they be achieved safely?'. In the section discussing the role of the pharmacist, however, readers were urged to 'pick up on those patients not reaching the JBS-2 targets of total cholesterol <4mmol/L and LDL cholesterol <2mmol/L. A referral back to the GP possibly with a recommendation of change in statin dose or drug entity (in accordance with NICE guidelines) might be seen as appropriate'. The supplement thus encouraged pharmacists to follow the JBS-2 guidance which was not national policy. In that regard the Panel considered that the supplement was misleading and a breach of the Code was ruled in Cases AUTH/1951/2/07 and AUTH/1952/2/07.

In Case AUTH/1953/2/07 the Panel noted that a cost-effectiveness model was presented in the supplement which showed the budget impact results for patients failing to reach either a total cholesterol target of <5mmol/L or a total cholesterol target of <4mmol/L. Two tables of data detailed the financial implications of having to use atorvastatin or rosuvastatin as second line therapy to simvastatin (the least expensive statin). Both tables referred to rosuvastatin 40mg ie the maximum daily dose which, according to the Crestor summary of product characteristics (SPC), should be under the supervision of a specialist with patients requiring routine follow-up. Crestor appeared to be unique in this regard as specialist supervision was not required with the maximum daily dose of any of the other statins. This important condition on the use of rosuvastatin was not referred to anywhere in the supplement. The Crestor SPC referred to the increased reporting rate of adverse reactions with the 40mg dose compared to lower doses. The maximum dose of 40mg should only be considered in patients with severe hypercholesterolemia at high cardiovascular risk who did not achieve their treatment goal on 20mg and in whom routine follow up would be performed. In the section on optimizing statin treatment strategies the possibility that rosuvastatin might be related to a higher incidence of side effects than other statins was discussed. This possibility was dismissed and it was stated that 'all currently marketed statins have a similar very low risk of serious adverse events' and that 'rosuvastatin gives rates of adverse events similar to those of other statins'. The Panel considered that the supplement was misleading and did not encourage the rational use of Crestor 40mg. Breaches of the Code were ruled on this point in Case AUTH/1953/2/07.

The Panel further noted in Case AUTH/1953/2/07 that two tables of cost-effectiveness data only accounted for the acquisition costs of the medicine. This was not entirely clear from the headings, 'Budget impact' and 'Treatment Strategy' and associated text which referred to 'cost-effectiveness', 'financial implications' and the need to look at other 'costs' associated with treatment', which implied more than simply acquisition costs. There was no account taken of the cost of specialist supervision and routine patient follow-up associated with the use of rosuvastatin 40mg which would have an impact on budget. The Panel considered that the data was thus misleading. A breach of the Code was ruled.

In Case AUTH/1954/2/07 the Panel noted that the cost-effectiveness data which showed the financial implications of using either atorvastatin or rosuvastatin as second line therapy in patients who had not reached lipid targets with simvastatin, was referenced to AstraZeneca data on file. The Panel considered that it was not necessarily unacceptable to cite data on file in promotional material. The supplement was thus not misleading in that regard. No breach of the Code was ruled.

Overall the Panel considered that AstraZeneca's failure to recognise that the supplement was, in effect, promotional material for Crestor, meant that high standards had not been maintained. A breach of the Code was ruled in all five cases. The Panel was concerned that the supplement, contrary to national guidance had encouraged pharmacists to follow JBS-2 cholesterol targets. The Panel was further very concerned that although the 40mg dose of rosuvastatin had been referred to in the supplement, there was no reference to the specialist supervision and routine patient follow-up needed with such a dose. The Panel considered that the omission of such information might prejudice patient care. The Panel considered that in these two matters, one or both of which had been raised in Cases AUTH/1951/2/07, AUTH/1952/2/07 and AUTH/1953/2/07, the supplement had brought discredit upon and reduced confidence in the pharmaceutical industry. A breach of Clause 2 was ruled in these cases. As these matters were not raised in Cases AUTH/1954/2/07 or AUTH/1955/2/07, no breach of Clause 2 was ruled in these cases on the basis of the allegations made.

Upon appeal, the Appeal Board accepted that the views expressed in the material were those genuinely held by the authors. The Appeal Board, however, was called upon to consider the merits of the piece in the context of AstraZeneca's involvement in the generation and production of it. Independent authors were at liberty to publish their views: however, when a pharmaceutical company became involved in such an activity it potentially became subject to the Code.

The Appeal Board noted that it was acceptable for companies to sponsor material. It had previously been decided, in relation to material aimed at health professionals, that the content would be subject to the Code if it was promotional in nature or if the company had used the material for a promotional purpose. Even if neither of these applied, the company would be liable if it had been able to influence the content of the material in a manner favourable to its own interests. It was possible for a company to sponsor material which mentioned its own products and not be liable under the Code for its contents, but only if it had been a strictly arm's length arrangement with no input by the company and no use by the company of the material for promotional purposes.

The Appeal Board noted the material in question had been sponsored/financially supported by AstraZeneca. AstraZeneca had paid the authors to write it and The Pharmaceutical Journal to distribute it. In that regard the material was a paid for insert from AstraZeneca; not a supplement sponsored by The Pharmaceutical Journal for which the editor would have been responsible. The insert had been initiated by AstraZeneca and its communications agency following an AstraZeneca statin advisory board meeting organised by AstraZeneca attended by the two authors who were subsequently asked to write the insert. AstraZeneca was aware of the outline of the material and had, when asked to do so by one of the authors, provided cost-effectiveness tables for rosuvastatin vs simvastatin as well as data on file. The material was reviewed by AstraZeneca to ensure that it was factually correct. The Appeal Board noted from the AstraZeneca representatives that on review of the insert AstraZeneca had suggested the inclusion of a table of budget impact results for a total cholesterol target of <5mmol/L to balance the <4mmol/L results already included, this was accepted by the authors. The Appeal Board noted that although two authors had full editorial control, AstraZeneca took the final decision about whether to publish or not.

The Appeal Board considered that AstraZeneca was inextricably linked to the production of the insert. There was no arm's length arrangement between the provision of the sponsorship and the generation of the material. Given the company's involvement and content, the Appeal Board considered that the material was, in effect, promotional material for Crestor. The Appeal Board considered that it was disguised promotion in that the material appeared to be independently written which was not so, the two authors had, in effect, been chosen by AstraZeneca. The Appeal Board upheld the Panel's ruling of a breach of the Code in all five cases.

In Cases AUTH/1953/2/07 to AUTH/1955/3/06 the Appeal Board noted its ruling above and as such considered that the material should have included the prescribing information for Crestor which it did not. The Appeal Board upheld the Panel's rulings of a breach of the Code in all three cases. The appeal on this point was unsuccessful.

The Appeal Board noted that the material stated that the NICE guidance on statins recognised the body of evidence for reduction in cardiovascular morbidity and overall mortality associated with statin use across a broad spectrum of the population. It did not give targets for cholesterol levels, stating this was outside its remit. With respect to the choice of statin NICE recommended that therapy should usually be initiated with a medicine with a low acquisition cost (taking into account required daily dose and product price per dose). For many patients, the least expensive statin would be simvastatin. The Appeal Board noted that the material recognised that simvastatin should be used first-line but put forward arguments for the use of rosuvastatin which was more expensive without stating that it was not licensed to reduce cardiovascular mortality and morbidity. The Appeal Board considered that without a statement to the contrary, the material, by implication, advocated the use of rosuvastatin to

reduce cardiovascular morbidity. Simvastatin was licensed for reduction of cardiovascular mortality and morbidity in certain patients. The Appeal Board considered that the material was misleading as to the licensed indication of Crestor. In this regard the Appeal Board upheld the Panel's rulings of breaches of the Code in Cases AUTH/1951/2/07 and AUTH/1952/2/07.

The Appeal Board noted that the material set out the evolving guidance on statin use. It also noted the timeframe regarding the writing, production and publication of the material. The Appeal Board considered that the timings were such that the statement issued by the national director for heart disease and stroke should have been referred to. By not referring to this important national statement the material was misleading and not up-to-date. The Appeal Board upheld the Panel's ruling of a breach of the Code in Cases AUTH/1951/2/07 and AUTH/1953/2/07 in this regard.

With regard to the allegation in Cases AUTH/1951/2/07 and AUTH/1952/2/07 about unachievable JBS targets, the Appeal Board noted that in the discussion on optimizing statin treatment strategies the supplement asked 'Are more challenging targets such as JBS-2, really achievable - and, more importantly, can they be achieved safely?'. In the section discussing the role of the pharmacist, however, readers were urged to 'pick up on those patients not reaching the JBS-2 targets of total cholesterol <4mmol/L and LDL cholesterol <2mmol/L. A referral back to the GP possibly with a recommendation of change in statin dose or drug entity (in accordance with NICE guidelines) might be seen as appropriate'. The Appeal Board noted that not only did the material encourage pharmacists to follow the JBS-2 guidance, which was not national policy, it did not advise them that the JBS-2 targets were for high risk patients. From the statement in the material it appeared that the JBS-2 targets should be the aim for all patients which was not so. The Appeal Board considered that the material was misleading in this regard and upheld the Panel's ruling of a breach of the Code in Cases AUTH/1951/2/07 and AUTH/1952/2/07.

The Appeal Board noted, in Case AUTH/1953/3/06, that a cost-effectiveness model was presented in the insert which showed the budget impact results for patients failing to reach either a total cholesterol target of <5mmol/L or a total cholesterol target of <4mmol/L. Two tables detailed the financial implications of having to use atorvastatin or rosuvastatin as second line therapy to simvastatin (the least expensive statin). Both tables referred to rosuvastatin 40mg ie the maximum daily dose. According to the Crestor SPC, in the light of increased reporting rate of adverse reactions with the 40mg dose compared to lower doses a final titration to the maximum dose of 40mg should only be considered in patients with severe hypercholesterolaemia at high cardiovascular risk (in particular those with familial hypercholesterolaemia) who did not achieve their treatment goal on 20mg and in whom routine follow-up would be preformed. Specialist supervision was recommended when the 40mg dose was initiated. Section 4.4 of the SPC stated that an assessment of renal function should be considered during routine follow-up of patients treated with a dose of 40mg. Crestor appeared to be different as specialist supervision was not required with the maximum daily dose of any of the other statins. This important condition on the use of rosuvastatin was not referred to anywhere in the insert. In the section on optimizing statin treatment strategies the possibility that rosuvastatin might be related to a higher incidence of side effects than other statins was discussed. This possibility was dismissed and it was stated that 'all currently marketed statins have a similar very low risk of serious adverse events' and that 'rosuvastatin gives rates of adverse events similar to those of other statins'. The Appeal Board considered that the material was misleading and did not encourage the rational use of Crestor 40mg. The Appeal Board upheld the Panel's rulings of breaches of the Code in this regard in Case AUTH/1953/2/07.

The Appeal Board further noted that the cost-effectiveness data presented in Tables 3 and 4 only accounted for the acquisition costs of the medicine. This was not entirely clear from the headings, 'Budget impact' and 'Treatment Strategy' and associated text which referred to 'cost-effectiveness', 'financial implications' and the need to look at other 'costs' associated with treatment, which implied more than simply acquisition costs. There was no account taken of the cost of specialist supervision and routine patient follow-up associated with the use of rosuvastatin 40mg which would have an impact on budget. The Appeal Board considered that the data was thus misleading. The Appeal Board upheld the Panel's ruling of a breach of the Code in this regard in Case AUTH/1953/2/07.

Overall, in all five cases, the Appeal Board considered that AstraZeneca's failure to recognise that the material was, in effect, promotional material for Crestor, meant that high standards had not been maintained. The Appeal Board upheld the Panel's ruling of a breach of the Code in all cases.
The Appeal Board was concerned that the material, contrary to national guidance had encouraged pharmacists to follow JBS-2 cholesterol targets.
The Appeal Board was further very concerned that although the 40mg dose of rosuvastatin had been referred to in the insert, there was no reference to the specialist supervision and routine patient follow-up needed with such a dose. The Appeal Board considered that the omission of such information might prejudice patient care. The Appeal Board considered that in these two matters, the material had brought discredit upon and reduced confidence in the pharmaceutical industry. The Appeal Board upheld the Panel's ruling of a breach of Clause 2 in Cases AUTH/1951/2/07 to AUTH/1953/2/07.

Five letters published in The Pharmaceutical Journal, 3 February 2007, criticised a twelve page supplement (ref

P10573) sponsored by AstraZeneca UK Limited. The supplement had been distributed with The Pharmaceutical Journal, 20 January.

The supplement was entitled 'The new NICE [National Institute for Health and Clinical Excellence] guidance on the use of statins in practice - Considerations for implementation' and had been written by a general practitioner and a pharmacist. The supplement detailed the NICE guidance on the use of statins and charted the evolving guidance on statin use from 2000 until 2005. Optimization of statin treatment strategies was discussed as was the cost of implementing the NICE guidance across a primary care trust population. A cost effectiveness model was presented wherein either atorvastatin or rosuvastatin (AstraZeneca's product Crestor) was used when patients had failed to reach cholesterol targets on simvastatin (the medicine with the lowest acquisition cost). Finally the role of the pharmacist in helping to tackle cardiovascular disease was discussed.

The supplement was financially supported by AstraZeneca as acknowledged by the statement 'Supported by AstraZeneca' on the front cover.

In accordance with established procedure, the matters were taken up by the Director as complaints under the Code.

Case AUTH/1951/2/07

COMPLAINT

In a letter from a pharmacist, headed 'Profoundly depressing', the complainant stated that she found the inclusion of the AstraZeneca document masquerading as NICE guidance within The Pharmaceutical Journal profoundly depressing. This was a time when hard working pharmacists and pharmacy technicians were striving to improve the cost-effectiveness and evidence base of statin prescribing through change programmes and advice to patients and prescribers, saving millions of pounds of NHS money to be channelled into other services.

Yet here was the pharmacists' own professional journal distributing a document which advocated JBS (Joint British Societies: British Cardiac Society; British Hypertension Society; Diabetes UK; HEART UK; Primary Care Cardiovascular Society; the Stroke Association) targets which were not national policy and were usually unachievable for the average patient, and the use of a statin [Crestor] for which there was no evidence to demonstrate that it saved lives or reduced cardiovascular events, and which was not even licensed as such.

The NHS statin of first choice for most patients was simvastatin based on a wealth of evidence well known to all who read the detail of the actual NICE guidance, and the targets to reach were those of the National Service Framework for coronary heart disease, affirmed by the cardiovascular disease 'tsar' in December 2006.

When writing to AstraZeneca, the Authority asked it to respond in relation to the requirements of Clauses 2, 7.2, 7.4, 9.1, 9.10 and 10.1 of the Code.

Case AUTH/1952/2/07

COMPLAINT

In a letter headed 'Concerns over "promotional brochure"', the complainant stated that rather than being a useful publication covering the evidence base for the use of statins and practical issues on cost-effective implementation of national guidance, the supplement appeared to be nothing more than a promotional brochure for Crestor.

The complainant stated that the brochure appeared to support the JBS-2 lipid targets of 4 and 2mmol/L. The complainant noted that these targets were not evidence based as recognised by the JBS itself in the statement 'There are no clinical trials which have evaluated the relative and absolute benefits of cholesterol lowering to different total and LDL-cholesterol targets in relation to clinical events' (JBS 2005). The vast majority of statin trials used fixed doses and were not chasing any particular lipid level.

The complainant stated that the Heart Protection Study had provided strong evidence that treating high-risk individuals (coronary heart disease, cardiovascular disease, peripheral arterial disease, diabetics over 40 years of age) with simvastatin 40mg/day for five years significantly reduced their chance of having a serious vascular event, irrespective of their lipid level (MRC/BHF Heart Protection Study 2002). The complainant noted that Crestor did not have this sort of patient-oriented evidence to support its use. It was patient-oriented evidence that mattered.

The complainant noted that the NICE guidance referred to in the supplement deemed it cost effective to extend access to statins on the NHS. Its cost-effectiveness analysis assumed that half of the prescriptions for statins would be simvastatin 20mg/day and half simvastatin 40mg/day. Arguably, more expensive statins would not be cost-effective and would waste scarce resources.

The complainant submitted that a policy of simvastatin 40mg/day for all those at high risk, irrespective of lipid level, was simple to implement, evidence based and cost effective.

The complainant stated that the bottom line was find the high risk patients, offer them simvastatin 40mg/day, strongly encourage them to take it, and do not worry too much about non-evidence based targets.

When writing to AstraZeneca, the Authority asked it to respond in relation to the requirements of Clauses 2, 7.2, 7.4, 9.1, 9.10 and 10.1.

Case AUTH/1953/2/07

COMPLAINT

In a letter headed 'Perturbed by Journal's distribution of AstraZeneca document', the complainant referred to elements of the supplement which he considered could be tackled at length, but stated that two points were of particular concern.

The first was that the supplement, although purporting to be a summary of the NICE guidance, was in fact a marketing case for Crestor and argued heavily for lipid goals of 4 and 2mmol/L. Yet nowhere in the supplement was it stated that confirmed national health policy was for targets of 5 and 3mmol/L, in simple terms (Boyle 2006). In this way the supplement undermined the NHS approach to managing this important risk factor.

The second concern was that AstraZeneca's own health economic data showed that if lipid goals of 4 and 2mmol/L were aimed for, nearly 40% of patients would require Crestor 40mg/day, a dose restricted to specialist use only due to safety concerns (Medicines and Healthcare products Regulatory Agency (MHRA) 2004).

The complainant queried if the requirements for specialist care had been factored into the economic analysis, never mind whether patients would actually want to use this therapy option if presented with the balanced data.

The complainant was concerned that distribution of the supplement via The Pharmaceutical Journal might have lent it an air of credibility it did not deserve.

Following publication of his letter in The Pharmaceutical Journal, the complainant wrote separately to the Authority. The complainant noted that despite the title of the supplement 'The new NICE guidance on the use of statins in practice' the NICE technology appraisal it related to barely featured. Instead the supplement presented a health economic argument for using rosuvastatin (Crestor) in preference to atorvastatin (Lipitor) as it would be more cost effective. The case for lipid goals of 4 and 2mmol/L (as opposed to 5 and 3mmol/L) was heavily featured despite this not being discussed at all in the NICE appraisal. No mention was made that confirmed national health policy was for targets of 5 and 3mmol/L, which had been made absolutely clear by the Department of Health just weeks previously.

The complainant stated that in his view the supplement was essentially a detailed advertisement for rosuvastatin, yet it did not contain appropriate prescribing information. Further despite the fact that the health economic case being strongly argued would end up with nearly 40% of the eligible population (or approximately 5% of the entire population) being treated with the 40mg dose, no mention was made of the MHRA warnings about this dose. Indeed, the supplement stated '… whether all currently marketed statins have a very similar low risk of serious adverse events. Based on the data thus far available, the answer is yes'. The complainant found this hard to reconcile with the MHRA advice and was concerned about the implications it could have for safe prescribing practice.

When writing to AstraZeneca, the Authority asked it to respond to the matters raised in the published letter in relation to Clauses 2, 7.2, 7.4, 9.1, 9.10 and 10.. When writing to the company about the complainant's additional comments, the Authority asked it to respond in relation to Clauses 4.1, 7.2, 7.4 and 7.10.

Case AUTH/1954/2/07

COMPLAINT

In a letter headed 'Disappointed', the complainant was, inter alia, disappointed to see that the pharmaceutical industry-supported supplement was included with The Pharmaceutical Journal. Whilst such documents were encountered not infrequently with journals which relied heavily on advertising revenue, such advertorials were entirely promotional and should be declared as such. Should readers contest the validity of the supplement's conclusions, as the complainant thought they should, would The Pharmaceutical Journal take editorial responsibility for its content?

Following publication of his letter in The Pharmaceutical Journal, this complainant wrote separately to the Authority. The complainant stated that in his view the supplement was promotional and breached the Code in at least two areas:

- It took the form of a discussion paper but made claims for the superior cost-effectiveness of rosuvastatin/simvastatin combinations compared to atrovastatin/simvastatin combinations. The evidence to support the claim was referenced as 'Data on File'. The insert was clearly promotional material but was not declared as such.
- Prescribing information on rosuvastatin was absent.

When writing to AstraZeneca, the Authority asked it to respond to the matters raised in the published letter in relation to Clauses 2, 9.1, 9.10 and 10.1. When writing to the company about the complainant's additional comments, the Authority asked it to respond in relation to Clauses 4.1, 7.2 and 7.4.

Case AUTH/1955/2/07

COMPLAINT

In a letter headed 'Where is the guidance for advertisers?', the complainant stated that she was a strong advocate of evidence-based medicine and had a strong sense of professional integrity. However, she was disappointed by the standards set by The Pharmaceutical Journal when it distributed the supplement in question.

The complainant considered that the supplement was disguised promotion for Crestor, but no prescribing

information was included as required. The complainant queried how the professional journal for pharmacy allowed this sort of material to be sent out and compared the extensive advice to advertisers issued by the BMJ with the little or no guidance offered by The Pharmaceutical Journal. The complainant, inter alia, asked when would The Pharmaceutical Journal require authors and contributors to declare competing interests? And how did the journal ensure fair and independent reporting on conferences when authors had been funded to attend by a pharmaceutical company.

When writing to AstraZeneca, the Authority asked it to respond in relation to Clauses 2, 4.1, 9.1, 9.10 and 10.1.

Cases AUTH/1951/2/07 to AUTH/1955/07

RESPONSE

AstraZeneca explained that the supplement was developed in 2006. AstraZeneca was told that the supplement would be published in January 2007 but this information was sent to an employee who was off at the time, therefore the company only knew that the supplement had been distributed when it was raised in discussion between a pharmacist and a member of the medical team. As well as the letters published in The Pharmaceutical Journal the editorial board responded in a leading article entitled, 'We call this free speech' which clearly presented its views on the nature and purpose of the article.

In addition, the authors' responses to the readers' comments were published in The Pharmaceutical Journal, 10 February. The journal had not invited AstraZeneca to comment.

During its regular discussions with health professionals, AstraZeneca became aware that they were unclear as to how the recommendations published in the NICE Statin Technology Appraisal in early 2006 should be implemented, taking into consideration seemingly conflicting advice from different sets of guidelines.

The initiation of the supplement arose out of awareness of this issue. AstraZeneca's agency asked if The Pharmaceutical Journal would be interested in such an educational discussion article and when the journal confirmed that it was, the agency contacted two of the health professionals who had previously identified the issue and were interested to co-develop an outline for the article. AstraZeneca was aware of the outline and the health professionals' input to this. These health professionals were well-respected, independent medical authors who frequently contributed articles to the medical press. The two authors wrote the article themselves and had full editorial control. One of the authors requested the cost-effectiveness tables and information from AstraZeneca's data on file and the content was reviewed by her. As required by the Code, AstraZeneca reviewed the document to ensure that it was factually correct and did not contravene the Code or the relevant statutory requirements. Other than this, the authors had full editorial control of the supplement and the views expressed therein. Prior to publication, The Pharmaceutical Journal editorial team reviewed the supplement to ensure it met editorial standards. The supplement had not been distributed by other means.

AstraZeneca noted that in Case AUTH/1951/2/07, the complainant had alleged that the supplement was 'masquerading' as NICE guidance. AstraZeneca noted that the supplement did not present itself as an official NICE document. No Department of Health (DoH), or NICE logos appeared anywhere on the article. The appropriate declaration of sponsorship from AstraZeneca, as required by the Code, was on the front cover. AstraZeneca considered that the title of the document, 'The new NICE guidance on the use of statins in practice - Considerations for implementation', made it clear that this was a review of issues and considerations surrounding the NICE guidance rather than any official document from the institute itself. AstraZeneca therefore denied a breach of Clause 10.1.

In relation to Case AUTH/1951/2/07 with regard to the JBS targets, AstraZeneca submitted that the authors had presented the NICE recommendation in the context of all the available guidelines, as well as indicating how guidelines' target recommendations had changed over time. Indeed in relation to the second edition of the JBS guidelines (JBS-2) the authors wrote, 'Are more challenging targets, such as JBS-2, really achievable - and, more importantly, can they be achieved safely?'. The targets available from all existing guidelines were included in a balanced way and represented in a factually accurate manner.

AstraZeneca noted that in Case AUTH/1951/2/07, the complainant had stated that the supplement advocated 'use of a statin for which there was no evidence to demonstrate that it saved lives or reduced cardiovascular events and which was not even licensed as such'. There was, however, no such statement within the supplement either in reference to rosuvastatin or atorvastatin. Where the authors had referred to use of either atorvastatin or rosuvastatin as a second choice statin, this was clearly set in the context of lowering total cholesterol and therefore was consistent with the licensed indication of both medicines. AstraZeneca thus denied breaches of Clauses 7.2 and 7.4.

With regard to the allegation in Case AUTH/1951/2/07 that the supplement ignored affirmation of national policy target made by the cardiovascular disease tsar, AstraZeneca submitted that the affirmation of the targets distributed by Professor Boyle in a DoH circular were not included by the authors as it had not been issued when this section was written. AstraZeneca referred to the authors' own responses on this issue. The company did not accept a breach of Clause 7.2.

With regard to the inference in Case AUTH/1951/2/07 that the supplement was not independent, AstraZeneca noted its involvement in the content and review of the

supplement as explained above. One of the authors had expressed her personal view with regard to this allegation in her own response.

AstraZeneca disagreed with the complainant's view in Case AUTH/1952/2/07 that the supplement was 'nothing more than a promotional brochure – it was neither intended to be or could be considered promotional. There was no intention to use the supplement promotionally; it was a valid educational discussion about the implementation of NICE guidance in relation to statins. The agency, having sought prior confirmation that this would be an interesting and valid education topic for readers of The Pharmaceutical Journal, commissioned two writers to write the article; both were independent of AstraZeneca. AstraZeneca sponsored the supplement, was aware of the proposed outline of the article and had reviewed the item in accordance with the Code to check that the content was not promotional and that the information contained therein was accurate and balanced. On this basis it was not appropriate to include prescribing information in the article.

AstraZeneca noted that a sponsorship statement appeared on the front cover. The company therefore denied a breach of Clause 10.1 in Case AUTH/1952/2/07.

With regard to the complainant's comments in Case AUTH/1952/2/07 about the JBS-2 lipid targets, AstraZeneca submitted that the targets were presented within the article, as well as all the other existing guidelines and evolution of lipid targets in a chronological order. No undue emphasis was placed on advocating the JBS-2 targets. Indeed if the authors had not included the JBS-2 targets then the information presented would not be up-to-date. The JBS guidelines were the most up to date robust clinical guidelines available in the UK. AstraZeneca thus denied breaches of Clauses 7.2 and 7.4.

In its response to Cases AUTH/1953/2/07 and AUTH/1954/2/07 AstraZeneca denied that the content of the supplement was promotional. It was a valid educational discussion about the implementation of NICE guidance in relation to statins. The agency engaged by AstraZeneca, having sought prior confirmation that this would be an interesting and valid educational topic for readers of The Pharmaceutical Journal, commissioned two writers to write the article; both were independent of AstraZeneca. AstraZeneca sponsored the supplement, was aware of the proposed outline of the article and had reviewed the item in accordance with the Code to check that the content was not promotional and the information contained therein was accurate and balanced. The review process confirmed that this was the case and on this basis it was not appropriate to include prescribing information in the article. The AstraZeneca sponsorship statement appeared on the front cover. The company did not accept that there had been a breach of Clause 4.1 or 10.1.

AstraZeneca noted the complainant's concern in Case AUTH/1953/2/07 that there was no mention that health policy was for targets of 5 and 3mmol/L. The title of the supplement clearly sets itself out as a 'considerations' article and therefore mentioned all the relevant existing guidelines and their targets which prescribing health professionals were aware of when making decisions for individual patients. The National Service Framework (NSF) for coronary heart disease, to which the complainant referred, and the General Medical Services contract targets which followed the NSF, were mentioned within the supplement on 7 out of the 9 pages. AstraZeneca knew that re-affirmation of the targets was made in a DoH circular, however as one of the authors indicated in her response, that circular had not been issued at the time she wrote this section. AstraZeneca therefore did not accept a breach of Clause 7.2 or 7.4.

AstraZeneca noted the complainant's concern in Case AUTH/1953/2/07 that the health economic arguments put forward would result in nearly 40% of the eligible population being on rosuvastatin 40mg. AstraZeneca submitted that the health economic page within the supplement contained two budget impact models depending on whether 5 or 4mmol/L was the total cholesterol target aimed for. The complainant had referred only to data presented in Table 4 of the model and not the other table, Table 3, which showed in a balanced way, the model for total cholesterol target of 5mmol/L. The information used by the authors was presented in a balanced and factual way and gave no recommendation or direction to use one treatment strategy over another. In relation to the specific details of the modelling, the cost-effectiveness was based on drug acquisition cost and did not include hospital cost for either the rosuvastatin or atorvastatin options. AstraZeneca denied a breach of Clause 7.10.

In its response to Cases AUTH/1953/3/06 and AUTH/1955/2/07, prescribing information was not included in the supplement as it was a review article written by two independent health professionals, not a promotional item written by AstraZeneca. The information contained within was the opinion of the independent authors and any information relating to rosuvastatin was presented in a balanced, factual and accurate manner taken from peer reviewed publications or publicly available documents (with the exception of the cost-effectiveness data which was supplied by AstraZeneca on request). There were no claims within the supplement that promoted the prescription, supply, sale or administration of rosuvastatin. As indicated in the editorial, 'We call this free speech' The Pharmaceutical Journal also did not consider it to be promotional in nature. AstraZeneca denied a breach of Clause 4.1.

With regard to the complainant's concern in Case AUTH/1953/2/07 that there had been a failure to mention MHRA warnings about the Crestor 40mg dose, AstraZeneca submitted that the supplement was a valid educational discussion item, written independently and over which the authors had full editorial control. AstraZeneca would have expected a balanced comment on safety of statins to be present in the article. Since the authors did not single out the 40mg dose, or any dose of any of the branded statins

for special mention, they did not add any dose specific warnings. AstraZeneca fulfilled its obligation to ensure that the supplement was non-promotional, balanced and accurate in accordance with the Code. The company denied a breach of Clause 4.1.

In its response to Case AUTH/1954/2/07 AstraZeneca submitted that industry support for an independently written article was a legitimate means of providing education and debate for health professionals. The company considered that the supplement provided valid educational content and topical discussion and was produced in accordance with the spirit and letter of the Code. The Pharmaceutical Journal editorial board had separately presented its views on the validity of the distribution and content of the article. The company denied a breach of Clause 10.1.

AstraZeneca stated that the supplement presented itself as a 'considerations' article and did not provide conclusions to direct the reader towards any prescribing recommendations. As indicated within the editorial response, 'We call this free speech' the readers were of course free to debate the validity of the points raised by the authors within the article and to come to their own conclusions, as they would of any article. The complainant in Case AUTH/1954/2/07 had not specifically raised any concerns relating to the validity of the supplement's content, but appeared to question the independence of the authors. AstraZeneca noted that its involvement in the development of the supplement had been explained above. The authors had publicly stated that the content and opinions expressed in the supplement were independent of AstraZeneca. AstraZeneca noted that none of the readers had contested the validity of the summary points presented in the article. The company denied a breach of Clause 7.2.

AstraZeneca reiterated that the cost-effectiveness data was requested for insertion by one of the authors. This data came from an unpublished cost-effectiveness model created by AstraZeneca and so it was correctly referenced as 'AZ Data on File'. Should the complainant in Case AUTH/1954/2/07, or other readers, wish to review this data they could request it from the medical information department. AstraZeneca denied a breach of Clause 7.4.

In response to Case AUTH/1955/2/07 AstraZeneca denied that the supplement was disguised promotion for Crestor as alleged. The title clearly set out the purpose and content of the document. This was an independently written article. AstraZeneca supported the article financially; however, the authors retained full editorial control. AstraZeneca did not accept that there had been a breach of Clause 10.1.

In its response to all five cases AstraZeneca submitted that industry support for an independently written article was a legitimate means of providing education and debate for health professionals. The company considered that the supplement provided valid educational content and topical discussion and had been produced in accordance with the spirit and letter of the Code. AstraZeneca aimed to maintain high standards in all aspects of its internal review process as well as wishing to be considered a respected source of information and education to health professionals. Whilst it was unfortunate that this article prompted the five letters from Pharmaceutical Journal readers, the company considered that this reflected the validity of this topical subject on statins and noted with interest that following publication of the authors' replies, in which they clarified their independence, no further comments had been published. AstraZeneca submitted that these reasons, in addition to the points made in response to the specific complaints, it did not accept that there had been any breaches of Clauses 2, 9.1 or 9.10.

PANEL RULING

The Panel noted that it was acceptable for companies to sponsor material. It had previously been decided, in relation to material aimed at health professionals, that the content would be subject to the Code if it was promotional in nature or if the company had used the material for a promotional purpose. Even if neither of these applied, the company would be liable if it had been able to influence the content of the material in a manner favourable to its own interests. It was possible for a company to sponsor material which mentioned its own products and not be liable under the Code for its contents, but only if it had been a strictly arm's length arrangement with no input by the company and no use by the company of the material for promotional purposes.

The supplement in question had been sponsored/financially supported by AstraZeneca. The supplement had been initiated by the company and its communications agency had contacted the two authors. AstraZeneca was aware of the outline of the supplement and had, when asked to do so by one of the authors, provided cost-effectiveness tables for rosuvastatin vs simvastatin as well as data on file. The supplement was reviewed by AstraZeneca to ensure that it was factually correct. The two authors had full editorial control.

The Panel considered that AstraZeneca was inextricably linked to the production of the supplement. There was no arm's length arrangement between the provision of the sponsorship and the generation of the supplement. Given the company's involvement and content, the Panel considered that the supplement was, in effect, promotional material for AstraZeneca's product Crestor. The supplement should have included the prescribing information for Crestor which it did not. Given that allegations were made in that regard in Cases AUTH/1953/2/07, AUTH/1954/2/07 and AUTH/1955/2/07, breaches of Clause 4.1 of the Code were ruled in those cases. The Panel considered that it was disguised promotion in that the supplement appeared to be independently written which was not so, the two authors had, in effect, been chosen by AstraZeneca. The statement on the front cover 'Supported by AstraZeneca' added to the impression of independence. A breach of Clause 10.1 was ruled in all five cases.

Clause 9.10 of the Code required that material relating to medicines and their uses, whether promotional in nature or not, which is sponsored by a pharmaceutical company must clearly indicate that it has been sponsored by that company. The Panel concluded that although the phrase 'supported by AstraZeneca' did not give details about the company's role, AstraZeneca's support was clearly stated on the front cover of the supplement. No breach of Clause 9.10 was ruled in all five cases.

The Panel considered that although the supplement was about the NICE guidance on the use of statins for the prevention of cardiovascular events, the document did not masquerade as NICE guidance as alleged in Case AUTH/1951/3/06. It was clear from the title on the front cover that the supplement discussed the implementation of the guidance. The Panel considered that the supplement was not misleading in that regard and no breach of Clause 7.2 was ruled.

In its consideration of Cases AUTH/1951/2/07 and AUTH/1952/2/07 the Panel noted that the NICE guidance on statins recognised the body of evidence for reduction in cardiovascular morbidity and overall mortality associated with statin use across a broad spectrum of the population. It did not give targets for cholesterol levels, stating this was outside its remit. With respect to the choice of statin NICE recommended that therapy should usually be initiated with a medicine with a low acquisition cost (taking into account required daily dose and product price per dose). For many patients, the least expensive statin would be simvastatin. The supplement recognised this but put forward arguments for the use of rosuvastatin which was more expensive. By implication, therefore, the supplement was advocating the use of rosuvastatin to reduce cardiovascular morbidity. Crestor, however, was not so licensed. Whereas simvastatin (Merck Sharp & Dohme's product, Zocor) was licensed for reduction of cardiovascular mortality and morbidity in patients with manifest atherosclerotic cardiovascular disease or diabetes mellitus, with either normal or increased cholesterol levels, as an adjunct to correction of other risk factors and other cardioprotective therapy, Crestor was only licensed for primary hypercholesterolaemia or homozygous familial hypercholesterolaemia. There would of course be benefits in lowering cholesterol but there was a difference between promoting a product for a licensed indication and promoting the benefits of treating a condition. The differences between the licensed indications was not made clear. Thus the Panel considered that by implication the supplement was misleading as to the licensed indication of Crestor. Breaches of Clauses 7.2 and 7.4 were ruled in Cases AUTH/1951/2/07 and AUTH/1952/2/07.

The Panel noted in Case AUTH/1951/2/07 that it was stated on the supplement that the date of preparation was December 2006. In November 2006, the national director for heart disease and stroke had issued guidance confirming the current national policy on statin prescribing. This stated that national policy currently accepted 5mmol/L for total cholesterol and 3mmol/L for LDL cholesterol as targets for therapy as per the NSF for CHD and that the JBS-2 guidance was not national policy. This guidance had not been included in the supplement. The Panel noted AstraZeneca's submission that the supplement had been developed before the guidance was written. Nonetheless, the date of preparation of the supplement was a month after the November guidance was issued and the supplement was not distributed until 20 January 2007. Given the time frame involved the Panel considered that it was misleading to distribute the supplement which did not refer to important national guidance and was thus not up-to-date. A breach of Clause 7.2 was ruled in Case AUTH/1951/2/07. A similar breach was ruled in Case AUTH/1953/2/07 where the Panel also noted a section of the supplement which discussed the role of the pharmacist, urging readers 'to pick up on those patients not reaching the JBS-2 targets of total cholesterol <4mmol/L and LDL cholesterol <2mmol/L'.

With regard to the allegation in Cases AUTH/1951/2/06 and AUTH/1952/2/07 about unachievable JBS targets, the Panel noted that in the discussion on optimizing statin treatment strategies the supplement asked 'Are more challenging targets such as JBS-2, really achievable - and, more importantly, can they be achieved safely?'. In the section discussing the role of the pharmacist, however, readers were urged to 'pick up on those patients not reaching the JBS-2 targets of total cholesterol <4mmol/L and LDL cholesterol <2mmol/L. A referral back to the GP possibly with a recommendation of change in statin dose or drug entity (in accordance with NICE guidelines) might be seen as appropriate'. The supplement thus encouraged pharmacists to follow the JBS-2 guidance which was not national policy. In that regard the Panel considered that the supplement was misleading and a breach of Clause 7.2 was ruled in Cases AUTH/1951/2/07 and AUTH/1952/2/07.

In Case AUTH/1953/2/07 the Panel noted that a cost-effectiveness model was presented in the supplement which showed the budget impact results for patients failing to reach either a total cholesterol target of <5mmol/L or a total cholesterol target of <4mmol/L. Two tables of data detailed the financial implications of having to use atorvastatin or rosuvastatin as second line therapy to simvastatin (the least expensive statin). Both tables referred to rosuvastatin 40mg ie the maximum daily dose which, according to the Crestor summary of product characteristics (SPC), should be under the supervision of a specialist with patients requiring routine follow-up. Crestor appeared to be unique in this regard as specialist supervision was not required with the maximum daily dose of any of the other statins (atorvastatin, fluvastatin, pravastatin and simvastatin). This important condition on the use of rosuvastatin was not referred to anywhere in the supplement. The Crestor SPC referred to the increased reporting rate of adverse reactions with the 40mg dose compared to lower doses. The maximum dose of 40mg should only be considered in patients with severe hypercholesterolemia at high cardiovascular risk who did not achieve their treatment goal on 20mg and in whom routine follow up would be performed. In the section on optimizing statin treatment strategies the possibility that rosuvastatin might be related to a higher incidence of side effects than other

statins was discussed. This possibility was dismissed and it was stated that 'all currently marketed statins have a similar very low risk of serious adverse events' and that 'rosuvastatin gives rates of adverse events similar to those of other statins'. The Panel considered that the supplement was misleading and did not encourage the rational use of Crestor 40mg. Breaches of Clauses 7.2 and 7.10 were ruled on this point in Case AUTH/1953/2/07.

The Panel further noted in Case AUTH/1953/2/07 that the cost-effectiveness data presented in Tables 3 and 4 only accounted for the acquisition costs of the medicine. This was not entirely clear given the tables were headed 'Budget impact' and 'Treatment Strategy' and the use of terms like 'cost-effectiveness', 'financial implications' and the need to look at other 'costs' associated with treatment', which implied more than simply acquisition costs. There was no account taken of the cost of specialist supervision and routine patient follow-up associated with the use of rosuvastatin 40mg which would have an impact on budget. The Panel considered that the data was thus misleading. A breach of Clause 7.2 was ruled.

In Case AUTH/1954/2/07 the Panel noted that the cost-effectiveness data which showed the financial implications of using either atorvastatin or rosuvastatin as second line therapy in patients who had not reached lipid targets with simvastatin, was referenced to AstraZeneca data on file. The Panel considered that it was not necessarily unacceptable to cite data on file in promotional material. The supplement was thus not misleading in that regard. No breach of Clause 7.2 was ruled.

Overall the Panel considered that AstraZeneca's failure to recognise that the supplement was, in effect, promotional material for Crestor, meant that high standards had not been maintained. A breach of Clause 9.1 was ruled in all five cases. The Panel was concerned that the supplement, contrary to national guidance had encouraged pharmacists to follow JBS-2 cholesterol targets. The Panel was further very concerned that although the 40mg dose of rosuvastatin had been referred to in the supplement, there was no reference to the specialist supervision and routine patient follow-up needed with such a dose. The Panel considered that the omission of such information might prejudice patient care. The Panel considered that in these two matters, one or both of which had been raised in Cases AUTH/1951/2/07, AUTH/1952/2/07 and AUTH/1953/2/07, the supplement had brought discredit upon and reduced confidence in the pharmaceutical industry. A breach of Clause 2 was ruled in these cases. As these matters were not raised in Cases AUTH/1954/2/07 or AUTH/1955/2/07 no breach of Clause 2 was ruled in these cases on the basis of the allegations made.

APPEAL BY ASTRAZENECA

AstraZeneca appealed against all of the Panel's rulings of breaches of the Code.

The company again explained, as in its response above, the reasons for the supplement and again gave details as to how it was produced and the company's relationship with the authors.

With regard to the ruling of a breach of Clause 10.1 of the Code AstraZeneca noted that the Panel had stated:

> '… AstraZeneca was inextricably linked to the production of the supplement. There was no arm's length arrangement between the provision of the sponsorship and the generation of the supplement. … that it was disguised promotion in that the supplement appeared to be independently written which was not so, the two authors had, in effect, been chosen by AstraZeneca'.

AstraZeneca did not deny a link with the authors, its communications agency contacted them following their discussion with The Pharmaceutical Journal, AstraZeneca sponsored the article and supplied the authors with data on request.

AstraZeneca submitted that it did not per se choose the authors, but acknowledged that this was done by the communications agency acting on its behalf. Although AstraZeneca agreed with the Panel that this meant that 'the two authors had, in effect, been chosen by AstraZeneca' it disagreed strongly with its unequivocally-stated conclusion that this meant 'that it appeared to be independently written which was not so' and that the item was disguised promotion.

AstraZeneca submitted that direct or indirect involvement in the choice of author for items such as company-sponsored journal supplements or inserts was an unavoidable part of the company's role in such projects. Journals and professional societies frequently collaborated with the pharmaceutical industry to produce educational information relevant for their audiences. The expert knowledge that existed within a company in relation to appropriately qualified external experts was commonly utilised.

AstraZeneca submitted that it would be an extreme position to make involvement in the choice of author for company-sponsored educational material a criterion for judging that material to be promotional. There would be very little sponsored educational material left that was not promotional.

AstraZeneca submitted that with respect to the Code, it was considered appropriate for companies to identify external expert presenters for educational meetings that they sponsored. In such situations they were expected to be aware of the presenter's views and might be involved in briefing and approving their materials, both without being subject to automatic allegations that the meeting was promotional. Why should educational supplements be treated any differently from these educational meetings? Elsewhere in the Panel's ruling it had stated it had been established that:

- '… it was acceptable for companies to sponsor material'.
- '… the content would be subject to the Code if it was promotional in nature or if the company had used the material for a promotional purpose'.

- '… if neither of these applied, the company would be liable if it had been able to influence the content of the material …'
- 'It was possible for a company to sponsor material which mentioned its own products and not be liable under the Code for its contents, but only if it had been strictly arm's length arrangement with no input by the company and no use by the company of the material for promotional purposes.'
- '… the supplement was, in effect, promotional material…'.

AstraZeneca submitted that it was fully aware of the application of the Code in relation to sponsored publications. AstraZeneca endorsed the selection of the two authors as it knew them to be independent, highly-principled medical writers. AstraZeneca made no attempt to abuse its position as sponsors by bringing any influence to bear on the way the article was written. The authors retained full editorial control throughout, including development of the outline. AstraZeneca's involvement was to exercise due diligence in ensuring that the materials could not be considered promotional.

AstraZeneca referred to Case AUTH/1644/10/04 and submitted that it had acted in a way entirely compliant with the Code as written and interpreted by this precedent.

AstraZeneca therefore submitted that its arrangements constituted an 'arm's length arrangement' by any definition.

AstraZeneca submitted that one of the authors in her response to allegations by correspondents in The Pharmaceutical Journal that she was 'motivated by undue influence from the pharmaceutical industry' responded: 'Your readers… imply that my failure to work to national guidelines which I consider… to be contrary to the best interests of patients must be motivated by undue influence from the pharmaceutical industry. I find such accusations offensive in the extreme'.

AstraZeneca submitted that the other author had also refuted allegations that the supplement was not the work of the authors. As well as having responded publicly to the readers' letters he had written to AstraZeneca, stating 'I would like to make it absolutely clear that the words within the supplement were my own based entirely on my own opinion and experience. I am not in the habit of putting my name to the words of others and I take exception to anyone suggesting that this could be otherwise'.

On the basis of the above, AstraZeneca submitted that it was clear that the authors were concerned by the seriousness of the Panel's allegations that the company might have exerted undue influence over them considering that they had previously and publicly confirmed their independence.

AstraZeneca submitted that the editor of The Pharmaceutical Journal, in a leading article entitled 'We call this free speech' in response to the previous week's correspondence, also supported the claim that the article was independent and not promotional, saying that, in their opinion, it 'was neither an advertisement nor an advertorial… As far as the Journal is concerned it was a discussion document written by two health professionals… inviting readers to consider how [NICE] guidance might be implemented'.

The Panel also stated that it considered that the statement on the front cover 'Supported by AstraZeneca' added to the impression of independence. AstraZeneca assumed that the Panel had no issue with the use of 'supported' as a synonym for 'sponsored', there was nothing in its ruling to suggest that there were any issues around this aspect of the item. However AstraZeneca was slightly confused by this point. The Code was straightforward in its advice in relation to sponsored material and the need to make that sponsorship clear at the outset. AstraZeneca had complied with the Code in this regard as the item was not promotional in nature.

As far as any activities beyond the inclusion of the supplement within The Pharmaceutical Journal, it had not and never had the intention to use this supplement in a promotional context.

AstraZeneca noted that the complainant in Case AUTH/1951/2/07 had made other allegations that could be considered as potential breaches of Clause 10.1. The Panel had chosen not to pursue these. On all the points made by the complainant and the Panel AstraZeneca denied a breach of Clause 10.1 of the Code.

AstraZeneca noted that in Cases AUTH/1953/2/07, AUTH/1954/2/07 and AUTH/1955/2/07 because the Panel had ruled the item at issue to be promotional it should have included prescribing information. AstraZeneca denied the item was promotional and hence not in breach of Clause 4.1.

AstraZeneca noted that Clauses 7.2 and 7.4 applied to promotional material. For the reasons already provided this item was not promotional, rather it was a sponsored journal supplement written by independent authors with no editorial input from AstraZeneca.

However, AstraZeneca submitted that the allegations that the item in question promoted Crestor in a manner that was not accurate, balanced, fair, objective, unambiguous and capable of substantiation were unfounded.

AstraZeneca noted as described previously this item, a Pharmaceutical Journal supplement entitled 'The new NICE guidance on the use of statins in practice – Considerations for implementation' covered several topics.

Firstly there was section headed 'The NICE guidance recommendations' covering relevant aspects of Technology Appraisal 94. This provided an outline of the main points from the document, referred to NICE's methodology for assessing risk reduction and introduced NICE's conclusion: LDL cholesterol

reduction resulted in a predictable relative risk reduction for cardiovascular mortality.

This was followed by another section, 'The UK cholesterol story' that summarised the evolution of the various lipid targets affecting UK clinical practice up to and including the 2006 JBS-2.

The next section concerned treatment strategies for achieving targets headed 'Reaching targets by optimising statin treatment strategies'. This unequivocally supported the NICE guidance by endorsing the use of simvastatin first-line in the treatment of dyslipidaemia. AstraZeneca noted that all the descriptions of the relative efficacy of statins in this section referred to their effect on LDL-C.

The next two sections, 'Calculating the cost of implementing NICE guidance across a primary care trust population' and 'Modelling the cost for a local health economy' provided estimates of the cost-effectiveness of the various treatment options for individual patients (as cost per % LDL-C or total cholesterol reduction) and for primary care organisations using the two available first- and second-line strategies (as budget impacts for total cholesterol targets of <5 and <4mmol/L).

The final section, 'Meeting the patient need – the role of the pharmacist' described some of the issues in the management of dyslipidaemia that might affect pharmacists seeing patients with this condition.

AstraZeneca submitted that the standard procedure in the clinical management of dyslipidaemia was in line with NICE guidance which stated 'it is recommended that therapy should usually be initiated with a drug with a low acquisition cost'. Usually this first-line therapy was generic simvastatin. If the patient failed to reach target on this option then they were normally switched to a second-line, more potent statin, usually rosuvastatin or atorvastatin (Lipitor, Pfizer). This treatment algorithm was widely recognised, had been endorsed informally by the DoH and represented, in most people's opinion, a realistic treatment protocol in line with NICE guidance.

AstraZeneca submitted that although the authors suggested that there might be justification for considering the use of a more potent statin first-line in a minority of patients with very severe dyslipidaemia, at no time in the supplement did they question the validity of alternative strategies. In this respect, it was fair to note firstly that NICE recommended that 'Therapy should usually be initiated with a drug with a low acquisition cost'. Secondly, that all the cost-benefit tables used simvastatin first-line before introduction of a more potent treatment option.

AstraZeneca noted that the Panel stated that it considered that:

> '… NICE recommended that therapy should usually be initiated with a medicine with low acquisition cost… For many patients, the least expensive statin would be simvastatin. The supplement recognised this but put forward arguments for the use of rosuvastatin, which was more expensive. By implication, therefore, the supplement was advocating the use of rosuvastatin to reduce cardiovascular morbidity…. Crestor was only licensed for primary hypercholesterolaemia …. There would of course be benefits in lowering cholesterol but there was a difference between promoting a product for a licensed indication and promoting the benefits of treating the condition. The differences between the licensed indications was not made clear.'

AstraZeneca submitted that the use of rosuvastatin as a more expensive replacement for simvastatin was only mentioned in the article in the context of it usually being an alternative treatment where patients had failed to reach target on first-line simvastatin. The text and figures on pages 6 to 8 of the supplement made this abundantly clear.

In relation to the Panel's concerns that there was an implied outcome benefit, AstraZeneca pointed out that NICE had accepted the relationship of cholesterol lowering and outcomes and included rosuvastatin in its guidance and analysis. NICE did not discriminate against it based on the fact that outcome data was still awaited. Therefore it was appropriate that rosuvastatin be included in a discussion in relation to the NICE guidance.

AstraZeneca submitted that whether it was blood pressure in hypertension, LDL-C in dyslipidaemia or HbA1c in diabetes there was an implied effect on outcomes in any discussion of surrogate endpoints in disease management. The role of a responsible company in dissemination of information in therapy areas where surrogate endpoints were the principal consideration was to ensure that it was entirely clear what was being discussed. This supplement presented the facts appropriately and without misleading: all of the figures and the text were unambiguous in referring to rosuvastatin's efficacy in managing LDL-C/total cholesterol and achieving targets.

AstraZeneca submitted that in this context, it was not inappropriate to mention that NICE had referred to rosuvastatin's efficacy in lowering LDL-C.

AstraZeneca noted that the Panel had not referred to Clause 3.2.

AstraZeneca noted that the Panel had further noted that:

> 'In November 2006 the national director for heart disease and stroke had issued guidance confirming the current national policy …. The date of preparation of the supplement was a month after the November guidance was issued and the supplement was not issued until 20 January …. It was misleading to distribute the supplement which did not refer to important national guidance and was thus not up-to-date …. Readers were urged "to pick up on those patients not reaching the JBS-2 targets …. A referral back to the GP possibly with a

recommendation of change of statin dose or drug entity (in accordance with NICE guidelines) might be seen as appropriate". The supplement thus encouraged pharmacists to follow the JBS-2 guidance which was not national policy.'

AstraZeneca submitted that it had previously acknowledged that the reminder of the National Service Framework (NSF) targets distributed by Professor Boyle in a DoH circular were not included by the authors as it had not been issued when this section had been written. The NSF targets were however specifically included within the supplement. The letter from Professor Boyle, the National Director for Heart Disease, was not a new national policy, nor was it a new review of the evidence base. It was merely a reminder of the NSF targets, which were included in the discussion within the supplement. Therefore, the article represented the balance of evidence by citing the various guideline targets, including the NSF.

AstraZeneca submitted that it was pleased to clear up any misunderstanding about the date of preparation included on the item. Many items took several months to prepare, this one was a case in point. In these instances it was common industry practice to insert the date of preparation at the time of issue of the item. On this occasion the final text of the article was agreed and the content reviewed and approved internally by 3 October 2006. For this reason the date of preparation was initially stated as November 2006 despite the fact the article was completed in advance of this date. On November 7 Professor Boyle posted his clarification of lipid targets. Subsequent delays to the preparation of the final layout and printing of the supplement meant the date of preparation was changed again, this time to December 2006, the anticipated date of inclusion in The Pharmaceutical Journal. Further administrative delays meant the supplement was not included in the journal until January 2007. AstraZeneca repeated its assertion that the circular was issued after the supplement had been completed. This was also referred to in the author's own response on this issue.

Notwithstanding the national director's awareness of the debate on lipid targets and his reaffirming of the existing NSF target of total cholesterol <5mmol/L, AstraZeneca noted that several areas of the UK had local lipid guidelines based on the JBS-2 recommendations. Numerous other local guidelines issued by primary care organisations included lipid targets based on JBS-2 (provided). Included in the list of organisations setting JBS-2 targets was the PCT of one of the authors. He mentioned this in response to criticism about his support of JBS-2 that was published in The Pharmaceutical Journal.

AstraZeneca submitted that several prominent GPs and cardiovascular clinicians considered that the debate on QOF/NSF targets of 5 or 5 and 3mmol/L or the JBS-2 recommendation of 4 and 2mmol/L for total cholesterol and LDL-C was valid. AstraZeneca was concerned that the Authority might stifle a relevant and perhaps critical debate on this important clinical issue by ruling AstraZeneca to be in breach of the Code. AstraZeneca had included a number of quotations from the medical press on this subject. All of these supported the position of the authors that the debate on whether the JBS-2 targets were viable in today's economic climate was far from over.

Wherever the national debate might be leading, AstraZeneca submitted that it was still appropriate to encourage pharmacists to assume a role in the management of dyslipidaemia working to whichever target applied in their area. In many instances this target would be based on JBS-2.

On all the points made by the complainant and the Panel AstraZeneca denied a breach of Clauses 7.2 and 7.4.

With regard to the rulings of breaches of Clauses 2 and 9, AstraZeneca noted that the Panel had stated:

> '… failure to recognise that the supplement was, in effect, promotional material for Crestor, meant that high standards had not been maintained. … by encouraging pharmacists to go beyond national policy …'.

AstraZeneca refuted that the supplement was intended to be promotional and that it was therefore disguised promotion and submitted that it had adequately covered this aspect of this complaint already.

AstraZeneca submitted that The Pharmaceutical Journal was an important part of the available range of UK health journals. One of the strengths of The Pharmaceutical Journal was the lively debate that frequently took place on its correspondence pages and the activities of the pharmaceutical industry were often debated. It was of note that five readers complained but these cases should be judged on the evidence pertaining to the development of the supplement. AstraZeneca welcomed the complainants' response to the clinical debate which showed that the matters covered in the article by the two independent writers were very topical.

AstraZeneca therefore also denied the associated breaches of Clauses 2 and 9.1.

COMMENTS FROM THE COMPLAINANTS

No comments were received in relation to Cases AUTH/1951/2/07 and AUTH/1953/2/07 to AUTH/1955/2/07.

Case AUTH/1952/2/07

The complainant alleged that it was clear that AstraZeneca had initiated the article. It must have anticipated some advantage from doing this. The two authors seemed to have been chosen because they were interested in the subject. Many had written on this subject in the medical and pharmaceutical press, so why were these two people chosen? Was it because their points of view were in line with those of AstraZeneca? AstraZeneca had submitted that the authors were well-respected, independent medical

authors who frequently contributed to articles to the medical press. The complainant noted that he had frequently written for both the medical and pharmaceutical journals and had had articles published in the BMJ, The New Generalist, The Pharmaceutical Journal, Pharmacy in Practice, and Prescriber among others, including discussions on appropriate statin use. The complainant was not asked to contribute and he suspected that this was because he would have written a very different article. The complainant did not dispute that the authors had written the article themselves but the complainant alleged that they were chosen for what they were likely to write and AstraZeneca was in fact inextricably linked to the production of this supplement. As this was in effect an opinion piece, were any independent editorial advisers involved? The complainant questioned if the authors wrote this altruistically because of their concerns about inappropriate use of statins or were they paid to write it? If the latter, then this was a potential conflict of interest and should have been declared. There would then inevitably be a perceived association with AstraZeneca.

In the complainant's experience sponsored supplements such as this normally included prescribing information for the sponsor's medicines. Was this not a requirement? The inclusion of such prescribing information would have enabled readers to know that one of the proposed treatment strategies was inappropriate in that rosuvastatin was not licensed for the prevention of cardiovascular events. As the reason for the supplement was to discuss the implementation of the NICE guidance and the NICE guidance was about the prevention of cardiovascular events and there were three other statins licensed for this indication, then this was seriously misleading. In addition, the rosuvastatin strategy included the use of the 40mg dose. The SPC for Crestor stated 'Specialist supervision is recommended when the 40mg dose is initiated'. This was not mentioned in the supplement despite the increased risk of adverse events with this dose and this was a serious omission.

The complainant alleged that the strategy suggested that simvastatin 40mg would only achieve a total cholesterol target of <5mmol/L in 63.7% of patients and used data on file to support the claim. This ignored published evidence to the contrary and was therefore misleading. The two randomised controlled trials that involved the use of dose-adjusted simvastatin strongly suggested that the vast majority of people given simvastatin 40mg would achieve a total cholesterol of <5mmol/L. In the 4S (Lancet 1994) and IDEAL studies (Pedersen et al 2005) patients were started on simvastatin 20mg and moved up to 40mg daily if necessary to achieve a total cholesterol <5.2mmol/L in 4S and <5mmol/L in IDEAL. The mean simvastatin dose in 4S was 27mg daily and in IDEAL 25mg daily, suggesting that most people would get below 5mmol/L on 40mg daily. The strategies also ignored simvastatin 80 mg daily as the appropriate step 1, as advocated in the widely publicised University College London Hospitals statin guideline 'Switching Statins' (BMJ 2006). These two adjustments would have had a dramatic effect on the cost-effectiveness analysis, which was therefore misleading.

The complainant noted the recently published Health Technology Assessment (HTA) review of statins for the prevention of coronary events (2007) was pertinent to the debate about the promotion of rosuvastatin without clinical endpoint evidence. It stated 'although there is evidence to suggest that rosuvastatin is more effective than atorvastatin, pravastatin and simvastatin in reducing both total cholesterol and LDL-C, it is not possible to prove that these reductions translate into comparable reductions in clinical events' and 'in the absence of strong and conclusive evidence on the exact relationship between cholesterol lowering and clinical end-points, cost-effectiveness results for rosuvastatin are subject to additional uncertainty'.

The complainant noted that the supplement put forward the strategies of either atorvastatin or rosuvastatin as appropriate second-line statins and therefore implied that they would have similar patient benefits. As atorvastatin had patient-orientated outcome evidence to support it and rosuvastatin had not, this was misleading. The majority of trusts would have atorvastatin as their second-line statin because it had been proven to reduce cardiovascular morbidity, unlike rosuvastatin. Reduction in cardiovascular morbidity could not be assumed from surrogate outcomes. There were too many examples where this had been shown not necessarily to follow. Such risks could not be taken with people's health when evidence-based medicines were available. The complainant alleged that AstraZeneca had been selective in providing guidelines that included its medicine when the majority did not.

The complainant noted that it was well known that the NSF cholesterol targets were still national policy and they were reflected in the QoF targets. The supplement did not highlight this fact and implied that it was appropriate to aim to achieve for JBS2 targets. Professor Boyle's letter was only issued because of activities leading to inappropriate promotion of the JBS-2 targets. Whether the supplement preceded the letter or vice versa was not actually relevant. The supplement encouraged following JBS-2 guidance rather than national policy and this reduced confidence in the integrity of the pharmaceutical industry. It was also well known that the JBS-2 targets were not evidence-based as the JBS admitted in its own document as highlighted in the letter to The Pharmaceutical Journal. The vast majority of trusts would have the national targets not the JBS-2 targets in their guidelines as it was well recognised that they were neither achievable or affordable. Once again AstraZeneca had been selective in the guidelines it had presented. It was of interest to note that the Scottish Intercollegiate Guidelines Network (SIGN), which one of the authors in his letter seemed to think would support his stance, rejected the JBS-2 targets and promoted simvastatin 40mg daily. Also, a recently published quality assessment (Minhas 2007) concluded that the JBS guidelines 'contain serious deficiencies, are of low quality and should not be recommended for clinical practice', thereby supporting the position of the majority of trusts with their evidence-based, cost-effective guidelines.

AstraZeneca argued that NICE referred to rosuvastatin in their guidance. The NICE guidance stated that specialist supervision was recommended when rosuvastatin 40mg was initiated and the 40mg dose was contraindicated in those of Asian origin, neither of which were mentioned in the supplement. NICE also stated that the guidance related only to the use of statins within their licensed indications, which effectively ruled out rosuvastatin, as it was not licensed for the prevention of cardiovascular events.

The complainant alleged that this was a promotional supplement and remained convinced that the Panel had made the correct decision and the appeal should be rejected.

APPEAL BOARD RULING

The Appeal Board accepted that the views expressed in the material were those genuinely held by the authors. The Appeal Board, however, was called upon to consider the merits of the piece in the context of AstraZeneca's involvement in the generation and production of it. Independent authors were at liberty to publish their views; however when a pharmaceutical company became involved in such an activity it potentially became subject to the Code.

The Appeal Board noted that it was acceptable for companies to sponsor material. It had previously been decided, in relation to material aimed at health professionals, that the content would be subject to the Code if it was promotional in nature or if the company had used the material for a promotional purpose. Even if neither of these applied, the company would be liable if it had been able to influence the content of the material in a manner favourable to its own interests. It was possible for a company to sponsor material which mentioned its own products and not be liable under the Code for its contents, but only if it had been a strictly arm's length arrangement with no input by the company and no use by the company of the material for promotional purposes.

The Appeal Board noted the material in question had been sponsored/financially supported by AstraZeneca. AstraZeneca had paid the authors to write it and The Pharmaceutical Journal to distribute it. In that regard the material was a paid for insert from AstraZeneca; not a supplement sponsored by The Pharmaceutical Journal for which the editor would have been responsible. The insert had been initiated by AstraZeneca and its communications agency following an AstraZeneca statin advisory board meeting organised by AstraZeneca attended by the two authors who were subsequently asked to write the insert. AstraZeneca was aware of the outline of the material and had, when asked to do so by one of the authors, provided cost-effectiveness tables for rosuvastatin vs simvastatin as well as data on file. The material was reviewed by AstraZeneca to ensure that it was factually correct. The Appeal Board noted from the AstraZeneca representatives that on review of the insert AstraZeneca had suggested the inclusion of a table of budget impact results for a total cholesterol target of <5mmol/L to balance the <4mmol/L results already included, this was accepted by the authors. The Appeal Board noted that although two authors had full editorial control, AstraZeneca took the final decision about whether to publish or not.

The Appeal Board considered that AstraZeneca was inextricably linked to the production of the insert. There was no arm's length arrangement between the provision of the sponsorship and the generation of the material. Given the company's involvement and content, the Appeal Board considered that the material was, in effect, promotional material for Crestor. The Appeal Board considered that it was disguised promotion in that the material appeared to be independently written which was not so, the two authors had, in effect, been chosen by AstraZeneca. The Appeal Board upheld the Panel's ruling of a breach of Clause 10.1 in all five cases. The appeal on this point was unsuccessful.

In Cases AUTH/1953/2/07, AUTH/1954/2/07 and AUTH/1955/3/06 the Appeal Board noted its ruling of a breach of Clause 10.1 and as such considered that the material should have included the prescribing information for Crestor which it did not. The Appeal Board upheld the Panel's rulings of a breach of Clause 4.1 of the Code in all three cases. The appeal on this point was unsuccessful.

The Appeal Board noted that the material stated that the NICE guidance on statins recognised the body of evidence for reduction in cardiovascular morbidity and overall mortality associated with statin use across a broad spectrum of the population. It did not give targets for cholesterol levels, stating this was outside its remit. With respect to the choice of statin NICE recommended that therapy should usually be initiated with a medicine with a low acquisition cost (taking into account required daily dose and product price per dose). For many patients, the least expensive statin would be simvastatin. The Appeal Board noted that the material recognised that simvastatin should be used first-line but put forward arguments for the use of rosuvastatin which was more expensive without stating that it was not licensed to reduce cardiovascular mortality and morbidity. The Appeal Board considered that without a statement to the contrary, the material, by implication, advocated the use of rosuvastatin to reduce cardiovascular morbidity. Simvastatin (Merck Sharp & Dohme's product, Zocor) was licensed for reduction of cardiovascular mortality and morbidity in patients with manifest atherosclerotic cardiovascular disease or diabetes mellitus, with either normal or increased cholesterol levels, as an adjunct to correction of other risk factors and other cardioprotective therapy. In this regard the Appeal Board noted that Lipitor was indicated for primary prevention in type II diabetes for reducing the risk of cardiovascular events in diabetic patients with at least one additional risk factor, without clinically evident coronary heart disease irrespective of whether cholesterol was raised. The Appeal Board considered that the material was misleading as to the licensed indication of Crestor. In this regard the Appeal Board upheld the Panel's rulings of breaches of Clauses 7.2 and 7.4 in Cases AUTH/1951/2/07 and

AUTH/1952/2/07. The appeal on this point was unsuccessful.

The Appeal Board noted that the material set out the evolving guidance on statin use. It also noted the timeframe regarding the writing, production and publication of the material. The Appeal Board considered that the timings were such that the statement issued by the national director for heart disease and stroke should have been referred to in the insert. By not referring to this important national statement the material was misleading and not up-to-date. The Appeal Board upheld the Panel's ruling of a breach of Clause 7.2 of the Code in Cases AUTH/1951/2/07 and AUTH/1953/2/07 in this regard. The appeal on this point was unsuccessful.

With regard to the allegation in Cases AUTH/1951/2/07 and AUTH/1952/2/07 about unachievable JBS targets, the Appeal Board noted that in the discussion on optimizing statin treatment strategies the supplement asked 'Are more challenging targets such as JBS-2, really achievable - and, more importantly, can they be achieved safely?'. In the section discussing the role of the pharmacist, however, readers were urged to 'pick up on those patients not reaching the JBS-2 targets of total cholesterol <4mmol/L and LDL cholesterol <2mmol/L. A referral back to the GP possibly with a recommendation of change in statin dose or drug entity (in accordance with NICE guidelines) might be seen as appropriate'. The Appeal Board noted that not only did the material encourage pharmacists to follow the JBS-2 guidance, which was not national policy, it did not advise them that the JBS-2 targets were for high risk patients. From the statement in the material it appeared that the JBS-2 targets should be the aim for all patients which was not so. The Appeal Board considered that the material was misleading in this regard and upheld the Panel's ruling of a breach of Clause 7.2 in Cases AUTH/1951/2/07 and AUTH/1952/2/07. The appeal on this point was unsuccessful.

The Appeal Board noted, in Case AUTH/1953/3/06, that a cost-effectiveness model was presented in the insert which showed the budget impact results for patients failing to reach either a total cholesterol target of <5mmol/L or a total cholesterol target of <4mmol/L. Two tables detailed the financial implications of having to use atorvastatin or rosuvastatin as second line therapy to simvastatin (the least expensive statin). Both tables referred to rosuvastatin 40mg ie the maximum daily dose. According to the Crestor SPC, in the light of increased reporting rate of adverse reactions with the 40mg dose compared to lower doses a final titration to the maximum dose of 40mg should only be considered in patients with severe hypercholesterolaemia at high cardiovascular risk (in particular those with familial hypercholesterolaemia) who did not achieve their treatment goal on 20mg and in whom routine follow-up would be performed. Specialist supervision was recommended when the 40mg dose was initiated. Section 4.4 of the SPC stated that an assessment of renal function should be considered during routine follow-up of patients treated with a dose of 40mg. Crestor appeared to be different as specialist supervision was not required with the maximum daily dose of any of the other statins (atorvastatin, fluvastatin, pravastatin and simvastatin). This important condition on the use of rosuvastatin was not referred to anywhere in the insert. In the section on optimizing statin treatment strategies the possibility that rosuvastatin might be related to a higher incidence of side effects than other statins was discussed. This possibility was dismissed and it was stated that 'all currently marketed statins have a similar very low risk of serious adverse events' and that 'rosuvastatin gives rates of adverse events similar to those of other statins'. The Appeal Board considered that the material was misleading and did not encourage the rational use of Crestor 40mg. The Appeal Board upheld the Panel's rulings of breaches of Clauses 7.2 and 7.10 in this regard in Case AUTH/1953/2/07. The appeal on this point was unsuccessful.

The Appeal Board further noted that the cost-effectiveness data presented in Tables 3 and 4 only accounted for the acquisition costs of the medicine. This was not entirely clear given the tables were headed 'Budget impact' and 'Treatment Strategy' and the use of terms like 'cost-effectiveness', 'financial implications' and the need to look at other 'costs' associated with treatment, which implied more than simply acquisition costs. There was no account taken of the cost of specialist supervision and routine patient follow-up associated with the use of rosuvastatin 40mg which would have an impact on budget. The Appeal Board considered that the data was thus misleading. The Appeal Board upheld the Panel's ruling of a breach of Clause 7.2 in this regard in Case AUTH/1953/2/07. The appeal in this point was unsuccessful.

Overall, in all five cases, the Appeal Board considered that AstraZeneca's failure to recognise that the material was, in effect, promotional material for Crestor, meant that high standards had not been maintained. The Appeal Board upheld the Panel's ruling of a breach of Clause 9.1 in all cases.

The Appeal Board was concerned that the material, contrary to national guidance had encouraged pharmacists to follow JBS-2 cholesterol targets. The Appeal Board was further very concerned that although the 40mg dose of rosuvastatin had been referred to in the insert, there was no reference to the specialist supervision and routine patient follow-up needed with such a dose. The Appeal Board considered that the omission of such information might prejudice patient care. The Appeal Board considered that in these two matters, the material had brought discredit upon and reduced confidence in the pharmaceutical industry. The Appeal Board upheld the Panel's ruling of a breach of Clause 2 in Cases AUTH/1951/2/07, AUTH/1952/2/07 and Case AUTH/1953/2/07. The appeal on these points was unsuccessful.

Proceedings commenced **5 February 2007**

Cases completed **3 July 2007**

CASE AUTH/1960/2/07

CONSULTANT IN ANAESTHESIA AND PAIN MANAGEMENT v GRÜNENTHAL

Versatis journal advertisement

A consultant in anaesthesia and pain management complained about an advertisement in the BMJ for Versatis (lidocaine medicated plaster) issued by Grünenthal.

The complainant alleged the advertisement was at best deliberately misleading, misrepresenting the product as it did, and at worst a deliberate attempt to influence prescribers to use the product off-licence. The clear and unambiguous message was that the product was for burning, shooting, stabbing (ie neuropathic) pains and that Versatis 'Works where it hurts'. The fact that Versatis was only licensed for post-herpetic neuralgia (PHN) was lost in the small print away from the main message. Additionally, the advertisement strongly suggested that the pain to be treated was one experienced by a young female which spread across a large area of both sides of the body. PHN was typically a unilateral single dermatomal pain in an elderly person.

The advertisement depicted a broad blue swathe running from the right shoulder to the bottom left-hand side of a young woman's back. The area of the right shoulder featured a fire apparently depicting pain, alongside the claim 'New for burning, shooting, stabbing pains' which was encased within a highlighted blue box. The licensed indication appeared in the bottom left-hand corner of the advertisement, beneath the blue swathe. The product logo appeared above the strapline 'Works where it hurts' in the bottom right-hand corner.

In the Panel's view any qualification required to ensure that a claim complied with the Code should appear in the same immediate visual field as the claim itself. The Panel considered that the prominent unqualified claim 'New for burning, shooting, stabbing pains' implied that Versatis was licensed to treat any such pain irrespective of its origin whereas it was only licensed to treat pain associated with post-herpetic neuralgia. Whilst the licensed indication appeared in the bottom left-hand corner the Panel considered that its size and location was such that it did not qualify the misleading impression given by the headline claim. The advertisement was inconsistent with the Versatis marketing authorization as alleged. A breach of the Code was ruled.

The Panel was concerned that the advertisement did not depict a typical patient with PHN. Whilst noting that it could potentially affect a patient of any age or either gender, PHN was much more likely to occur in the elderly rather than in the younger patient depicted. The Panel noted the company's submission that the purpose of the blue swathe was to lead the reader's eye from the symptoms to the licensed indication but considered that it implied that the burning, shooting, stabbing pains to be treated were typically bilateral spread across a large area of the body and that was not so. The Panel considered that the advertisement, in its depiction of PHN, was misleading and thus did not encourage the rational use of Versatis. Breaches of the Code were ruled which were appealed by Grünenthal.

Upon the appeal, the Appeal Board noted that whilst the advertisement did not depict a typical patient with PHN, the patient shown was within the licensed indication for Versatis and therefore the image was acceptable in that regard. With regard to the blue swathe the Appeal Board noted from Grünenthal's representatives that it represented the potential spread of pain and sensitivity beyond the original rash. This differed from the company's response to the complaint when it stated that the purpose of the blue swathe was to lead the reader's eye from the symptoms to the licensed indication. In any event the Appeal Board considered that the spikes, flames and lightening graphics, shown on the 'patient's' right shoulder, clearly depicted PHN and the blue swathe did not mislead as alleged. The Appeal Board ruled no breach of the Code.

A consultant in anaesthesia and pain management complained about an advertisement in the BMJ (ref 042/GRTUK/VERS 12/06-12/08) for Versatis (lidocaine medicated plaster) issued by Grünenthal Ltd.

COMPLAINT

The complainant alleged the advertisement was at best deliberately misleading, misrepresenting the product as it did, and at worst a deliberate attempt to influence prescribers to use the product off-licence. The clear and unambiguous message was that the product was for burning, shooting, stabbing (ie neuropathic) pains and that Versatis 'Works where it hurts'. The fact that Versatis was only licensed for post-herpetic neuralgia (PHN) was lost in the small print away from the main message. Additionally, the advertisement strongly suggested that the pain to be treated was one experienced by a young female which spread across a large area of both sides of the body. PHN was typically a unilateral single dermatomal pain in an elderly person.

When writing to Grünenthal, the Authority asked it to respond in relation to Clauses 3.2, 7.2 and 7.10 of the Code.

RESPONSE

Grünenthal stated that the advertisement had appeared in a number of medical journals since the launch of Versatis. The company noted the complainant's statement that 'The clear and unambiguous message is that the product is for burning, shooting, stabbing (ie neuropathic) pains and that Versatis 'Works where it hurts''.

These symptoms were routinely experienced by sufferers of PHN; market research had shown that these symptoms were common in PHN and this was supported by reports in the published literature eg Baron *et al*. As the licence for Versatis was for neuropathic pain associated with previous herpes zoster infection (PHN) it should not be surprising to see common symptoms featured in an advertisement for the product. The claim 'Works where it hurts' described how Versatis worked locally for patients with PHN.

This important licensed indication information was positioned deliberately adjacent to the brand name to minimise ambiguity. The blue swathe led the reader's eye from the 'burning, stabbing, shooting pains' through the dramatical representation of those expressions directly to the licensed indication.

PHN could affect people of almost any age or gender and could affect large areas of skin. The female image represented was within the licensed demographic group eligible for treatment (ie 18 years of age and over). The visual representation of the descriptive terms used by patients was relatively confined on the visual. The purpose of the blue swathe was to lead the reader directly from the symptoms to the licensed indication, the product name (to its right) and thereby the prescribing information immediately below. It was not meant to illustrate the spread or extent of affected area from the single dermatome concerned, but it did illustrate that the symptoms could be related to any one of a number of dermatomes (not exclusive, of course).

The advertisement was one of many promotional items used to communicate every aspect of Versatis to prescribers to ensure they were fully informed. The role of the Versatis advertisement was to raise awareness and create interest in the product and empathy for patients suffering with a very painful condition. The success in achieving these goals was confirmed by market research prior to launch. Grünenthal submitted that this creative approach in achieving these goals was not dissimilar to other medical advertisements, a selection of which were provided.

The Code did not state that advertisements should communicate precise patient types and conditions. In this situation it would be impossible because PHN patients presented at all ages, sexes and stages of illness. In addition there were differences in perception and understanding between GPs and hospital doctors. The Versatis advertisement aimed to create an emotional response from health professionals of all types – especially empathy with their patients.

As stated previously, it was not intended that the advertisement would provide a text book representation of PHN nor did it attempt to specify one presentation of PHN, ie unilateral dermatomal pain in an elderly person. PHN could affect patients of any age, a variety of sites on the body and sometimes more than one dermatome. The advertisement was designed to communicate information about the product licence and engage stakeholders in an interesting manner, whilst providing these messages within the Code.

In conclusion, PHN presented as localised, burning, stabbing or shooting pain, and therefore the advertisement could not be said to influence the prescriber to use Versatis off-label. Rather than being deliberately misleading, the advertisement communicated what patients experienced with PHN, accurately and with emotion. Grünenthal refuted the accusation that the advertisement attempted to influence prescribers to use Versatis off-label and trusted that the Authority would concur.

PANEL RULING

The Panel noted that Versatis was licensed for the treatment of neuropathic pain associated with previous herpes zoster infection (post-herpetic neuralgia, PHN).

The advertisement depicted a broad blue swathe running from the right shoulder to the bottom left-hand side of a young woman's back. The area of the right shoulder featured a fire apparently depicting pain, alongside the claim 'New for burning, shooting, stabbing pains' which was encased within a highlighted blue box. The licensed indication appeared in the bottom left-hand corner of the advertisement, beneath the blue swathe. The product logo appeared above the strapline 'Works where it hurts' in the bottom right-hand corner.

The Panel noted that the supplementary information to Clause 7 stated that claims in promotional material must be capable of standing alone as regards accuracy etc. In general claims should not be qualified by footnotes and the like. In the Panel's view any qualification required to ensure that a claim complied with the Code should appear in the same immediate visual field as the claim itself. In the advertisement at issue readers were required to zigzag down the page in order to get all of the information needed to understand what Versatis was licensed for. The Panel considered that the prominent unqualified claim 'New for burning, shooting, stabbing pains' implied that Versatis was licensed to treat any such pain irrespective of its origin whereas it was only licensed to treat pain associated with post-herpetic neuralgia. Whilst the licensed indication appeared in the bottom left-hand corner in a white typeface against a dark background the Panel considered that its size and location was such that it did not qualify the

misleading impression given by the headline claim. The advertisement was inconsistent with the Versatis marketing authorization as alleged. A breach of Clause 3.2 was ruled. This ruling was accepted.

The Panel was concerned that the advertisement did not depict a typical patient with PHN. Whilst noting that it could potentially affect a patient of any age or either gender, PHN was much more likely to occur in the elderly rather than in the younger patient depicted. The Panel noted the company's submission that the purpose of the blue swathe was to lead the reader's eye from the symptoms to the licensed indication but considered that it implied that the burning, shooting, stabbing pains to be treated were typically bilateral spread across a large area of the body and that was no so. The Panel considered that the advertisement, in its depiction of PHN, was misleading and thus did not encourage the rational use of Versatis. Breaches of Clauses 7.2 and 7.10 were ruled. This ruling was appealed by Grünenthal.

APPEAL BY GRÜNENTHAL

Grünenthal submitted that the advertisement at issue was one of a series planned for the launch of Versatis which would show a variety of appropriate patient types. The patient shown was clearly within the licensed indication for Versatis (18 years and over). Future advertisements would include elderly and male patients.

Market research confirmed that the vast majority of customers understood that the Versatis promotional campaign (of which the advertisement was the key component) communicated that the product should be used for neuropathic pain associated with PHN.

There was no intention to mislead the reader as the advertisement depicted a patient for which Versatis was licensed (female over 18 years of age); therefore it was not a breach of Clause 7.2. Moreover, the advertisement did not breach Clause 7.10 as it did not exaggerate the patient type or encourage irrational use of Versatis.

Grünenthal submitted that the typical rash of shingles with its distribution over a single dermatome underestimated the extent of the neurological symptoms of PHN. A symptom such as allodynia was not confined to the distribution of the rash but was more widespread; Watson *et al* (2001) and the review by Gilron *et al* (2006) showed allodynia to be extensive. Thus allodynia could appear to merge over several dermatomes (as more or less depicted by the blue swathe in the advertisement).

Hope-Simpson (2001) reported that herpes zoster and PHN could appear almost anywhere on the body, but mainly on the torso. Grünenthal stated that it considered it appropriate to show the posterior aspect of the torso in its advertisement.

In summary, the advertisement showed a common area for PHN and thus Grünenthal did not consider that it breached Clause 7.2. Therefore as the advertisement did not mislead customers to use Versatis outside of its labelled indication, the company did not consider that it breached Clause 7.10.

COMMENTS FROM THE COMPLAINANT

The complainant initially responded to the emailed appeal and response to the complaint without their enclosures as he was unable to receive them.

The complainant did not question that the product was an effective topical application for neuropathic pain which 'works where it hurts', the issue was the separation of this (correct) statement (in the advertisement) from that of the only licensed indication for the product. PHN could affect any age group but, except in the immunocompromised patient it would be restricted to one dermatome on one side of the body which might be a 'large area of skin' but hardly akin to the blue swath; even though allodynia often extended beyond the confines of the rash it did not cross the midline.

The complainant alleged that if the advertisement was truly one of a series then why did the first one feature one of the most unlikely sufferers and where were the details of the planned series with irrefutable evidence (timeline) that this was in place before the complaint was lodged?

The complainant noted a reference text (Waldman 2007) dealt with PHN in volume 1; it stated 'Post herpetic neuralgia … along a single dermatome. Pain develops along the same dermatome as the rash'. '… generally localised to the segmental distribution of the posterior spinal ganglion affected … 52% thoracic …. This most common and feared complication of herpes zoster is called postherpetic neuralgia, and the elderly are affected at a higher rate than the general population …'. At 1 year only 8% of those aged <20 would have postherpetic neuralgia compared with 92% of those >70 who had survived'.

Upon receipt of the enclosures to the appeal the complainant alleged that Grünenthal's response did not answer the concerns raised. The advertising schedule was extensive and just that; no indication of a previously planned series of different approaches. Most common symptoms in PHN based upon 883 GPs were as known/expected. The advertisements for other medicines included by Grünenthal in its response, had not raised any concerns equivalent to those for Versatis.

The complainant stated that Baron *et al* confirmed the expected efficacy for a '… chronic pain syndrome that disproportionately affects the elderly' which '… showed a favourable safety profile … in this predominantly elderly population'.

The complainant submitted that Hope-Simpson *et al* neither supported nor contradicted Grünenthal's position. Gilron *et al* clearly confirmed PHN as

unilateral and dermatomal with allodynia limited to the dermatomes above and below the lesion which Watson *et al* also reiterated, far from the 'blue swathe'! The Medix market research, unfortunately for Grünenthal, showed that the campaign had communicated licensed usage to only 64% of GPs.

The complainant had attended a recent British Pain Society meeting sponsored by Grünenthal in support of Versatis. Efficacy was not in doubt, nor the dermatomal nature of the condition, nor the elderly as the main group to target who should be the initial focus particularly as their co-morbidities made alternative treatment options difficult.

APPEAL BOARD RULING

The Appeal Board noted that whilst the advertisement did not depict a typical patient with PHN, the patient shown was within the licensed indication for Versatis and therefore the image was acceptable in that regard. With regard to the blue swathe the Appeal Board noted from Grünenthal's representatives that it represented the potential spread of pain and sensitivity beyond the original rash. This differed from the company's response to the complaint when it stated that the purpose of the blue swathe was to lead the reader's eye from the symptoms to the licensed indication. In any event the Appeal Board considered that the spikes, flames and lightening graphics, shown on the 'patient's' right shoulder, clearly depicted PHN and the blue swathe did not mislead as alleged. The Appeal Board ruled no breach of Clauses 7.2 and 7.10. The appeal on this point was successful.

Complaint received	**16 February 2007**
Case completed	**17 May 2007**

PRIMARY CARE TRUST PHARMACEUTICAL ADVISER v ASTRAZENECA

Report presented at a meeting

A primary care trust pharmaceutical adviser complained about a report presented at a meeting of local practice managers sponsored by AstraZeneca. The report, 'Budget Impact Model for Asthma & COPD [chronic obstructive pulmonary disease]', related to Symbicort (budesonide/formoterol).

The complainant stated that the local practice managers were concerned that the information presented was contrary to local prescribing guidelines. The complainant alleged that the report appeared to be inappropriate for a group of practice managers who had no responsibility for prescribing budgets.

The Authority told AstraZeneca that it need not comment on the statement that the information was of a clinical nature contrary to local prescribing guidelines as this was not a matter for the Code.

The Panel noted that it was not necessarily unacceptable to provide practice managers with promotional information about medicines so long as the material was appropriate and tailored towards their role.

The presentation highlighted the current prescribing split between the two available combination inhalers, Symbicort and Seretide, using local prescribing data and illustrated the budgetary impact of adopting new treatment strategies for asthma and COPD versus the current strategies. Background information on the local patient population was provided as was the local annual cost saving as a result of a change in prescribing strategies. The report did not discuss clinical data for either product. References to the products were within a budgetary context.

The meeting organisers, the local primary care managers team, had invited an AstraZeneca representative to present the Symbicort budget impact model to twelve local general practice managers. The Panel was concerned that the presentation was not referred to on the agenda – it had been dealt with under matters arising; there was however no complaint on this point. Whilst the chairman had indicated that the model was suitable material for the audience, the Panel noted that it was for AstraZeneca to satisfy itself that the arrangements and material met the requirements of the Code. The Panel considered that the practice managers were appropriate administrative staff for the purposes of the presentation and that the material was tailored towards their needs. No breach of the Code was ruled.

The Panel considered that overall the meeting was an appropriate one to sponsor. The meeting lasted four hours and covered topics relevant to practice management. The costs incurred were reasonable. No breach of the Code was ruled.

The pharmaceutical adviser at a primary care trust complained about a report (ref SYMB 06 P10639) presented in a meeting of local practice managers by a representative from AstraZeneca UK Limited. The report related to Symbicort (budesonide/formoterol) and was titled 'Budget Impact Model for Asthma & COPD [chronic obstructive pulmonary disease]'.

COMPLAINT

The complainant stated that local practice managers, having attended a meeting sponsored by AstraZeneca, were concerned that the information presented by the representative was of a clinical nature contrary to local prescribing guidelines. The complainant alleged that the report at issue appeared to be inappropriate for a group of practice managers who had no responsibility for prescribing budgets.

The complainant noted that Clause 19.1 discussed the provision of hospitality for appropriate administrative staff and required that meetings should be 'scientific, promotional and other such meetings'. The complainant could not see how the information in the report was appropriate to non-clinical managers.

When writing to AstraZeneca, the Authority asked it to respond in relation to Clause 12.1 of the Code in addition to Clause 19.1 cited by the complainant. The company was informed that it need not comment on the statement that the information was of a clinical nature contrary to local prescribing guidelines as this was not a matter for the Code.

RESPONSE

AstraZeneca explained that the meeting in question was organised and run by the local primary care managers team; a meeting agenda and list of attendees were provided. The meeting was held at a hospice and the organisers asked a local representative to provide a short presentation on the Symbicort budget impact model to a group of twelve local general practice managers. Prior to the meeting, the chairman had verbally agreed that AstraZeneca could sponsor the meeting and that the Symbicort budget impact model would be suitable to demonstrate to the attendees. AstraZeneca's sponsorship was clearly stated at the top

of the front page of the minutes arising from this meeting. This form of recognition of the sponsor was standard practice for this independent professional group rather than including it on the meeting agenda.

AstraZeneca paid £100 towards the meeting for a standard buffet sandwich lunch, tea and coffee ie £8.33 per head. There were no other costs associated with the meeting. Only appropriate administrative staff were invited to the meeting which had a clear educational content for the local practice managers attending as indicated by the agenda. The venue was appropriate and conducive to the purpose of the event. Subsistence was extended only to appropriate staff and the level of subsistence offered was in proportion to the size of the event and within industry standards. AstraZeneca denied a breach of Clause 19.1.

The chairman of the meeting asked the representative to present for 10 minutes on the Symbicort budget impact model at the beginning of the meeting as indicated in the agenda under matters arising from the minutes of the previous meeting. Symbicort was a combination inhaler therapy licensed for use in asthma and COPD. The Symbicort budget impact model had been developed to engage with appropriate NHS staff on the issue of local affordability. NHS budget holders were under increasing pressure to ensure that scarce resources were allocated efficiently and that spending stayed within their local constrained budgets. It was therefore important for pharmaceutical companies to demonstrate that their products were not only clinically effective but also delivered value for money. The model had been designed to estimate the potential financial impact of adopting Symbicort at a local population level. The model was populated with a default dataset drawn from published studies, national estimates of the prevalence of disease, national sales data and treatment patterns and NHS costs. The model allowed the user to vary a wide number of inputs to examine their effect on the model outputs.

In this particular case the Symbicort budget impact model illustrated the budgetary impact of adopting a particular treatment strategy for asthma and COPD using combination inhaler therapy. The presentation illustrated the current prescribing split between the two available combination inhaler products, Symbicort and Seretide using local prescribing data that provided detail on the volume dispensed of the different formulations of these products. A proposed strategy in terms of adjusting the split between these two combination products for treating asthma and COPD in this prescribing region was then presented. The budgetary impact was then compared of employing this new treatment strategy versus the status quo. The budget impact model was intended solely for an audience that had accountability for administering local prescribing budgets. The representative handed out printed copies of the presentation to attendees so that they could discuss the findings with prescribing colleagues in their respective practices.

The practice managers at the meeting were accountable for their practice budgets. AstraZeneca representatives presented clinical and promotional items to actual prescribers in these GP surgeries. By presenting the economic argument to the practice managers this involved all key stakeholders in any decision making process, of which the practice manager was part. It was appropriate to discuss financial matters relating to budget impact models to practice managers who were accountable for their practice budgets. One of the many roles undertaken by practice managers was management of practice prescribing budgets through the creation of the practice formulary. They would ensure that all prescriptions were sent to the Prescription Pricing Authority (PPA) on a monthly basis to guarantee that the reimbursement process ran smoothly. Managers could monitor the prescribing habits of the practice and each individual prescriber via Prescribing Analysis and Cost Tabulation (PACT) data provided by the PPA on a quarterly basis. In general, practice managers should be familiar with all aspects of prescribing and the different mechanisms for primary care in the UK. It was therefore appropriate and relevant to present budgetary material to practice managers who had a local responsibility for their own prescribing budgets in their practices. This was also relevant given that Symbicort was listed on the local joint formulary in this particular primary care trust and hence the audience could be assumed to take an interest in this particular information.

AstraZeneca therefore denied a breach of Clause 12.1 of the Code in relation to the presentation and handout of this budgetary material to the practice managers at this meeting.

PANEL RULING

The Code applied to the promotion of medicines to members of the United Kingdom health professions and to appropriate administrative staff (Clause 1.1). Clause 12.1 and its supplementary information stated that promotional material should only be sent or distributed to those categories of persons whose need for, or interest in the particular information could reasonably be assumed. Promotional material should be tailored to the audience. The Panel noted that it was thus not necessarily unacceptable to provide practice managers with promotional information about medicines so long as the material was appropriate and tailored towards their role.

The Panel noted that the presentation highlighted the current prescribing split between the two available combination inhalers, Symbicort and Seretide, using local prescribing data and illustrated the budgetary impact of adopting new treatment strategies for asthma and COPD versus the current strategies. Background information on the local patient population was provided. The local annual cost saving as a result of a change in prescribing strategies was given as £363,980. The Panel noted that the report did not discuss clinical data for either product. References to the products were within a budgetary context.

The Panel noted that the meeting organisers, the local primary care managers team, had invited the representative to present the Symbicort budget impact

model to twelve local general practice managers. The Panel was concerned that the presentation was not referred to on the agenda – it had been dealt with under matters arising; there was however no complaint on this point. Whilst the chairman had indicated that the model was suitable material for the audience, the Panel noted that it was for AstraZeneca to satisfy itself that the arrangements and material met the requirements of the Code. Nonetheless it was unlikely that a chairman would have asked a representative to talk about irrelevant issues. The Panel noted AstraZeneca's submission about the role and responsibilities of practice managers and considered that they were appropriate administrative staff for the purposes of the presentation and that the material was tailored towards their needs. No breach of Clause 12.1 was ruled.

The Panel considered that overall the meeting was an appropriate one to sponsor in relation to the requirements of Clause 19.1. The agenda indicated that the meeting lasted from 9am to 1pm and covered topics relevant to practice management. The costs incurred of £8.33 per head were reasonable. No breach of Clause 19.1 was ruled.

During its consideration of this case the Panel noted AstraZeneca's submission that recognition of its sponsorship appeared at the top of the front page of the meeting's minutes rather than on the agenda as this was standard practice for this independent professional group. This did not meet the requirements of Clause 19.3 of the Code and its supplementary information which required that such sponsorship must be disclosed in all papers relating to the meeting and in any published proceeding. The declaration should thus have appeared on the invitation and the agenda. Declaring sponsorship retrospectively in the minutes of the meeting was wholly inadequate; customers' wishes could not override the requirements of the Code. There was, however, no allegation on this point. The Panel thus asked that the company be advised of its views in this regard.

Complaint received	**19 February 2007**
Case completed	**3 May 2007**

CASES AUTH/1968/2/07 and AUTH/1969/2/07

ANONYMOUS v GENUS and PROSTRAKAN

Tabphyn MR journal advertisement

An anonymous complainant alleged that an advertisement for Tabphyn MR (tamsulosin) included a hanging comparison, 'Spend fewer pennies on the treatment of BPH', and was misleading. The advertisement, published in Prescriber on 5 February, referred to Genus and ProStrakan and the matter was taken up with both companies.

The complainant provided a copy of a price list from a company specialising in generic medicines which showed a tamsulosin MR product (Stronazon) with an invoice price of £3.69 per pack of 30x400mg and a promotional price of £3.32.

Genus explained that it held the marketing authorization for Tabphyn. The product had been licensed to ProStrakan in March 2006. Genus had had no involvement in promotion of any kind for the product after March 2006 and had no knowledge of the advertisement in question.

The Panel noted the ProStrakan corporate logo and website address appeared in the advertisement which also included the statement 'Further information is available on request from: Genus Pharmaceuticals Ltd'. Both medical information enquiries and adverse event reports should be directed to Genus. It thus appeared from the advertisement that Genus had a current role beyond being the marketing authorization holder. The Panel considered that Genus was jointly responsible with ProStrakan for the advertisement under the Code.

The Panel ruled a breach of the Code as it considered that the claim 'Spend fewer pennies on the treatment of BPH' was a hanging comparison. It was not clear whether the comparison was with other generic or branded formulations of tamsulosin or all other treatments for BPH.

The Panel noted ProStrakan's submission that the price list used by the complainant was not in the public domain. The Panel also noted that at the date of the advertisement, according to data available to ProStrakan, Tabphyn MR was the least expensive tamsulosin product at NHS list price - £7.99 for one month's treatment. The basic price for tamsulosin 400mg modified release capsules (30) was £8.68 (Drug Tariff January 2007). The Panel considered that although it might be possible to buy tamsulosin at less than the NHS list price, it was not unreasonable for companies to base price comparisons on prices that were publicly available. Thus the Panel ruled no breach of the Code.

An anonymous complainant complained about an advertisement (ref M014/042) for Tabphyn MR (tamsulosin) which featured the claim 'Spend fewer pennies on the treatment of BPH [benign prostatic hyperplasia]' beneath the brand name. The advertisement, published in Prescriber on 5 February, referred to Genus Pharmaceuticals Ltd and ProStrakan Group plc and so the matter was taken up with both companies.

COMPLAINT

The complainant alleged that the advertisement clearly breached Clause 7.2 of the Code. It was a hanging comparison and it was misleading. The complainant provided a copy of a price list from a company specialising in generic medicines which showed a tamsulosin MR product (Stronazon) with an invoice price of £3.69 per pack of 30x400mg and a promotional price of £3.32.

Case AUTH/1968/2/07

RESPONSE

Genus explained that it held the marketing authorization for Tabphyn. The product had been licensed to ProStrakan on 10 March 2006. Genus had had no involvement in promotion of any kind for the product after March 2006 and had no knowledge of the advertisement in question for which the date of preparation was given as December 2006.

Case AUTH/1969/3/07

RESPONSE

ProStrakan stated that when the advertisement was approved one month's treatment with Tabphyn MR was £7.99. The list price quoted in MIMS February 2007 for generic tamsulosin was £8.68. In addition an internet search for the prices of approved generic products showed that in relation to tamsulosin and BPH, Tabphyn MR was the least expensive product available at NHS listed price. A copy of the results from the internet search were provided.

The price list used by the complainant as the basis for the complaint was not in the public domain, and as such ProStrakan was unaware of the prices offered.

As ProStrakan always compared its prices with NHS official list prices it considered that it was not in breach of Clause 7.2.

However, in light of this new information ProStrakan had now withdrawn all promotional materials with

the claim in question.

Case AUTH/1968/2/07

PANEL RULING

The Panel noted that details for each company appeared on the advertisement. The corporate logo for ProStrakan, together with its website address appeared in the bottom right hand corner of the main photograph. Small text in the top right hand corner of the advertisement read 'Further information is available on request from: Genus Pharmaceuticals Ltd'. Boxed text stated that both medical information enquiries and adverse event reports should be directed to Genus. It thus appeared from the advertisement that Genus had a current role in relation to the product beyond being the marketing authorization holder. That would certainly be the impression given to the reader. The Panel thus considered that Genus was jointly responsible with ProStrakan for the advertisement under the Code.

Cases AUTH/1968/2/07 and AUTH/1969/2/07

PANEL RULING

The Panel considered that the claim 'Spend fewer pennies on the treatment of BPH' was a hanging comparison as alleged. It was not clear whether the comparison was with other generic or branded formulations of tamsulosin or all other treatments for BPH. A breach of Clause 7.2 was ruled.

The Panel noted the cost data showing tamulosin MR (Stronazon) capsules at £3.32, February 2007 as provided by the complainant. It also noted ProStrakan's submission that the price list used by the complainant was not in the public domain. The Panel also noted that at the date of the advertisement, according to data available to ProStrakan, Tabphyn MR was the least expensive tamsulosin product at NHS list price - £7.99 for one month's treatment. The basic price for tamsulosin 400mg modified release capsules (30) was £8.68 (Drug Tariff January 2007). The Panel considered that although it might be possible to buy tamsulosin at less than the NHS list price, it was not unreasonable for companies to base price comparisons on prices that were publicly available. Thus the Panel ruled no breach of Clause 7.2.

Complaint received 28 February 2007

Case completed **AUTH/1968/2/07 15 May 2007**

AUTH/1969/2/07 13 April 2007

CASE AUTH/1974/3/07

ANONYMOUS EMPLOYEES v MERCK SHARP & DOHME

Provision of a service and representative call rates

An anonymous group of Merck Sharp & Dohme employees complained about the provision of a service by the company and representatives' call rates.

The complainants alleged that Merck Sharp & Dohme had misled the Authority in its appeal of the Panel's ruling of a breach of Clause 2 in relation to the conduct of the forearm DEXA placement initiative operated from 2002 to 2004 by the FROSST division of the Merck Sharp & Dohme sales force (Case AUTH/1859/6/06).

The complainants noted that in its appeal, Merck Sharp & Dohme had claimed that the 'DEXA placements DIY Guide' slide presentation was shared with a small group of representatives and not the entire FROSST sales division (approximately 60 representatives reporting to six regional managers with the first line sales responsibility for Fosamax promotion). This was untrue; the small group of representatives (six representatives and four sales managers) was the 'Fosamax Best Practice Team', which met two or three times each year to facilitate sharing of ideas (best practice) in relation to selling activities across the entire FROSST sales division.

According to both current and past members of the FROSST sales division the best practice team would 'cascade' ideas to each regional team. The slide presentation 'DEXA Placements DIY Guide' was one such example. The complainants now provided a copy of the generic objectives document for FROSST sales representatives for 2003 – the 'Performance Planning Form'. In relation to Merck Sharp & Dohme's denial of an intended link between DEXA placements and product promotion the complainants noted the sub-heading under Objective 1: 'Implementation of xxxx Market Expansion (e.g. DEXA placements) project placements ensuring an at least 40% diagnostic hit rate and at least 80% of all Osteoporotic patients identified are treated with Fosamax Once Weekly by December 2003'.

FROSST sales personnel based their personal objectives upon this generic template. However, as the complainants were not prepared to reveal their identity they could not provide named representatives' objective documents.

The complainants had obtained copies of two slides on the national overview of the DEXA programme used by the national sales management team in presentations to Merck Sharp & Dohme's UK senior management. Two slides were provided regarding the 2002 programme throughput up to May and the plan for 2003. These slides correlated with the target of 80% Fosamax usage amongst patients identified as osteoporotic as stated within the representatives' objectives document. This supported the complainants' original contention in Case AUTH/1859/6/06 that the new managing director for Merck Sharp & Dohme UK, who was business unit director for the musculoskeletal business unit responsible for the FROSST sales division, was aware of the conduct and linkage of product promotion to service to medicine of this initiative. The FROSST national sales manager from 2002 to 2004 was appointed to co-chair Merck Sharp & Dohme's compliance oversight committee formed in response to Case AUTH/1814/3/06. The complainants noted the potential conflict of interest given that the other co-chair of the compliance oversight committee was the business unit director responsible for the activities in question in Case AUTH/1814/3/6.

The Panel noted that, according to the complainants, the Best Practice Team (which Merck Sharp & Dohme had stated was a small number of representatives, managers and marketing specialists) to whom the 'DEXA Placements DIY Guide' was presented would share ideas in relation to selling activities across the entire FROSST sales division. At the appeal in Case AUTH/1859/6/06, although the Appeal Board had been alarmed at the document and concerned that anyone could have produced it, it had ruled that there was no evidence on the balance of probabilities that the document had been used to train representatives, had otherwise been disseminated beyond the meeting or had otherwise influenced the behaviour of representatives in the field.

Turning to the case now before it the Panel noted the implied allegation that the 'DEXA Placements DIY Guide' had been shared amongst the FROSST representatives and not just the Best Practice Team. As evidence the complainants had noted the statement 'Implementation of xxxx Market Expansion (e.g. DEXA placements) project placements ensuring an at least 40% diagnostic hit rate and at least 80% of all Osteoporotic patients identified are treated with Fosamax Once Weekly by December 2003' in a 2003 Performance Planning Form for FROSST sales representatives.

The complainants had also supplied two slides used to brief senior managers. One related to the DEXA placement programme and compared a number of features planned for 2002 and the outcome for the year to date (May 2002). The data stated that the planned number of osteoporotic patients was 33% of those scanned with the actual figure for the actual year to date being 30%. The planned number of 'Anecdotal Fosamax patients' was 80% whereas the year to date figure was 109%.

The second slide related to the objective for 2003 which was similar to 2002 ie 25-30 patients scanned per day with 30% being osteoporotic and 80% of those being treated with Fosamax Once Weekly.

The Panel noted Merck Sharp & Dohme's submission that the slides were used as briefing materials by managers to managers and were not within the scope of representative training materials and thus were not disclosed to the Authority but the content of the slides were part of briefings to representatives about their objectives.

The Panel considered that market expansion *per se* was not necessarily a breach of the Code. Any activity covered by the Code needed to comply with the Code. The Panel was concerned about the differences between the parties about the use of the 'DEXA Placements DIY Guide'.

The Panel did not consider that the Performance Planning Form provided evidence that, on the balance of probabilities, the 'DEXA Placements DIY Guide' had been used to train representatives. Neither the form nor the slides referring to market share linked the offer of the service to the promotion of Fosamax Once Weekly. Thus the Panel ruled no breach of the Code. These rulings were appealed by the complainant.

The Appeal Board noted that in Case AUTH/1859/6/06 the complainants had been anonymous and not contactable which was unfortunate as some of their current allegations could have been addressed if they had been involved in the previous case. The complaints procedure was designed to fully involve both parties. One of the unfortunate but unavoidable consequences of truly anonymous complaints was that the complainant forfeited their right as regard the appeal process.

The Appeal Board noted that the allegation now being considered was that Merck Sharp & Dohme had previously misled the Appeal Board. The Appeal Board considered that this was a serious allegation but that little evidence had been provided other than that previously considered. The Appeal Board did not accept that the documents supplied by the complainants that were not submitted in the previous case, demonstrated that, on the balance of probabilities, the Appeal Board had been misled. In the Appeal Board's view no credible evidence had been supplied.

The Appeal Board upheld the Panel's ruling that the Performance Planning Form provided no evidence that, on the balance of probabilities, the 'DEXA Placements DIY Guide' had been used to train representatives. Neither the form nor the slides referring to market share linked the offer of the service to the promotion of Fosamax Once Weekly. Thus the Appeal Board upheld the Panel's ruling of no breach of the Code.

In addition to their concerns about the provision of a service, the complainants also noted the following call rates cited in the Performance Planning Form: 'Ensure 100% coverage and frequency of 6 for 1:1 contacts on Super Targets (n=40) by December 2003; ensure 80% coverage and frequency of 4 for 1:1 contacts on Targets (n=80) by December 2003'.

The issue of excessive pressure on representatives to ignore the Code restriction of three unsolicited calls per year had been highlighted recently. Here was evidence that this was Merck Sharp & Dohme practice.

In the Panel's view representatives' briefing material should clearly distinguish between expected call rates and expected contact rates. The Panel noted that a 2003 presentation on the requirements of the Code, used with representatives, set out the requirements regarding call frequency. Nonetheless the Performance Planning Form was a stand alone document. The Panel noted that the form referred to contacts on targets and not call rates. The consequence of the form was that in addition to three 1:1 calls, representatives had to have three 1:1 contacts with targets as a result of meetings, requested call backs etc. An additional activity objective required representatives to 'Increase 1:1 GP activity (both call volume and call rate) relative to 2002 performance'. There was no mention that if 2002 performance was a call rate of 3 it was not possible to increase the call rate without breaching the Code.

The Panel considered that without further explanation that the 2002 call rate could not be increased beyond 3, the Performance Planning Form advocated a course of action which was likely to breach the Code. A breach of the Code was ruled. This ruling was not appealed. The Panel noted that a document detailing a 2006 salesforce incentive scheme clearly referred to the requirements of the Code regarding call frequency.

An anonymous group of employees of Merck Sharp & Dohme Limited complained about the provision of a service by the company and representatives' call rates.

1 Provision of a service

COMPLAINT

The complainants alleged that Merck Sharp & Dohme had misled the Authority in its appeal of the Panel's ruling of a breach of Clause 2 in relation to the conduct of the forearm DEXA placement initiative operated from 2002 to 2004 by the FROSST division of the Merck Sharp & Dohme sales force (Case AUTH/1859/6/06).

In Case AUTH/1859/6/06 the complainants had, *inter alia*, raised concerns regarding the ethical conduct of services offered by Merck Sharp & Dohme's musculoskeletal business unit, FROSST division. The complainants had considered the recently published case report for Case AUTH/1859/6/06, and now provided further documents for consideration by the Authority.

Merck Sharp & Dohme had claimed in its appeal that the 'DEXA placements DIY Guide' slide presentation was shared with a small group of representatives and not the entire FROSST sales division (the team with the first line sales responsibility for Fosamax promotion). This was untrue; the small group of representatives, comprised of six representatives and four sales managers, was the 'Fosamax Best Practice Team'. This team would meet two or three times each year to facilitate sharing of ideas (best practice) in relation to selling activities across the entire FROSST sales division. The FROSST division was comprised of approximately 60 representatives reporting to six regional managers who in turn reported to the national sales manager.

According to a considerable number of current and past members of the FROSST sales division the best practice team would 'cascade' ideas to each regional team. The slide presentation 'DEXA Placements DIY Guide' was one such example. FROSST division newsletters would illustrate this point; however, the complainants could not source examples of these on account of recent IT upgrades and subsequent file deletions. However, they provided a copy of the generic objectives document for FROSST sales representatives for 2003 – the 'Performance Planning Form'. In relation to Merck Sharp & Dohme's denial of an intended link between DEXA placements and product promotion the complainants noted the sub-heading under Objective 1:

- 'Implementation of xxxx Market Expansion (e.g. DEXA placements) project placements ensuring an at least 40% diagnostic hit rate and at least 80% of all Osteoporotic patients identified are treated with Fosamax Once Weekly by December 2003.'

Every member of the FROSST sales division based their personal objectives upon this generic template. However, as the complainants were not prepared to reveal their identity they could not provide named representatives' objective documents.

The complainants also provided copies of two slides on the national overview of the DEXA programme used by the national sales management team in presentations to Merck Sharp & Dohme's UK senior management. The slides were in relation to the 2002 programme throughput up to May and the plan for 2003. These slides correlated with the target of 80% Fosamax usage amongst patients identified as osteoporotic as stated within the representatives' objectives document. This supported the complainants' original contention in Case AUTH/1859/6/06 that the new managing director for Merck Sharp & Dohme UK, who was business unit director for the musculoskeletal business unit responsible for the FROSST sales division, was aware of the conduct and linkage of product promotion to service to medicine of this initiative. The FROSST national sales manager from 2002 to 2004 was appointed to co-chair Merck Sharp & Dohme's compliance oversight committee formed in response to Case AUTH/1814/3/06 and was therefore presumably consulted by the managing director to respond to the complainants' original complaint. The complainants noted the potential conflict of interest here given that the other co-chair of the compliance oversight committee was the business unit director responsible for the activities in question in Case AUTH/1814/3/6.

When writing to Merck Sharp & Dohme, the Authority asked it to respond in relation to Clauses 2, 9.1, 18.1 of the 2003 Code.

RESPONSE

Merck Sharp & Dohme was concerned that the Authority's procedures permitted the re-investigation of a complaint in this way, on the basis of further anonymous information from complainants who had chosen not to take part in or receive information on the earlier investigation. The company had serious reservations as to the propriety and fairness of such a course of action. Merck Sharp & Dohme was certain that there was no need for any current employee to seek anonymity if they wished to comment on or raise objections to any of its activities as the company maintained a confidential helpline for employees with any ethical concerns about its activities. Such concerns were taken seriously and investigated on their merits. Their reporting did not affect in any way the employee's standing within Merck Sharp & Dohme.

By seeking anonymity the complainants had excluded themselves from the full investigation of their concerns. They would not have seen Merck Sharp & Dohme's response to the previous complaint, its written submissions to the Appeal Board and did not attend the appeal itself. These would have provided proper opportunities to put forward further evidence and to challenge Merck Sharp & Dohme's evidence. To do so now, having read only the summary case report, amounted to an abuse of the Authority's processes. Further, this action caused Merck Sharp & Dohme to readdress issues fully subject to prior proceedings.

Merck Sharp & Dohme submitted that it did not mislead the Appeal Board in Case AUTH/1859/9/06 or in any of its prior responses. The allegation to the contrary was without foundation and appeared to be motivated more by an intention to damage Merck Sharp & Dohme's reputation than to identify new issues under the Code which merited the Authority's attention.

The complainants provided no evidence that the 'DEXA Placements DIY Guide' was sent to all representatives. Merck Sharp & Dohme further noted that the complainants did not refer to the DIY guide in their original complaint and had not been able to provide a copy of it or the names of anyone who had received it. There was nothing in the complainants' letter to suggest they had ever seen the contents of the DIY guide or had ever heard of it before they read the case report.

The DIY guide was disclosed voluntarily by Merck Sharp & Dohme, even though it was clearly not an officially sanctioned document; the company had

previously provided evidence suggesting that it had not been seen by anyone outside the small 'Best Practice Team'. Merck Sharp & Dohme found only one copy of the presentation during the course of its previous investigation and even the employee on whose computer the document was found could not recall the circumstances in which it was produced or who produced it. None of the other employees interviewed had any knowledge of the document.

At the appeal hearing Merck Sharp & Dohme suggested that whoever had sent or presented the document to the 'Best Practice Team' might have been told in no uncertain terms that its contents were unacceptable and should not be used in representative briefings. In any event, Merck Sharp & Dohme found no evidence that it was ever used in such briefings or sent to other representatives. Merck Sharp & Dohme presented positive evidence that the DIY guide had not influenced the behaviour of any of the representatives it interviewed, which tended to confirm its conclusion and their recollection that they had not seen it. Merck Sharp & Dohme had included it in its response to Case AUTH/1859/6/06 because more than one representative sat on the 'Best Practice Team' and so it strictly fell into the definition of material shown to representatives. Merck Sharp & Dohme made it quite clear in its response to the original complaint and in its appeal submissions that it should not be regarded as representative training materials either official or unofficial.

The Appeal Board must be regarded as having taken all the evidence into account in reaching its decision in Case AUTH/1859/6/06 and the complaint now at issue contained no further substantiated evidence in relation to the DIY guide which the Appeal Board could have considered. Merck Sharp & Dohme did not understand how the complainants' new and unsubstantiated allegation that the DIY guide was used in official Merck Sharp & Dohme briefing material for new representatives would have changed the Appeal Board's conclusion because such an allegation was effectively answered in Merck Sharp & Dohme's evidence and the evidence of its employees. As part of the appeal hearing, Merck Sharp & Dohme brought six witness statements given by former Fosamax representatives and their managers and offered those in evidence to the Chairman. While the Appeal Board did not require these statements as part of its decision, it was undeniable that these six statements, signed with a statement of truth and drawn up to the evidential standards of the civil and criminal courts of the UK, should be given greater weight than further anonymous and unsubstantiated allegations made by unknown persons not participating in proceedings.

The only 'new' evidence that the complainants had provided was an extract from a Performance Planning Form. This form referred to DEXA placements as an example of a market expansion activity. In Merck Sharp & Dohme's initial response to Case AUTH/1859/6/06 it explained that, because osteoporosis was best diagnosed by a DEXA scan, and Fosamax Once Weekly was indicated in patients with diagnosed osteoporosis, it was likely that some patients scanned as a result of a DEXA machine placement in general practice would be diagnosed as osteoporotic, and a proportion of these patients would likely be prescribed Fosamax Once Weekly. This was a market expansion activity in the same way that measuring blood pressure or blood sugar or peak flow was a market expansion activity. If undiagnosed or untreated disease was identified, the market for treatment of that disease expanded. This could not be a breach of the Code. What would be a breach of the Code would be to link the provision or sponsorship of a diagnostic service with the use of a particular product once a diagnosis had been made. Merck Sharp & Dohme was adamant that there was no such linkage in the case of Fosamax Once Weekly.

Merck Sharp & Dohme also noted that it had referred to market expansion or market development in the documents it disclosed to both the Panel and the Appeal Board; it was not new evidence. These references appeared in slide sets which represented representative briefings about performance goals for 2002 and 2003. The complainants did not refer to these documents but to slides used as briefing materials by managers to managers. These did not fall within the scope of representative training materials and were not, therefore, disclosed to the Authority. The information those slides contained supported rather than detracted from Merck Sharp & Dohme's original defence to the allegations. The objective of the DEXA programme was to increase the diagnosis and treatment of patients at high risk of osteoporosis. This was exactly as Merck Sharp & Dohme explained it in its original response to the Authority. There was no reference to the improper linkage of the DEXA service provision and the use of Fosamax Once Weekly.

Merck Sharp & Dohme reiterated that it was inevitable that a substantial proportion of patients diagnosed in the course of the DEXA programme would be treated with Fosamax Once Weekly. It was an important therapeutic choice for physicians to consider for patients with osteoporosis and it was not at all surprising, or improper, that many patients identified by scanning would be prescribed Fosamax Once Weekly. The reference to market share in the objectives form and the management slides simply reflected an estimate of the proportion of patients diagnosed to be at high risk of osteoporosis who might be prescribed Fosamax Once Weekly after a scan. The choice of Fosamax Once Weekly or another treatment was entirely one for the treating physician to make and was not linked to the provision of the scan. Merck Sharp & Dohme submitted that through its representatives it was perfectly entitled to engage in other activities to promote Fosamax Once Weekly. The concept that representatives might make promotional calls to discuss Fosamax Once Weekly with GPs, which were kept quite separate from any other involvement, such as it was, with the provision of a DEXA placement, was clearly referred to in Merck Sharp & Dohme's response, both to the Panel and to the Appeal Board.

The Authority asked for some information on market share for Fosamax Once Weekly. As mentioned above, the reference to 'market share' simply reflected an

estimate of the proportion of patients diagnosed to be at high risk of osteoporosis who might be prescribed Fosamax Once Weekly after a scan. Merck Sharp & Dohme could not see how determining whether market share went up, down, or stayed the same had any bearing on the complaint that it had misled the Appeal Board or that such evidence could substantiate any breach of the Code. Merck Sharp & Dohme promoted Fosamax Once Weekly in 2002 and 2003; if activity were successful in either maintaining or increasing market share, this could not constitute a breach of the Code. The DEXA placement programme was not a promotional activity.

In conclusion, therefore, Merck Sharp & Dohme denied any breach of the 2003 Code in relation to the DEXA programme and denied misleading the Appeal Board on in Case Auth/1859/6/06

PANEL RULING

The Panel noted that in Case AUTH/1859/6/06, although the 'DEXA Placements DIY Guide' had been considered by both the Panel and the Appeal Board, due to its submission by Merck Sharp & Dohme, this was the first complaint the Authority had received about the document. It was on this basis that this case, Case AUTH/1974/3/07, had proceeded.

The Panel noted that the osteoporosis audit took place in 2002 to 2004. Clauses 2 and 18.1 of the 2001 Code were the same as the 2003 Code. Clause 9.1 of the 2001 Code included the requirement of Clause 9.1 of the 2003 Code that high standards must be maintained at all times. Thus the Panel considered the matter in relation to the 2003 edition of the Code.

The Panel noted that the complainants had stated that the Best Practice Team (which according to Merck Sharp & Dohme, was a small number of representatives, managers and marketing specialists) to whom the 'DEXA Placements DIY Guide' was presented would share ideas in relation to selling activities across the entire FROSST sales division. At the appeal in Case AUTH/1859/6/06 the Appeal Board had been alarmed at the document and concerned that anyone could have produced it. The Appeal Board had ruled that there was no evidence on the balance of probabilities that the 'DEXA Placements DIY Guide' had been used to train representatives or had otherwise been disseminated beyond the meeting or to indicate that it had otherwise influenced the behaviour of representatives in the field.

Turning to the case now before it the Panel noted the implied allegation that the 'DEXA Placements DIY Guide' had been shared amongst the FROSST representatives and not just the Best Practice Team. As substantiating evidence for their allegation the complainants had noted the statement 'Implementation of xxxx Market Expansion (e.g. DEXA placements) project placements ensuring an at least 40% diagnostic hit rate and at least 80% of all Osteoporotic patients identified are treated with Fosamax Once Weekly by December 2003' in a 2003 Performance Planning Form for FROSST sales representatives.

The complainants had also supplied two slides used to brief senior managers. One related to the DEXA placement programme and compared a number of features planned for 2002 and the outcome for the year to date (May 2002). The data stated that the planned number of osteoporotic patients was 33% of those scanned with the actual figure for the actual year to date being 30%. The planned number of 'Anecdotal Fosamax patients' was 80% whereas the year to date figure was 109%.

The second slide related to the objective for 2003 which was similar to 2002 ie 25-30 patients scanned per day with 30% being osteoporotic and 80% of those being treated with Fosamax Once Weekly.

The Panel noted Merck Sharp & Dohme's submission that the slides were used as briefing materials by managers to managers and were not within the scope of representative training materials and thus were not disclosed to the Authority but the content of the slides were part of briefings to representatives about their objectives.

The Panel considered that market expansion *per se* was not necessarily a breach of the Code. Any activity covered by the Code needed to comply with the Code. The Panel was concerned about the differences between the company's submission about the use of the 'DEXA Placements DIY Guide' and the complainant's comments about its use.

The Panel did not consider that the Performance Planning Form provided evidence that, on the balance of probabilities, the 'DEXA Placements DIY Guide' had been used to train representatives. Neither the form nor the slides referring to market share linked the offer of the service to the promotion of Fosamax Once Weekly. Thus the Panel ruled no breach of Clause 18.1 and hence Clauses 9.1 and 2. In reaching this decision the Panel did not refer to the confidential market share data. These rulings were appealed by the complainant.

APPEAL BY COMPLAINANTS

The complainants alleged that an email from a national sales manager enclosing a slide set, 'DXA Placement Programme, Recording Data within Genesys' provided further unequivocal evidence of inappropriate ethical conduct of the DEXA initiative through recording the outcome of the placements, in terms of patients' diagnoses, on Merck Sharp & Dohme's electronic territory management system (ETMS). The programme breached Clause 18 of the Code as the complainants had been informed from a significant number of sales representatives employed in the FROSST division at the time that they were instructed to ensure that 80% of patients identified as being osteoporotic were prescribed Fosamax on account of this target being incorporated into their annual objectives documents as previously provided.

The complainants noted the email sent from a

national sales manager for the FROSST GP sales division at the time, to the regional sales managers and copied to the then Fosamax marketing manager and the Fosamax business analyst. This email requested that regional sales managers instruct their sales representatives to enter data regarding the DEXA placement program into the company's ETMS. Whilst the complainants had copies of this email that had been forwarded to representatives, to provide the Authority with these copies would potentially expose their colleagues which was not acceptable in light of the potential impact on the individuals concerned. The wording of the email in question provided sufficient evidence to the Appeal Board that the presentation attached to the email was intended for implementation by, and disseminated to, all FROSST division sales representatives.

The slide presentation attached to the email told representatives how to enter data about the surgery DEXA placements into the ETMS system. The complainants alleged that such activities were completely inappropriate conduct for pharmaceutical sales representatives; why were representatives being provided with this audit data? Indeed, this activity in its own right potentially constituted a breach of Clause 18.1 of the 2003 Code. The supplementary information of Clause 18.1 Provision of Medical and Educational Goods and Services stated: '(v) Neither the company nor its medical/generic representatives may be given access to data/records that could identify, or could be linked to, particular patients'.

The complainants submitted that the majority of the DEXA placements in question involved a radiographer scanning 20-30 patients on one day at a particular surgery. Of these, routinely 6-10 patients would be identified as osteoporotic and requiring treatment. Whilst they did not have evidence for, and were not suggesting that sales representatives had access to individual patient records which would clearly be a breach of patient confidentiality, reporting of the diagnostic data to the sales representatives without the patient's prior consent could well represent a breach of the Code. One might never know whether the patients in question would be happy to have, albeit, anonymised data regarding their medical history entered onto a pharmaceutical company's data base.

Reporting of the diagnostic outcomes of the DEXA placements would presumably require the representatives to request this information directly from the surgery staff or from the radiographers themselves. The complainants noted that the DEXA placements were referred to as 'Fos Market Expansion Programmes' (presumably 'Fos' referring to Fosamax) rather than 'Osteoporosis Market Expansion Programmes'. This provided further evidence to support the previous allegations that senior management intended that the representatives responsible for implementing these programs would conceptually and practically link provision of the DEXA service to resultant sales of Fosamax.

The complainants alleged that the email referred to the fact that entry of data into the ETMS would permit analysis at both HQ and regional sales team levels. Not surprisingly, the analysis in question correlated Fosamax sales performance against DEXA activity in particular postal bricks.

The complainants noted that Merck Sharp & Dohme stated that the only 'new' evidence they had submitted above and beyond that previously reviewed in Case AUTH/1859/6/06 was an extract from a generic Performance Planning Form. The complainants clearly understood that Clause 18 of the Code permitted representatives to introduce a service to medicine to health professionals and they had not raised any objection to the concept of expanding the market in terms of the numbers of patients identified, diagnosed and treated. The complainants also accepted Merck Sharp & Dohme's point that a significant percentage of patients diagnosed with osteoporosis by the DEXA placement initiative would be treated with Fosamax as a consequence of the prevailing market dynamics. The issue with the conduct of this programme was the pressure placed upon sales representatives to ensure that 80% patients identified by DEXA placements, that they themselves had set-up, received Fosamax. The explicit link between market expansion programs and resultant product usage was stated in the Performance Planning Form:

> 'Implementation of xxxx Market Expansion (e.g. DEXA placements) projects ensuring an at least 40% diagnostic hit rate and at least 80% of all Osteoporotic patients identified are treated with Fosamax Once Weekly by December 2003.'

Representatives were required to select which practices would be offered the service, to act as a point of contact for the surgery with the radiographer and then to ensure that 80% of osteoporotic patients be treated with Fosamax. Clearly, a sales representative's primary responsibility was to sell product and thus all of their activities in the process of setting up a DEXA placement would be geared towards this objective. Obviously, this would influence which surgeries were chosen for provision of the service and inevitably encourage representatives to sell Fosamax to the GPs to whom they had provided a valuable diagnostic service. Armed with the diagnostic data from each placement, the national sales management team was able to apply an 80% target treatment rate for those patients identified as osteoporotic and correlate service to medicine placement against increased sales return in particular postal bricks, as intimated in the national sales manager's email. The email also stated that entry of the diagnoses data for the DEXA placements would enable the regional sales managers to analyse the impact of these programs – self-evidently, a regional sales manager was concerned with, and conducted analyses upon, sales performance; the analysis in question related to Fosamax sales performance associated with the DEXA placements.

The complainants noted that the reason they requested anonymity was self-evident from Merck Sharp & Dohme's conduct in responding to the complaint. Merck Sharp & Dohme blatantly refused to accept that it had breached the Code in this matter, regardless of

the fact that several staff members raised concerns about the conduct of this program at the time. The complainants drew parallels with this case and Case AUTH/1814/3/06 in that regard.

The complainants alleged that Merck Sharp & Dohme's counter submission that they were motivated by an intention to damage Merck Sharp & Dohme's reputation was remarkable. The unethical actions led by Merck Sharp & Dohme senior management that resulted in the company's suspension from the ABPI during 2006 irreversibly damaged collective and individual reputations, at least for the foreseeable future. The intention of raising concerns regarding ethical conduct across Merck Sharp & Dohme's business with the Panel was to purge a company that the complainants were once proud to serve, of unethical practice once and for all. Upon reading the case report for Case AUTH/1859/6/06 the complainants were very disappointed to realise that the new open and honest ethical culture presented during the last 12 months at Merck Sharp & Dohme in response to Case AUTH/1814/3/06, was not prepared to expose all of the skeletons in the corporate closet. The new senior management team had an opportunity to reveal to the Panel that the compliance culture at Merck Sharp & Dohme had been institutionally flawed until Case AUTH/1814/3/06. This senior management team had not grasped that opportunity and rather mis-represented historical conduct in relation to its original defence of Case AUTH/1859/6/06. Worse still, when the Panel correctly ruled a breach of Clause 18.1 and 2, Merck Sharp & Dohme senior management misled the Appeal Board.

The complainants noted that without revealing their identities or the identities of colleagues that had provided information regarding the conduct of the DEXA placement initiative they were unable to provide documentary evidence to counter Merck Sharp & Dohme's claims regarding the limited dissemination of the 'DEXA Placements DIY Guide'. Indeed, a recent company-wide records management initiative to clean-up and delete 'non-essential' historical files/emails/etc meant that most records of the company's programs at this time were lost. The complainants nonetheless submitted that they were sincerely and honestly convinced that all representatives in the FROSST division during 2002 to 2004 were instructed to ensure that the DEXA placement programme directly contributed to growth of their territories' Fosamax sales. This was supported by the additional evidence submitted regarding reporting of diagnostic outcomes of the DEXA placements on Merck Sharp & Dohme's ETMS.

COMMENTS FROM MERCK SHARP & DOHME

Merck Sharp & Dohme stated that it was remarkable, given that the essence of the complaint was that it had misled the Appeal Board in Case AUTH/1859/6/06, that the appellants sought to rely on two documents, both of which had already been disclosed voluntarily by Merck Sharp & Dohme and were before the Appeal Board when it considered Merck Sharp & Dohme's appeal in Case AUTH/1859/6/06. Had the complainants taken part in the earlier appeal, as they were entitled to do and had done on this occasion, they would have been able to make submissions on both these documents, at the proper time, before and during the appeal in Case AUTH/1859/6/06. The Appeal Board's ability to make a fair and final ruling must be compromised if complainants were allowed to manipulate the Authority's procedures in this way. It was also the case that the complainants on this occasion, relied on a document (already disclosed by Merck Sharp & Dohme itself in any event) a copy of which they submitted to the Authority after the date by which Merck Sharp & Dohme's response to the complaint had been received by the Authority. Merck Sharp & Dohme had had no opportunity to make submissions on this aspect of the appeal until this letter.

Merck Sharp & Dohme submitted that the complainants had relied on a PowerPoint presentation telling representatives how to enter certain data relating to the DEXA programme into the company's ETMS. This was simply another copy of a document that Merck Sharp & Dohme submitted to the Appeal Board for its appeal against the Panel's ruling in Case AUTH/1859/6/06. The copy that Merck Sharp & Dohme submitted was provided by one of the recipients named on the covering email from a national sales manager. The complainants seemed unaware that the Appeal Board had already seen this document and read and heard submission on it from Merck Sharp & Dohme.

Merck Sharp & Dohme had referred to the document at the appeal to show that no instructions were given to enter sales metrics onto the ETMS as alleged in Case AUTH/1859/6/06. Merck Sharp & Dohme noted that there was simply no field in the ETMS in which sales metrics could have been entered. It was true that the ETMS recorded how many DEXA placements had been made and their location. Merck Sharp & Dohme could speculate, knowing the average rate of scanning and the incidence of osteoporosis and osteopenia generally to be found in the at-risk population, as to how the market for osteoporosis treatments, including Fosamax, could expand. This did not, however, involve the disclosure by either practice staff or prescribers of any confidential data. The sales representatives would simply have to know whether the radiographers operating the DEXA machines actually attended the practice as arranged; the rest of the data could simply be derived as 'best guesses' from known metrics, such as the usual rate of scanning. In some cases the radiographers might have told representatives how many scans had been performed. This was a sensible means of keeping the service provision under review. It would clearly not be sensible for Merck Sharp & Dohme to invest in the service if very few patients were benefiting from it or if organisational problems could be identified which were preventing at-risk patients from taking advantage of it. Such considerations could not be described as relating to product promotion nor did they amount to a breach of Clause 18.1 of the 2003 Code. There was and never

had been any suggestion of inducements being offered to any prescriber or member of the health professions in connection with the DEXA service.

Merck Sharp & Dohme noted that in its appeal in Case AUTH/1859/6/06, it brought to the hearing signed witness statements from a range of representatives from the FROSST team that described to the best of their recollection what involvement they had had with the service. In no case, had this included entering sales metrics on the ETMS. The complainants, on the other hand, merely offered not only unattributed and untestable hearsay but also pure conjecture.

Merck Sharp & Dohme noted that the second element of the complainants' appeal returned yet again to the set of slides described as the 'DEXA placements DIY Guide', which Merck Sharp & Dohme disclosed with its response to Case AUTH/1859/6/06. These slides were not authorized by Merck Sharp & Dohme and did not represent any official training provided to representatives. The Appeal Board accepted Merck Sharp & Dohme's submission that there was no evidence that these slides had ever been used to train representatives generally and might not have been seen by anyone beyond a small group of perhaps ten managers and representatives. In the appeal in Case AUTH/1974/3/07 the complainants had nothing new to say about these slides; they merely recorded their 'conviction' that their assumptions were true. These assumptions appeared to be based not on their own experiences or observations but allegedly on those of unnamed colleagues who were not party to the complaint. Merck Sharp & Dohme had already noted in its response that the complainants did not refer to these slides until after they had seen them referred to in the case report for Case AUTH/1859/6/06. This strongly suggested that they had no knowledge at all of their existence before then. This in itself tended to support Merck Sharp & Dohme's submissions that there was no evidence that the slides were disseminated to representatives generally.

FURTHER COMMENTS FROM THE COMPLAINANTS

The complainants noted Merck Sharp & Dohme's view that they were attempting to manipulate the Authority's procedures. The complainants assured the Authority that this was absolutely not so and that Case AUTH/1974/3/07 stemmed from their collective outrage at the substance of Merck Sharp & Dohme's appeal in Case AUTH/1859/6/06 which only became apparent to them on publication of the case report.

The complainants noted that Merck Sharp & Dohme had stated that data entry on the ETMS relating to diagnostic outcomes of patients that attended the DEXA placements was based upon 'best guesses'. This was not so. Representatives were asked to ascertain this data from either the practice staff or the radiographer for every DEXA placement that took place. The complainants noted that in the slide presentation relating to data entry regarding the DEXA placements, representatives were not advised to 'best guess' this information. If the fields were created in the ETMS system with the intention of being filled by best guesses, why did they exist in the first place? On this basis, all that would be required to estimate the number of patients in each diagnostic category, and therefore estimate how many patients were treated with Fosamax, could be derived from the total number of patients scanned on the day(s).

The complainants alleged that Merck Sharp & Dohme also failed to comment upon why the ETMS marker relating to the DEXA placement was referred to as 'Fos Market Expansion Programmes' rather than 'Osteo(porosis) Market Expansion Programmes'. The complainants noted their previous comments regarding patient consent. Patients' diagnostic data was proactively requested by Merck Sharp & Dohme senior management for entry into the ETMS by representatives as demonstrated in the presentation attached to the email to the FROSST regional sales management group. Why would the osteoporosis/ osteopenia data fields have been created if they were to be populated with guess work? A knowledge of the number of osteoporotic diagnoses would allow for application of the 80% Fosamax treatment target set for representatives in their annual Performance Planning Grid objectives document that was provided to the Panel.

The complainants sincerely hoped that the Appeal Board would re-instate the original rulings in relation to Case AUTH/1859/6/06 as the Panel had arrived at the right verdict first time around.

APPEAL BOARD RULING

The Appeal Board noted that in Case AUTH/1859/6/06 the complainants had been anonymous and not contactable. This was unfortunate as some of the complainants' current allegations could have been addressed if they had been involved in the appeal in Case AUTH/1859/6/06. The complaints procedure was designed to fully involve both parties. One of the unfortunate but unavoidable consequences of truly anonymous complaints was that the complainant forfeited his right as regards the appeal process.

The complainants had read the published outcome in Case AUTH/1859/6/06 and had shortly thereafter submitted the current complaint which included allegations about the DEXA Placement DIY Guide and two new documents, the Performance Planning Form and two slides on the national overview of the DEXA programme. As the complaint satisfied the criteria set out in Paragraph 5.1 of the Constitution and Procedure it was allowed to proceed.

The Appeal Board was concerned that the complainants had not taken part in the appeal in Case AUTH/1859/6/06 but instead had submitted a fresh complaint.

The Appeal Board noted the complainant's request that the Appeal Board ruling in Case AUTH/1859/6/06 be

overturned. This was not possible, that case had completed.

The Appeal Board noted that the allegation now being considered was that Merck Sharp & Dohme had misled the Appeal Board in the previous case. The Appeal Board considered that this was a serious allegation but that little evidence had been provided other than that previously considered by the Appeal Board as part of the appeal in Case AUTH/1859/6/06.

The Appeal Board noted Merck Sharp & Dohme accepted that the reference to 'FOS Market Expansion Programme' was unfortunate. Further the company stated that whilst it was prepared to accept that the Performance Planning Form might have been used, it had no evidence either way as to whether it was an authentic document. Merck Sharp & Dohme had not found the document when responding to Case AUTH/1859/6/06. Merck Sharp & Dohme stated that it would have expected to have found it.

The Appeal Board did not accept that the documents supplied by the complainants, that were not submitted in the previous case, demonstrated that, on the balance of probabilities, the Appeal Board had been misled. In the Appeal Board's view no credible evidence had been supplied.

The Appeal Board upheld the Panel's ruling that the Performance Planning Form provided no evidence that, on the balance of probabilities, the 'DEXA Placements DIY Guide' had been used to train representatives. Neither the form nor the slides referring to market share linked the offer of the service to the promotion of Fosamax Once Weekly. Thus the Appeal Board upheld the Panel's ruling of no breach of Clause 18.1 and hence no breach of Clauses 9.1 and 2.

Following its consideration of this case the Appeal Board was concerned about the difficulties of dealing with anonymous complaints particularly when a complainant who had been non contactable made a subsequent complaint. The Appeal Board was also concerned that this might lead to an abuse of process.

2 Representative call rates

COMPLAINT

The complainants noted the following call rates cited in the Performance Planning Form:

3 'Ensure 100% coverage and frequency of 6 for 1:1 contacts on Super Targets (n=40) by December 2003

4 Ensure 80% coverage and frequency of 4 for 1:1 contacts on Targets (n=80) by December 2003.'

The issue of excessive pressure imposed by companies on representatives to ignore the Code restriction of three unsolicited calls per year had recently been highlighted in the industry press. Here was clear evidence that this practice had been imposed by senior management at Merck Sharp & Dohme for many years.

When writing to Merck Sharp & Dohme, the Authority asked it to respond in relation to Clauses 15.2, 15.4 and 15.9.

RESPONSE

Merck Sharp & Dohme noted that the complainants' final, and only new, allegation related to call rates on the Fosamax target audience in 2003, as referred to in an unidentified representative's Performance Planning Form. The Performance Planning Form related to call rates generally, rather than only or specifically to unsolicited call rates. The complainants had not provided any evidence that FROSST representatives were pressured to breach Clause 15.4 in respect of unsolicited call rates. There was no breach of the Code if representatives made promotional calls or contacts with doctors at their request and there was no breach of the Code if they were rewarded for doing so. The call rates assessed in the representative's objectives analysis could include contacts of both types. Merck Sharp & Dohme provided a copy of a presentation made to trainee representatives at their foundation training in 2003 which explained the requirements of the Code in relation to call rates. Merck Sharp & Dohme also enclosed relevant extracts from the 2003 Sales Incentive Plan for the relevant representatives; for the purposes of bonus calculation, the total volume of contact activity of all types was measured against an industry average. For completeness, Merck Sharp & Dohme provided a copy of its 2006 Sales Incentive Plan, which now included a prominent reference to Clause 15.4.

In conclusion, Merck Sharp & Dohme denied any breach of the Code.

PANEL RULING

The Panel noted that the complainants had referred to two activity objectives cited on the Performance Planning Form. Firstly 'Ensure 100% coverage and frequency of 6 for 1:1 contacts on Super Targets (n=40) by December 2003' and 'Ensure 80% coverage and frequency of 4 for 1:1 contacts on Targets (n=80) by December 2003'.

The Panel noted that the supplementary information to Clause 15.4 of the 2003 Code stated that the number of calls made on a doctor each year should normally not exceed three on average excluding attendance at group meetings and the like, a visit requested by the doctor or a visit to follow up a report of an adverse reaction. Thus although a representative might proactively call on a doctor or other prescriber three times a year, the number of contacts with that health professional in a year might be more than that. In the Panel's view material should clearly distinguish between expected call rates and expected contact rates.

The Panel noted that a 2003 presentation on the requirements of the Code, used with representatives,

set out the requirements of Clause 15. Nonetheless the Performance Planning Form was a stand alone document. The Panel noted that the form referred to contacts on targets and not call rates. The consequence of the form was that in addition to three 1:1 calls, representatives had to have three 1:1 contacts with targets as a result of meetings, requested call backs etc. As an additional activity objective the Performance Planning Form also required representatives to 'Increase 1:1 GP activity (both call volume and call rate) relative to 2002 performance'. There was no mention that if 2002 performance was a call rate of 3 it was not possible to increase the call rate without breaching the Code.

The Panel considered that without further explanation that the 2002 call rate could not be increased beyond 3, the Performance Planning Form advocated a course of action which was likely to breach the Code. A breach of Clause 15.9 was ruled. This ruling was not appealed. The Panel noted that a document detailing a 2006 salesforce incentive scheme clearly referred to the requirements of Clause 15.4 regarding call frequency.

Complaint received	**1 March 2007**
Case completed	**14 June 2007**

GENERAL PRACTITIONER/DIRECTOR v SANOFI-AVENTIS

Acomplia journal advertisement

A general practitioner complained about an advertisement for Acomplia (rimonabant) produced by Sanofi-Aventis and published in Update. As this involved an alleged breach of undertaking, that element of the case was taken up by the Director as it was the responsibility of the Authority to ensure compliance with undertakings.

The complainant stated that the advertisement identified HbA1c, HDL-C and triglycerides as cardiometabolic risk factors. It also stated that, in addition to improvements in weight, Acomplia demonstrated significantly greater improvements in these particular cardiometabolic risk factors. The statement clearly suggested that Acomplia had a direct effect on these cardiometabolic risk factors independent of weight reduction. The advertisement continued 'An estimated 50% of the effects of Acomplia on these Cardiometabolic Risk Factors are beyond those expected from weight loss alone'.

The complainant alleged that the advertisement was misleading as it invited doctors to prescribe Acomplia outside its specific indication for treating obesity in patients with associated risk factors such as type 2 diabetes and dyslipidaemia ie for the primary and sole purpose of addressing HbA1c, HDL-C and triglycerides. There was no evidence to show that Acomplia had a direct effect on these cardiometabolic risk factors as opposed to an indirect effect mediated through weight reduction. Was it reasonable for an advertisement to invite unfounded speculation as to where the other 50% of the effect of Acomplia on cardiometabolic risk factors arose from?

The complainant alleged that the advertisement was misleading as it implied that HbA1c, HDL-C and triglycerides were the only markers of cardiometabolic risk that were relevant and needed to be addressed in obese patients with diabetes or dyslipidaemia. Total-C and LDL-C were also well recognized important cardiometabolic risk factors, however the impact of Acomplia on these was not referred to. Could this be due to the fact that the summary of product characteristics (SPC) stated that generally Acomplia 20mg had no significant effect on Total-C or LDL-C levels. Surely this omission was misleading given the emphasis on the importance of addressing cardiometabolic risk factors and the positive effect of Acomplia on these?

The Panel considered that an undertaking was an important document. It included an assurance that all possible steps would be taken to avoid similar breaches of the Code in the future. It was very important for the reputation of industry that companies complied with undertakings.

The Panel noted that the advertisement at issue in the previous case, Case AUTH/1871/7/06, featured an outline of an overweight patient with the statement 'Cardiometabolic risk factors in overweight patients can be where you least expect them'. The right hand side was headed 'Discover Acomplia' followed by the licensed indication. This was followed by reference to cardiometabolic risk factors listing established risk factors as elevated blood glucose, high LDL-C and high blood pressure and emerging risk factors as low HDL-C, abdominal obesity, high triglycerides, insulin resistance and inflammatory markers. These were followed by information about reductions in weight and waist circumference. The final part of this section stated that Acomplia compared to placebo demonstrated significantly greater improvements in glycaemic control, HbA1c, increases in HDL-C and reductions in triglycerides. This was followed by the claim 'An estimated 50% of the effects of Acomplia on Cardiometabolic Risk Factors are beyond those expected from weight loss alone'. In Case AUTH/1871/7/06, the Panel (and upon appeal by Sanofi-Aventis, the Appeal Board) had considered that the advertisement had not placed the cardiometabolic risk factors sufficiently within the context of the licensed indication. In the Panel's view the most prominent message was that Acomplia was to be prescribed for its effects on cardiometabolic risk factors in overweight patients and this was inconsistent with the SPC. A breach of the Code was ruled which was upheld on appeal. The Panel did not accept the submission that the claim 'An established 50% of the effects of Acomplia on Cardiometabolic Risk Factors are beyond those expected from weight loss alone' applied to three risk factors, HbA1c, HDL-C and triglycerides; it appeared to apply to them all. The claim was misleading in this regard and thus not capable of substantiation. Breaches of the Code had been ruled which on appeal by Sanofi-Aventis were upheld.

The advertisement at issue in the present case, Case AUTH/1976/3/07, featured an outline of an overweight person with the prominent claim 'In obese patients cardiometabolic risk factors can increase the problem'. Adjacent text introduced Acomplia by reference to its licensed indication. Reference was made to the impact of obesity on cardiometabolic risk factors which contributed to the development of type-2 diabetes and cardiovascular disease. The final paragraph

discussed improvements in three cardiometabolic risk factors: improvements in glycaemic control: increases in HDL-C and reductions in triglycerides and concluded 'An estimated 50% of the effects of Acomplia on these Cardiometabolic Risk Factors are beyond those expected from weight loss alone'. A strapline beneath the product logo in the bottom right-hand corner of the advertisement read 'It's not what you lose. It's what you gain'.

The Panel considered that the advertisement was materially different to that considered in Case AUTH/1871/7/06. The prominent claim superimposed over the outline of the overweight patient began 'In obese patients …' thus making the patient population clear at the outset. The final paragraph made it clear that the cardiometabolic risk factors were those three listed. The Panel considered the changes to the present advertisement were such that it was not caught by the undertaking given in the previous case. No breach of the Code was ruled.

The Panel considered that there was a difference between promoting a product for a licensed indication and promoting the benefits of using that product, albeit that some of these benefits were mentioned in the SPC.

Overall, the Panel did not accept that the advertisement invited the prescription of Acomplia for the primary and sole purpose of addressing of HbA1c, HDL-C and triglycerides as alleged. The prominent claim 'In obese patients cardiometabolic risk factors can increase the problem' made the patient population clear. The adjacent text began by stating the licensed indication at the outset. Obesity was described as having an impact on multiple cardiometabolic risk factors. The Panel queried whether the strapline 'It's not what you lose. It's what you gain' gave sufficient emphasis to weight loss. Nonetheless on balance the Panel considered that the overall tone of the advertisement placed the cardiometabolic risk factors sufficiently within the context of Acomplia's licensed indication. No breach of the Code was ruled.

The Panel did not consider that the advertisement misleadingly stated or implied that those cardiometabolic risk factors mentioned were the only ones relevant and needed to be addressed in obese patients with diabetes or dyslipidaemia. Nor did the Panel consider that the failure to refer to the statement in the Acomplia SPC that, 'Generally Acomplia 20mg had no significant effect on Total-C or LDL-C levels' was misleading as alleged. No breach of the Code was ruled.

A general practitioner complained about a journal advertisement (ref ACO 07/1049) for Acomplia (rimonabant) produced by Sanofi-Aventis and published in Update, March 2007. As this case involved an alleged breach of undertaking, that element of the case was taken up by the Director as it was the responsibility of the Authority to ensure compliance with undertakings.

COMPLAINT

The complainant stated that the advertisement identified HbA1c, HDL-C and triglycerides as cardiometabolic risk factors. It also stated that, in addition to improvements in weight, Acomplia demonstrated significantly greater improvements in these particular cardiometabolic risk factors. The statement clearly suggested that Acomplia had a direct effect on these cardiometabolic risk factors independent of weight reduction.

The advertisement continued by claiming that 'An estimated 50% of the effects of Acomplia on these Cardiometabolic Risk Factors are beyond those expected from weight loss alone'.

The complainant alleged that the advertisement was misleading as it invited doctors to prescribe Acomplia outside its specific indication for treating obesity in patients with associated risk factors such as type 2 diabetes and dyslipidaemia ie for the primary and sole purpose of addressing HbA1c, HDL-C and triglycerides. The latter suggestion was also invited by the wording that some of its effects were due to effects beyond those expected from weight loss alone.

There was no evidence to show that Acomplia had a direct effect on these cardiometabolic risk factors as opposed to an indirect effect mediated through weight reduction.

Was it reasonable for an advertisement to invite unfounded speculation as to where the other 50% of the effect of Acomplia on cardiometabolic risk factors arose from? If this was acceptable then it would seem reasonable for the statins to promote their many well documented plieotropic effects outside their specific indications?

The complainant alleged that the advertisement was misleading as it implied that HbA1c, HDL-C and triglycerides were the only markers of cardiometabolic risk that were relevant and needed to be addressed in obese patients with diabetes or dyslipidaemia. Total-C and LDL-C were also well recognized important cardiometabolic risk factors, however the impact of Acomplia on these was not referred to. Could this be due to the fact that the summary of product characteristics (SPC) stated that generally Acomplia 20mg had no significant effect on Total-C or LDL-C levels. Surely this omission was misleading given the emphasis on the importance of addressing cardiometabolic risk factors and the positive effect of Acomplia on these?

When writing to Sanofi-Aventis, the Authority asked it to respond in relation to Clauses 7.2 and 7.4 of the Code and, in addition, to Clauses 2, 9.1 and 22.

RESPONSE

Sanofi-Aventis noted that the complainant raised an issue that the Authority had already considered, ie the claim that 'An estimated 50% of the effects of

Acomplia … are beyond those expected from weight loss alone'. The question as to whether this claim was acceptable arose in Case AUTH/1871/7/06, and Sanofi-Aventis provided information that supported this claim, which was a quotation from the marketing authorization. Although the Panel accepted that this statement was firmly evidence-based and acceptable with respect to three risk factors (HbA1c, HDL-C and triglycerides), the lack of an explicit link between the statement and these three risk factors was found to be a fault. With this in mind, the advertisement now at issue made this explicit link - the list of three risk factors was followed immediately by the claim 'An estimated 50% of the effects of Acomplia **on these cardiometabolic risk factors** are beyond those expected from weight loss alone' [emphasis added by Sanofi-Aventis]. Sanofi-Aventis believed that this amendment removed all ambiguity as to the weight-independent effects of Acomplia. It had previously been accepted that this claim was capable of substantiation (in accordance with Clauses 7.2 and 7.4), and the text had been specifically amended to address the shortcomings in the previous case (in accordance with Clause 22). Sanofi-Aventis was satisfied therefore that in this respect high standards had been maintained.

Sanofi-Aventis noted that the complainant was concerned that the advertisement sought to position Acomplia as a treatment for risk factors in the absence of obesity, by virtue of the fact that it 'invited doctors to prescribe Acomplia outside its specific indication for treating obesity in patients with associated risk factors', partly in light of the statement regarding the effects on risk factors being partially independent of weight loss (although this had been deemed acceptable). This was related to the complaint in Case AUTH/1871/7/06 in which it was considered that a previous advertisement implied that Acomplia was to be prescribed for its effects on risk factors rather than obesity; the current advertisement addressed these shortcomings. Sanofi-Aventis did not agree that the advertisement sought to encourage prescription in non-obese patients because:

- The product licence specifically identified patients (body mass index (BMI) 27-30kg/m^2) with risk factors (such as type 2 diabetes and dyslipidaemia) as being the specific population in whom the product was indicated. In view of this, Sanofi-Aventis considered it appropriate and essential to discuss risk factors - indeed a failure to do so would leave it open to the criticism that it was seeking to promote outside of the licensed indication by failing to draw attention to a patient group in whom the presence of risk factors was an absolute prerequisite to treatment.
- In contrast to the previous advertisement, the current advertisement had a primary focus on obesity. Following criticism of the previous banner headline in which 'Cardiometabolic Risk Factors' was the initial and most prominent text, this had been re-worked to open with the phrase 'In Obese Patients', making obesity the most prominent message and the focus of this advertisement. This sentence continued to refer to cardiometabolic risk factors, but this mention was specifically linked to obesity.
- The uppermost text on the right hand side of the page outlined the indication in accordance with the marketing authorization, and was followed by a sentence outlining the effect that obesity had on cardiometabolic risk factors.
- Below this, the effects of Acomplia were outlined, initially on weight (as its primary effect), and then on the three cardiometabolic risk factors referred to in the licence, agreed to be acceptable in the previous case (Case AUTH/1871/7/06). These effects were again specifically expressed in the context of being in addition to the effects of weight, indicating that this was in the primary context of the treatment of obesity.
- There was no mention of effect on cardiometabolic risk factors in isolation (ie outside of the context of treatment of obesity/weight reduction).

In summary, this advertisement had been re-written with the focus on obesity and weight loss as the primary message, in accordance with both the SPC and the findings of the Panel in respect to the previous version. These were now the leading messages in all sections of the advertisement, and in particular obesity was the most prominent component of the banner headline. Most importantly, there was no mention of cardiometabolic risk factors without these having been prefaced by statements on obesity or weight - these being an essential requirement for treatment in patients with a BMI 27-30kg/m^2. For these reasons Sanofi-Aventis disagreed that this advertisement promoted Acomplia for the treatment of risk factors in the absence of obesity - the very opposite was stated in the first paragraph of text (where treatment was advocated in accordance with the licence on the basis of BMI plus or minus risk factors). Sanofi-Aventis believed that this advertisement was consistent with the product licence, took into account the undertaking to comply with the findings of Case AUTH/1871/7/06 (in accordance with Clause 22), and that high standards had been maintained.

Finally, Sanofi-Aventis noted that the complainant suggested that omission of risk factors other than the three in the advertisement, misleadingly implied that Acomplia was to be used for the treatment of all risk factors. This opinion was contrary to that of the Panel in Case AUTH/1871/7/06, in which it was decided that the mention of risk factors beyond the three in the SPC implied that Acomplia would have effects on all risk factors. The criticism that the original extended list was misleading had been addressed by removing reference to risk factors other than the three specifically affected by Acomplia. This would be expected to address the concerns of the Panel, but had now given rise to criticism that the list of three risk factors was misleading through being too short. Faced with these contradictory opinions, Sanofi-Aventis considered that its decision to remove reference to all risk factors other than the three mentioned above was a responsible and reasonable approach, as this was consistent with the SPC and addressed the Panel's concerns in Case AUTH/1871/7/06. It would be impractical to include a list of risk factors unaffected by Acomplia - as would be the case with all medicines

a list of conditions or parameters upon which no effect had been demonstrated would be of prohibitive length, and there would be no rational basis to select a shortened list from these. With this respect, Sanofi-Aventis again considered that the advertisement was consistent with the product licence, took into account the undertaking to comply with the findings of Case AUTH/1871/7/06 (in accordance with Clause 22), and that high standards had been maintained.

In conclusion, Sanofi-Aventis believed that the advertisement in question was consistent with the product licence, all claims regarding Acomplia were substantiable (entirely by data contained within the SPC), and most importantly it took into account the outcome of Case AUTH/1871/7/06. In view of this, Sanofi-Aventis was confident that no breach of Clauses 7.2, 7.4 or 22 had occurred, that high standards had been maintained throughout and that there was no reason for particular censure.

PANEL RULING

The Panel considered that an undertaking was an important document. It included an assurance that all possible steps would be taken to avoid similar breaches of the Code in the future. It was very important for the reputation of industry that companies complied with undertakings.

The Panel noted that the advertisement at issue in the previous case, Case AUTH/1871/7/06, featured an outline of an overweight patient with the statement 'Cardiometabolic risk factors in overweight patients can be where you least expect them'. The right hand side was headed 'Discover Acomplia' followed by the licensed indication. This was followed by reference to cardiometabolic risk factors listing established risk factors as elevated blood glucose, high LDL-C and high blood pressure and emerging risk factors as low HDL-C, abdominal obesity, high triglycerides, insulin resistance and inflammatory markers. These were followed by information about reductions in weight and waist circumference. The final part of this section stated that Acomplia compared to placebo demonstrated significantly greater improvements in glycaemic control, HbA1c, increases in HDL-C and reductions in triglycerides. This was followed by the claim 'An estimated 50% of the effects of Acomplia on Cardiometabolic Risk Factors are beyond those expected from weight loss alone'. In Case AUTH/1871/7/06, the Panel (and upon appeal by Sanofi-Aventis, the Appeal Board) had considered that the advertisement had not placed the cardiometabolic risk factors sufficiently within the context of the licensed indication. In the Panel's view the most prominent message was that Acomplia was to be prescribed for its effects on cardiometabolic risk factors in overweight patients and this was inconsistent with the SPC. A breach of Clause 3.2 of the Code was ruled which was upheld on appeal. The Panel did not accept the submission that the claim 'An established 50% of the effects of Acomplia on Cardiometabolic Risk Factors are beyond those expected from weight loss alone' applied to three risk factors, HbA1c, HDL-C and triglycerides; it appeared to apply to them all. The claim was misleading in this regard and thus not capable of substantiation. Breaches of Clauses 7.2 and 7.4 were ruled which were upheld on appeal.

The advertisement at issue in the present case, Case AUTH/1976/3/07, featured an outline of an overweight person with the prominent claim 'In obese patients cardiometabolic risk factors can increase the problem'. Adjacent text introduced Acomplia by reference to its licensed indication. Reference was made to the impact of obesity on cardiometabolic risk factors which contributed to the development of type-2 diabetes and cardiovascular disease. The final paragraph discussed improvements in three cardiometabolic risk factors: improvements in glycaemic control: increases in HDL-C and reductions in triglycerides and concluded 'An estimated 50% of the effects of Acomplia on these Cardiometabolic Risk Factors are beyond those expected from weight loss alone'. A strapline beneath the product logo in the bottom right-hand corner of the advertisement read 'It's not what you lose. It's what you gain'.

The Panel considered that the advertisement at issue was materially different to that considered in Case AUTH/1871/7/06. The prominent claim superimposed over the outline of the overweight patient began 'In obese patients …' thus making the patient population clear at the outset. The final paragraph made it clear that the cardiometabolic risk factors were those three listed. The Panel considered the changes to the present advertisement were such that it was not caught by the undertaking given in the previous case. No breach of Clause 22, and thus Clauses 9.1 and 2 was ruled.

The Panel considered that there was a difference between promoting a product for a licensed indication and promoting the benefits of using that product albeit that some of these benefits were mentioned in the SPC.

Section 5.1 of the SPC referred to a study in type 2 diabetic patients who were overweight or obese which estimated that approximately half of the mean improvement in HbA1c in patients receiving Acomplia 20mg was beyond that expected from weight loss alone. In the non-diabetic study it was estimated that approximately half of the observed improvement in HDL-C and triglycerides in patients who received Acomplia 20mg was beyond that expected from weight loss alone.

Overall, the Panel did not accept that the advertisement invited doctors to prescribe Acomplia for the primary and sole purpose of addressing of HbA1c, HDL-C and triglycerides as alleged. The prominent claim 'In obese patients cardiometabolic risk factors can increase the problem' made the patient population clear. The adjacent text began by stating the licensed indication at the outset. Obesity was described as having an impact on multiple cardiometabolic risk factors. The Panel queried whether the strapline 'It's not what you lose. It's what

you gain' gave sufficient emphasis to weight loss. Nonetheless on balance the Panel considered that the overall tone of the advertisement placed the cardiometabolic risk factors sufficiently within the context of Acomplia's licensed indication. No breach of Clauses 7.2 and 7.4 was ruled.

The Panel did not consider that the advertisement misleadingly stated or implied that those cardiometabolic risk factors mentioned were the only ones relevant and needed to be addressed in obese patients with diabetes or dyslipidaemia. Nor did the Panel consider that the failure to refer to the statement in the Acomplia SPC that, 'Generally Acomplia 20mg had no significant effect on Total-C or LDL-C levels' was misleading as alleged. No breach of Clauses 7.2 and 7.4 was ruled.

Complaint received **15 March 2007**

Case completed **21 May 2007**

CASE AUTH/1978/3/07

PRIMARY CARE TRUST ASSISTANT DIRECTOR OF MEDICINES MANAGEMENT v TAKEDA

Amias mailing

The assistant director, medicines management, at a primary care trust (PCT) complained about a mailing produced by Takeda entitled 'Reducing Hypertension Spend in … PCT' which discussed the potential local cost savings if Amias (candesartan) was prescribed.

The mailing had been sent without any cover note or identification to each GP in the PCT. The information had been used and presented in a misleading way. GPs had contacted the complainant to ask if this had been officially endorsed by the PCT as the presentation appeared to make it so.

The Panel noted that the leaflet, 'Reducing Hypertension Management Spend in … PCT' was subtitled 'A review of the current financial status of … PCT and a strategy to reduce practice spend in the treatment of hypertension'. The inside front cover discussed a financial review and asked what steps could be taken to: assist in the achievement of this year's financial targets; help patients with hypertension and reduce prescribing costs. The third page was headed 'How To Reduce Angiotension Reception Blocker (ARB) Spend in … PCT by up to £106,000/1,000 patients treated for a year', and discussed the cost of prescribing Amias compared with losartan and valsartan. There was no indication that it had been produced by Takeda or that it was promotional material for Amias. The inclusion of prescribing information on the back cover did not suffice in this regard.

The Panel considered that the source of the leaflet was not sufficiently clear. Whilst the leaflet did not use the logo of the PCT it nonetheless referred to the organisation ten times. Conversely Takeda's name appeared only twice, in small print on the back page in the prescribing information. According to the complainant a number of GPs had queried whether the leaflet had been endorsed by the PCT as its presentation appeared to make it so. The Panel considered that the failure to indicate at the outset that this was company produced material gave the impression that the leaflet was something other than promotional material and was misleading and disguised in this regard. Breaches of the Code were ruled.

The assistant director, medicines management, at a primary care trust (PCT) complained about a mailing (ref TA070111) produced by Takeda UK Ltd. The mailing was entitled 'Reducing Hypertension Spend in … PCT' and discussed the potential local cost savings if Amias (candesartan) was prescribed.

COMPLAINT

The complainant stated that the mailing had been sent without any cover note or identification to each GP in the PCT. Whilst the information had been accessed from public documents, it had been used and presented in a misleading way. A number of GPs had contacted the complainant to ask if this had been officially endorsed by the PCT as the presentation appeared to make it so, especially as there was no company logo or covering letter to identify the author/source.

The complainant was uncertain as to whether any code had been breached but the PCT found this method of promotion unacceptable.

When writing to Takeda, the Authority asked it to respond in relation to Clauses 7.2 and 10.1 of the Code.

RESPONSE

Takeda stated that it was obviously concerned that a health professional considered that the piece was misleading and it took this allegation very seriously. It was absolutely not Takeda's intention for any of its materials to be misleading and it had thoroughly reviewed the mailing with particular focus, as requested, on Clauses 7.2 and 10.1.

Takeda noted that the mailing was an A5 size folded leaflet consisting of four pages of information. It was sent on its own in a plain envelope to GPs in the PCT.

Takeda explained that following the reorganisation of the company in 2004, it had moved away from traditional, highly product branded promotional materials to a more formal, clinical or corporate style. This style and corporate branding had been consistent since 2004 and had been used for the majority of Takeda materials as well as its corporate branded stationary and website. Examples of this were provided. The mailing at issue did not, and was not designed to mimic an NHS document/template and did not use either NHS or the PCT branding or logos anywhere. The PCT had a clear and consistent branding which was used on its publications and website – copies were provided. The mailing did not resemble the PCT material in any way, including the publicly available annual report from which the financial information was sourced. Takeda's regional account director who covered the PCT area had produced the mailing; it was a locally focused piece, produced specifically for local GPs. The reference to the PCT was used to define a particular geography and the local

healthcare economy applicable to the recipients of the mailer. This local information was more relevant and applicable than, for example, national figures. There was nothing in the mailing that suggested the information was endorsed by, or produced by the PCT. It just stated the current financial situation in the local healthcare economy that was relevant to the audience. The information included on page 2 was publicly available on the PCT website. This financial information was provided to set the scene and reinforce the environment that the local GPs currently faced.

Takeda noted that page 3 (which formed the bulk of the mailer) provided promotional information about Amias. It reinforced both the clinical and financial benefits of using candesartan compared with the other two leading angiotension receptor blockers within the PCT region.

The final page was taken up by the Amias prescribing information. This was clearly a promotional piece and there had been no attempt to disguise that fact. Page 4 also included the required contact details for adverse event reporting and for obtaining further information on Amias.

The inclusion of prescribing information *per se*, demonstrated that the piece was an intentionally promotional piece for a medicine and not an official NHS document which would not include such information.

Takeda noted that the piece met all the necessary requirements of a promotional piece. It was certified prior to use and included the unique job code number, date of preparation, prescribing information and prominent information relating to adverse event reporting. The piece generally included the non-proprietary name of the product in preference to brand name although the brand name did appear in the main body of the piece as well as the prescribing information. There was no specific requirement in the Code for a piece to include a company logo.

Based on the above, Takeda did not believe that the piece was intentionally misleading, nor was it disguised promotion and did not believe that it was in breach of Clauses 7.2 and 10.1. However, to prevent any further misunderstanding, Takeda would ensure that all future promotional pieces included a clear product or corporate logo.

PANEL RULING

The Panel noted that the leaflet, 'Reducing Hypertension Management Spend in … PCT' was subtitled 'A review of the current financial status of … PCT and a strategy to reduce practice spend in the treatment of hypertension'. The inside front cover discussed a local operating and financial review and asked what steps could be taken to: assist in the achievement of this year's financial targets; help patients with hypertension and reduce prescribing costs. The third page was headed 'How To Reduce Angiotension Reception Blocker (ARB) Spend in … PCT by up to £106,000/1,000 patients treated for a year', and discussed the cost of prescribing Amias compared with losartan and valsartan. Prescribing information appeared on page 4 (the back cover). There was no indication on the front page or within that this leaflet had been produced by Takeda or that it was promotional material for Amias. The inclusion of prescribing information did not suffice in this regard.

The Panel considered that the source of the leaflet was not sufficiently clear. Whilst the leaflet did not use the logo of the PCT it nonetheless referred to the organisation ten times throughout the leaflet. Conversely Takeda's name appeared only twice, in small print on the back page in the prescribing information. Similarly, apart from the prescribing information 'Amias' appeared only twice, in brackets in the main part of the leaflet; 'candesartan' was used seven times. According to the complainant a number of GPs had queried whether the leaflet had been endorsed by the PCT as its presentation appeared to make it so. The Panel considered that the failure to indicate at the outset that this was company produced material gave the impression that the leaflet was something other than promotional material and was misleading and disguised in this regard. Breaches of Clauses 7.2 and 10.1 were ruled.

Complaint received	**19 March 2007**
Case completed	**15 May 2007**

CASE AUTH/1981/3/07

CONSULTANT IN RESPIRATORY MEDICINE v ALK-ABELLÓ

Unsolicited emails

A consultant in respiratory medicine complained that he had received several unsolicited emails, which he understood were unacceptable under the Code, from ALK-Abelló about Grazax (SQ-T oral lyophilisate). He had also received an absolute barrage of information through more conventional means. The complainant did not believe that he had given blanket approval to be contacted by email.

The Panel noted that the covering letter sent by an agency to health professionals about its specialist database stated that the main aim of its website was to give GPs a wider knowledge of consultants' special interests, clinic times, waiting times etc. Reference was made to its use by primary and secondary care staff as well as, inter alia, pharmaceutical and insurance companies. The use to which the data would be put by pharmaceutical companies was not stated.

The Panel noted that an email from the agency to ALK-Abelló explained that 'The consultants are sent entry forms via mail/post or they give their details over the phone to our editorial team. The editors explain to the doctors where the data will be displayed and what types of user will have access to it. They are given the choice of whether they want to submit an email address for our users to be able to contact them on'. There did not appear to be a conversation between the consultant and the editorial team other than if they amended their details by phone. The Panel had no evidence to show whether such conversations expressly covered the receipt of promotional as opposed to other material from a pharmaceutical company. In any event the Panel noted that the complainant had updated a hard copy of his form in manuscript. The form included his email address. The Panel noted the respondent's submission that the agency guaranteed in writing that it had permission of all physicians on the database for them to be contacted via email.

The Panel considered that the Code required companies to be able to demonstrate that health professionals had agreed to receive promotional material by email. The Panel considered that ALK-Abelló did not have explicit consent to send physicians on the database promotional material. Whilst it was implicit that users might email a consultant, the Code required such consent to be explicit and the nature of the material to be sent electronically to be made clear. ALK-Abelló had not demonstrated that the complainant had given express consent to receive promotional material by email. The emailed material was clearly promotional. The Panel ruled a breach of the Code.

The Panel noted the limitation on the number of promotional mailings sent by a company following the launch of a new medicine set out in the supplementary information to the Code; it was not clear whether the term mailing referred to post, email or both. Four mailings had been sent to the complainant between 2 January and 26 February. In addition invitations to three meetings had been sent. The Panel considered that an invitation to a meeting in Manchester on 20 April was a promotional mailing. It included product claims. Thus the company had not complied with the Code and a breach was ruled.

A consultant in respiratory medicine complained about unsolicited emails received from ALK-Abelló (UK) Limited about Grazax (SQ-T oral lyophilisate).

COMPLAINT

The complainant stated that he had received several unsolicited emails about Grazax. He had also received an absolute barrage of information through more conventional means. The complainant understood that unsolicited emails were not acceptable under the Code.

The complainant did not believe that he had given blanket approval to be contacted by email and his secretary knew that he did not wish to be contacted thus.

When writing to ALK-Abelló, the Authority asked it to respond in relation to Clauses 9.1, 9.9 and 12.2 of the Code.

RESPONSE

ALK-Abelló strongly refuted the allegation that it had breached Clause 9.1 as it had always maintained high standards of ethical promotion of Grazax; all materials had been prevetted by the Medicines and Healthcare products Regulatory Agency (MHRA), the launch meetings were CPD accredited and it had adhered to the Code at all times.

In relation to Clause 9.9, ALK-Abelló had used an agency to obtain the complainant's email address from a third party agency which guaranteed in writing to ALK-Abelló (email provided) that it had the permissions of all physicians on its database for a third party to contact them through email.

ALK-Abelló obtained the complainant's email address in good faith and had only used it to invite him to educational meetings with continuing professional development (CPD) accreditation. Therefore ALK-Abelló refuted the alleged breach of Clause 9.9 as it had prior permission of the recipient. Further, the emails were not promotional in nature, only containing invitations and logistical information relating to CPD accredited educational meetings.

The supplementary information to Clause 12.2 stated that 'In the first six months following the launch of a new medicine, a health professional may be sent an initial mailing and no more than three other mailings about the medicine'.

ALK-Abelló launched Grazax on 2 January 2007. An initial mailing containing a 'Dear Dr' letter and summary of product characteristics (SPC) was sent to hospital physicians, including the complainant, who routinely treated allergic rhinitis ie specialist in allergy/immunology, ENT and respiratory medicine. A further three promotional mailings for Grazax were sent to the same doctors on 22 January, 5 February and 26 February. All of these mailings were prevetted and approved by the MHRA.

Invitations to CPD accredited educational meetings (these were not promotional mailings) were also sent to hospital doctors on:

- 11 January – invitations to CPD accredited educational meetings being held at London, Birmingham, Manchester;
- 5 March – update to original invitation to inform of date change to Manchester meeting;
- 8 March – update to London meeting to inform of additional date due to extreme weather conditions affecting delegates during first London meeting.

The meeting invitation and agenda were both prevetted and approved by the MHRA and the educational meetings had received CPD accreditation. Speakers at the meetings were recognised experts in treating allergic rhinitis.

ALK-Abelló submitted that it had fully complied with the requirements of Clause 12.2 and therefore refuted the allegation of any breach.

In response to a request for further information, ALK-Abelló provided a copy of the covering letter and the database form sent to consultants by the third party agency and the form that was amended and returned by the complainant. The covering letter clearly stated that this information might be provided to pharmaceutical companies. In a personal communication, the third party agency confirmed that its database was used by a large number of pharmaceutical companies for a similar use with no previous alleged breach of Clause 9.9.

The invitation, agenda and delegate pack for the 'Novel Therapy for Allergic Rhinitis' meeting that was held in Manchester on 20 April were also provided. As previously stated, all these materials were prevetted and approved by the MHRA as was standard for a new chemical entity. Prescribing information was included on the invitation and agenda following a request from the MHRA through the prevetting process.

PANEL RULING

The Panel noted that the covering letter sent by the third party agency to health professionals about the specialist database stated that the main aim of the website was to give GPs a wider knowledge of consultants' special interests, clinic times, waiting times etc. Reference was made to its use by primary and secondary care staff as well as, *inter alia*, pharmaceutical and insurance companies. The use to which the data would be put by pharmaceutical companies was not stated.

The Panel noted an email to ALK-Abelló explained that 'The consultants are sent entry forms via mail/post or they give their details over the phone to our editorial team. The editors explain to the doctors where the data will be displayed and what types of user will have access to it. They are given the choice of whether they want to submit an email address for our users to be able to contact them on'. There did not appear to be a conversation between the consultant and the editorial team other than if they amended their details by phone. There was no evidence before the Panel to indicate whether such conversations expressly covered the receipt of promotional as opposed to other material from a pharmaceutical company. In any event the Panel noted that the complainant had updated a hard copy of his form in manuscript. The form included his email address. The Panel noted the respondent's submission that the third party agency guaranteed in writing that it had the permission of all physicians on the database for other parties to contact them via email.

The Panel considered that Clause 9.9 required companies to be able to demonstrate that health professionals had agreed to receive promotional material by email. The Panel considered that ALK-Abelló did not have explicit consent to send physicians on the third party agency database promotional material. Whilst it was implicit that users might contact a consultant by email Clause 9.9 required such consent to be explicit and the nature of the material to be sent electronically to be made clear. ALK-Abelló had not been able to demonstrate that the complainant had given express consent to receive promotional material by email. The emailed material was clearly promotional. The Panel ruled a breach of Clause 9.9.

The Panel noted the limitation on the number of promotional mailings sent by a company following launch of a new medicine set out in the supplementary information to Clause 12.2. It noted that the Code did not make it clear whether the term mailing referred to post, email or both. Four mailings

had been sent to the complainant between 2 January and 26 February. In addition invitations to three meetings had been sent. The Panel considered that the invitation to the meeting in Manchester on 20 April was a promotional mailing. It included product claims. Thus the company had not complied with Clause 12.2 and a breach was ruled.

The Panel did not consider that the circumstances warranted a ruling of a breach of Clause 9.1.

Complaint received **27 March 2007**

Case completed **3 July 2007**

ANONYMOUS CONSULTANT PHYSICIAN v SANOFI-AVENTIS and PROCTER & GAMBLE

Actonel leavepiece

An anonymous consultant physician complained about a leavepiece for Actonel (risedronate sodium) issued by Sanofi-Aventis and Procter & Gamble, as the Alliance for Better Bone Health (ABBH).

The complainant took issue with the selective conclusions in the leavepiece at issue which referred to Silverman *et al* (2007) (the risedronate and alendronate (REAL) cohort study). The leavepiece contended that the REAL study unequivocally demonstrated a reduced incidence of hip fracture for Actonel relative to alendronate.

The complainant considered that single-patient, meta-analysis of results informed by randomized, controlled trials was the best type of evidence but in the absence of such data, evidence obtained from observational studies was probably reasonable. That was clearly not the case in this situation.

A substantial body of evidence concerning the efficacy of medicines such as Actonel and alendronate suggested fracture rates, including hip fracture, might be halved during three years of therapy. No randomized, controlled trial had demonstrated differential anti-fracture efficacy for the two products in question. Indeed, comparative studies had shown superior response in terms of surrogate markers (bone density) for alendronate rather than Actonel.

Perhaps most importantly, current guidelines from the National Institute of Health and Clinical Excellence (NICE) did not recognise a difference in terms of the relative efficacy of these products. The current draft of the updated guidelines recommended alendronate as first line treatment for postmenopausal osteoporosis and explicitly did not recommend Actonel as appropriate use of NHS resources. Whilst this was draft guidance, and therefore not to be relied upon per se, the rationale for it related to the substantial difference in price between the two; alendronate had been available generically in the UK for almost two years and had a Drug Tariff price of £7.22 compared with £20.30 for weekly Actonel.

The results of the pharmacoeconomic analysis conducted by NICE for two probably similarly efficacious products, predictably, and correctly in the complainant's view, dominated for alendronate over Actonel in all modelling scenarios.

The REAL study was not representative of the substantial evidence base for Actonel and alendronate. Furthermore, the complainant considered that the inappropriately aggressive (and inaccurate) conclusions presented within the leavepiece attempted to dissuade practitioners from using alendronate in preference to Actonel, contrary to current and likely future NICE guidance.

The Panel noted that there were differences in the indications for Actonel and Fosamax. In the UK Actonel Once Weekly was indicated for the treatment of established postmenopausal osteoporosis to reduce the risk of hip fractures as well as for the treatment of postmenopausal osteoporosis to reduce the risk of vertebral fracture. Whereas Fosamax Once Weekly was indicated for the 'Treatment of postmenopausal osteoporosis, 'Fosamax' reduces the risk of vertebral and hip fractures'.

The Panel noted that the leavepiece at issue was headed 'In established postmenopausal osteoporosis' and referred to the REAL study which had been sponsored by the ABBH. The study had been conducted in the US and was a retrospective observation of bisphosphonate patients which compared the annual incidence of fracture with either once-weekly 35mg Actonel (n=12,215) or once-weekly alendronate (n=21,615). Women for inclusion were aged 65 and over with any use of once-a-week dosing of Actonel or alendronate after July 2002 (when once-weekly versions of both therapies became available). The Panel noted that 8% of the alendronate patients received only 35mg weekly compared with 70mg weekly which was the dose licensed in the UK for the treatment of postmenopausal osteoporosis. Page 2 of the leavepiece presented a comparison of the incidence of hip fracture during therapy at 6 and 12 months. The percentage of women with a hip fracture on alendronate was 0.29% and 0.58% at 6 and 12 months respectively. The percentage of women with a hip fracture on Actonel was 0.17% and 0.37% at 6 and 12 months respectively; an absolute difference of 0.12% (p=0.02) and 0.21% (p=0.01) respectively. In that regard the Panel queried the clinical significance of the results. The relative reductions for patients on Actonel were 46% and 43% at 6 and 12 months respectively. The leavepiece presented that data in a bar chart which noted the absolute percentages of women with a hip fracture together with prominent downward arrows showing the relative differences of 46% and 43% at 3 and 6 months respectively. Below the bar chart was the claim 'Actonel reduces the incidence of hip fracture compared to alendronate as early as 6 months in real life'.

The REAL study concluded that, 'within this observational study of clinical practice, a cohort of patients receiving risedronate had lower rates of hip

and nonvertebral fractures during their first year of therapy than a cohort of patients receiving alendronate. These results do not appear to be explained by baseline differences in fracture risk between cohorts. In addition, the observed rates of fracture were consistent with the fracture rates in clinical trials. Thus it appears, patients receiving risedronate are better protected from hip and nonvertebral fractures during their first year of therapy than patients receiving alendronate'.

The Panel considered that the leavepiece was more positive about the differences between Actonel and alendronate than the study authors. In that regard, although NHS resources were not referred to per se, the leavepiece encouraged the use of Actonel and not alendronate. Although a statistically significant difference between the two products had been identified in favour of Actonel, the absolute difference was small. Furthermore the results might have been biased against alendronate given that 8% of the alendronate patients had only received half the weekly dose licensed for the treatment of established postmenopausal osteoporosis ie 35mg vs 70mg.

Taking all the factors into consideration the Panel considered that the leavepiece was misleading and thus ruled breaches of the Code.

Upon appeal by Sanofi-Aventis and Procter & Gamble the Appeal Board noted that the REAL study authors had performed a sensitivity analysis whereby the 1768 patients who received 35mg alendronate were removed from the study population and the data was reanalysed. The ABBH submitted that the result was consistent with the primary analysis and remained statistically significant. The sensitivity analysis was included in the leavepiece.

The Appeal Board considered that the leavepiece was not inconsistent with the study authors' comments about the differences between Actonel and alendronate. NHS resources were not referred to. Although the absolute difference was small, a statistically significant difference between the two products had been identified in favour of Actonel. The Appeal Board noted the complainant's comments about scientific rigour and observational studies. The Appeal Board noted the companies' submission that such studies provided a measure of effectiveness across a range of patients and health practices. The Appeal Board noted that observational studies did not measure efficacy. They might nonetheless be used to complement clinical decisions. The Appeal Board also noted the submission that the products were suitable subjects for an observational study as their licensed indications were similar and the baseline characteristics of the two study cohorts were similar.

Taking all the factors into account the Appeal Board did not consider that the leavepiece was misleading and thus ruled no breach of the Code.

An anonymous consultant physician with a specialist interest in metabolic bone disease complained about a leavepiece (ref ACT 3356/IE.RIS.06.12.02) for Actonel (risedronate sodium) issued by Sanofi-Aventis and Procter & Gamble Pharmaceuticals UK Limited, as the Alliance for Better Bone Health (ABBH).

COMPLAINT

The complainant stated that for the last decade he had been responsible for development of osteoporosis services within his trust to provide local general practice with bone densitometry and expert opinion on management issues. Tragically, the plight of the frail elderly had attracted little material prioritisation from the Department of Health (DoH) resulting in patients and generalists alike coming to disproportionately rely upon the activities of enthusiasts such as himself.

Throughout his career, the complainant had enjoyed a constructive relationship with the pharmaceutical industry and indeed the industry had contributed substantially to progress in the management of osteoporosis both in terms of therapeutics and with regard to medical education. The complainant stated that he was thus saddened that he felt compelled to complain about an example of very poor judgement. The leavepiece at issue referred to Silverman *et al* (2007) (the risedronate and alendronate (REAL) cohort study) and drew inferences regarding the comparative efficacy of the two agents. The leavepiece contended that the REAL study unequivocally demonstrated a significant benefit in terms of hip fracture reduction for Actonel relative to the generically available alendronate.

Observational cohort studies certainly served a purpose in an appropriate context. However, given the plethora of well conducted, randomized, controlled, osteoporosis trials available for critical appraisal, the complainant took issue with the selective conclusions in the leavepiece. Single-patient, meta-analysis of results informed by randomized, controlled trials resided at the pinnacle of the evidence hierarchy. In the absence of such data, reliance on evidence obtained from observational studies was probably reasonable. That was clearly not the case in this situation.

A substantial body of evidence concerning the efficacy of anti-fracture medicines including Actonel and alendronate suggested fracture rates, including hip fracture, might be halved during three years of therapy. No randomized, controlled trial had demonstrated differential anti-fracture efficacy for the two products in question. Indeed, comparative studies, that were insufficiently powered to demonstrate differential effects on fracture reduction, had shown superior response in terms of surrogate markers (bone density) for alendronate rather than Actonel.

Perhaps most importantly, current guidelines from the National Institute of Health and Clinical Excellence (NICE) (Health Technology Appraisal 87) did not recognise a difference in terms of the relative efficacy of these products. NICE would imminently update its guidance and also provide recommendations on the primary prevention of osteoporotic fracture in separate

guidance. This guidance was likely at the final Appraisal Consultation Document (ACD) phase and was available on the NICE website. The complainant noted that the current draft of the ACD recommended alendronate as first line treatment for postmenopausal osteoporosis and explicitly did not recommend Actonel as appropriate use of NHS resources. Whilst this was draft guidance, and therefore not to be relied upon per se, the rationale for NICE's prioritisation of alendronate was contingent upon the substantial difference in price between the two; alendronate had been available generically in the UK for almost two years and had a Drug Tariff price of £7.22 compared with £20.30 for weekly Actonel.

The results of the pharmacoeconomic analysis conducted by NICE for two probably similarly efficacious products, predictably, and correctly in the complainant's view, dominated for alendronate over Actonel in all modelling scenarios.

Thus was the central tenet of the complaint. The REAL study did not represent the substantial evidence base derived for Actonel and alendronate. Furthermore, the complainant considered that the inappropriately aggressive (and inaccurate) conclusions presented within the leavepiece attempted to dissuade practitioners from using alendronate in preference to Actonel, contrary to current and likely future NICE guidance. Such promotional messages confused practitioners and potentially diverted scant NHS resources to fund non-competitively priced branded medicines that offered no clinical benefit relative to generically available alternatives. The consequence for specialists such as the complainant was very unappealing.

The complainant requested the Authority to compel the ABBH to withdraw the leavepiece and issue a corrective statement to those health professionals exposed to a campaign of mis-information.

When writing to the companies the Authority asked them to bear in mind the requirements of Clauses 7.2 and 7.4 of the Code.

RESPONSE

Procter & Gamble responded on behalf of both companies.

The companies stated that there were no published, randomized, head-to-head, clinical trials of Actonel and alendronate which had the clinically relevant endpoint of fracture. There were some direct comparisons which used the surrogate endpoint of bone mineral density (BMD) changes, but surrogate endpoints in general were not satisfactory as BMD was not a good predictor of fracture risk (Cummings *et al* 2002; Li *et al* 2001; Watts *et al* 2004).

Furthermore, the Code did not require randomized trials to substantiate claims; other types of study were also acceptable depending on the claim in question.

The REAL cohort study was an observational study. Such studies provided a measure of effectiveness across a range of patients and health care practices as they extended the knowledge of randomized, controlled trials (RCTs).

RCTs by design had strict inclusion and exclusion criteria. It had been shown that approximately 80% of patients would not be accepted into clinical trials for numerous reasons (Dowd *et al* 2000). Therefore RCTs excluded a large number of patients for whom medical professionals would consider treatment in daily practice.

The aim of the REAL study was to observe, in clinical practice, the incidence of hip and nonvertebral fractures among postmenopausal women in the year following initiation of once-weekly Actonel or alendronate.

The Actonel and alendronate groups were compared for baseline characteristics for six months prior to starting bisphosphonate therapy and were of very similar age, comorbidities, and fracture history before therapy. For the first three months of therapy, the two groups had nearly identical fracture rates – which suggested a similarity in fracture risk before the effect of therapy began. The Actonel group could be considered slightly less healthy and at slightly greater risk of fracture based on statistically significant differences in things like concomitant medications, steroid usage, osteoporosis diagnoses, and rheumatoid arthritis diagnosis, however, all results were risk-adjusted for potential differences in baseline fracture risk with standard statistical methods.

In this observational study of women 65 and older, at 6 months Actonel patients had a 46% (p=0.02) lower incidence of hip fractures and a 19% (p=0.05) lower incidence of nonvertebral (hip, wrists, humerus, clavicle, pelvis and leg) fractures, than those on alendronate. At 12 months, Actonel patients had a 43% (p=0.01) lower incidence of hip fractures and an 18% (p=0.03) lower incidence of nonvertebral fractures than patients on alendronate.

There was no opportunity for manipulation – all five of the authors were involved in the development of the study plan, had access to all of the data, and each of the statisticians completed independent analysis. The analysis for this study was performed independently by all authors to ensure no errors or misinterpretations.

The REAL study had been published in the peer reviewed medical journal Osteoporosis International and provided medical professionals with new information on osteoporotic therapies in a real-life setting which had not been observed before and which complemented the finding of the Actonel RCTs as shown in the copy. The leavepiece clearly stated the study description, shared details of the statistical analysis and accurately represented the study findings. The data in the leavepiece was a direct representation of the data in the published paper. The companies believed the data presented were accurate, capable of substantiation and did not mislead physicians

especially in regard to the use of NHS resources as noted by the complainant. The companies noted that current NICE guidelines recommended bisphosphonates (alendronate, etidronate, Actonel) as first line options, and this was what NHS practitioners should base their decisions on today.

The complaint was based on pure speculation of future discussions and future NICE guidelines and furthermore, the complainant specifically referred to NICE pharmacoeconomic analyses – these were not the same as real life clinical outcome data as presented in the REAL study, so in effect the complainant was comparing apples and pears.

There was no obligation to replicate the views of NICE in promotion. Promotion must be within licence with claims in line with the summary of product characteristics (SPC) and capable of substantiation – all of which criteria were met in the leavepiece in question.

The companies therefore, denied any breach of the Code.

PANEL RULING

The Panel noted that there were differences in the indications for Actonel and Fosamax. In the UK Actonel Once Weekly was indicated for the treatment of established postmenopausal osteoporosis to reduce the risk of hip fractures as well as for the treatment of postmenopausal osteoporosis to reduce the risk of vertebral fracture. Whereas Fosamax Once Weekly was indicated for the 'Treatment of postmenopausal osteoporosis, 'Fosamax' reduces the risk of vertebral and hip fractures'.

The Panel noted that the leavepiece at issue was headed 'In established postmenopausal osteoporosis' and referred to the REAL study which had been sponsored by the ABBH. The study had been conducted in the US and was a retrospective observation of bisphosphonate patients which compared the annual incidence of fracture with either once-weekly 35mg Actonel (n=12,215) or once-weekly alendronate (n=21,615). Women for inclusion were aged 65 and over with any use of once-a-week dosing of Actonel or alendronate after July 2002 (when once-weekly versions of both therapies became available). The Panel noted that 8% of the alendronate patients received only 35mg weekly compared with 70mg weekly which was the dose licensed in the UK for the treatment of postmenopausal osteoporosis. Page 2 of the leavepiece presented a comparison of the incidence of hip fracture during therapy at 6 and 12 months. The percentage of women with a hip fracture on alendronate was 0.29% and 0.58% at 6 and 12 months respectively. The percentage of women with a hip fracture on Actonel was 0.17% and 0.37% at 6 and 12 months respectively; an absolute difference of 0.12% (p=0.02) and 0.21% (p=0.01) respectively. In that regard the Panel queried the clinical significance of the results. The relative reductions for patients on Actonel were 46% and 43% at 6 and 12 months respectively. The leavepiece presented that data in a bar chart which noted the absolute percentages of women with a hip fracture together with prominent downward arrows showing the relative differences of 46% and 43% at 3 and 6 months respectively. Below the bar chart was the claim 'Actonel reduces the incidence of hip fracture compared to alendronate as early as 6 months in real life'.

The REAL study concluded that, 'within this observational study of clinical practice, a cohort of patients receiving risedronate had lower rates of hip and nonvertebral fractures during their first year of therapy than a cohort of patients receiving alendronate. These results do not appear to be explained by baseline differences in fracture risk between cohorts. In addition, the observed rates of fracture were consistent with the fracture rates in clinical trials. Thus it appears, patients receiving risedronate are better protected from hip and nonvertebral fractures during their first year of therapy than patients receiving alendronate'.

The Panel considered that the leavepiece was more positive about the differences between Actonel and alendronate than the study authors. In that regard, although NHS resources were not referred to per se, the leavepiece encouraged the use of Actonel and not alendronate. Although a statistically significant difference between the two products had been identified in favour of Actonel, the absolute difference was small. Furthermore the results might have been biased against alendronate given that 8% of the alendronate patients had only received half the weekly dose licensed for the treatment of established postmenopausal osteoporosis ie 35mg vs 70mg.

Taking all the factors into consideration the Panel considered that the leavepiece was misleading and thus ruled breaches of Clauses 7.2 and 7.4. This ruling was appealed by Procter & Gamble and Sanofi-Aventis.

APPEAL BY PROCTER & GAMBLE AND SANOFI-AVENTIS

The ABBH noted that the Panel had noted that 8% (n=1768) of the alendronate patients received 35mg weekly (licensed in the US for prevention of postmenopausal osteoporosis) compared to 92% who received 70mg weekly (licensed in the UK for the treatment of postmenopausal osteoporosis). The Panel was concerned that this 8% of the population might have biased the results against alendronate.

The ABBH submitted that the authors considered this point and performed a sensitivity analysis that proved that the overall results were not affected by groups that could have introduced potential bias, eg the 8% of patients taking 35mg alendronate. As part of the overall sensitivity analysis the authors removed the patients who took alendronate 35mg from the study population and reanalysed the data. The results were similar to the main study, remaining statistically significant and were presented in the publication and the leavepiece in question. The ABBH therefore had confidence in the robustness of the overall study

results due to the consistent results of the sensitivity analysis.

The ABBH noted that the Panel ruling had noted that the percentage of women with a hip fracture who took alendronate was 0.29% and 0.58% at 6 and 12 months, respectively. The percentage of women with a hip fracture who took Actonel was 0.17% and 0.37% at 6 and 12 months, respectively. The Panel was concerned that whilst the difference between the groups was statistically significant, the absolute percentage difference was small (0.12% and 0.21% at 6 and 12 months, respectively) and queried the clinical significance.

The ABBH submitted that there were three points to consider: the need for observational data; consistency of the REAL data compared to clinical trials demonstrating reliability and clinical significance of the results.

The ABBH submitted that health professionals looked to make comparisons of active treatments with clinically relevant endpoints such as fractures in the case of osteoporosis. Often this could only be done by relying on individual trial data as head-to-head trials were not feasible.

As the incidence of hip fractures in the general population was low, it would not be realistic to perform a head-to-head clinical trial with hip fracture as a primary endpoint. In order to show a statistically significant difference in hip fracture incidence between two active treatments in a clinical trial, it would require screening more than 150,000 patients in order to enrol the required number of patients to show a difference, ie 30,000. This was based on feasibility studies that showed only 20% of osteoporotic patients might be eligible for inclusion in randomised controlled trials due to the strict inclusion/exclusion criteria (Dowd et al).

In order to perform such comparative analyses other sources of data, such as health databases for retrospective analyses could be looked at. Such databases contained large volumes of data and allowed screening of large numbers of patients for possible inclusion in such cohort analyses. Thus in the REAL study, 182,772 patients were screened and the analysis included 33,830 patients.

The authors stated 'In the current study, the annual fracture rates following initiation of therapy (~2.0% for nonvertebral fractures and ~ 0.5% for hip fractures) were consistent with the annual rates in the treated population of clinical trials (between 2.0 and 2.3% for non-vertebral fractures and **between 0.4% and 0.7% for hip fractures**)' [emphasis added]. This meant that the fracture incidences observed in the REAL study at 12 months, 0.37% and 0.58% for risedronate and alendronate, respectively, were comparable to those clinical trials.

Fundamentally, it was important to note that the REAL study compared two active cohorts, ie there was no placebo group. This could be highlighted as the magnitude of treatment effect between active comparators was, as expected, lower than between treatment and placebo.

In the UK in 2006, approximately 766,554 patients were taking a bisphosphonate (IMS Data, March 2007). If it was assumed that all were taking alendronate, from the REAL study, 0.58% would experience a hip fracture by 12 months, ie 4,446 hip fractures. If it was assumed that all patients were taking risedronate, 0.37% would experience a hip fracture by 12 months, ie 2,836 hip fractures. The difference was 1,610 hip fractures. Considering the impact hip fractures had on mortality and the patient's quality of life, the clinical significance of this study should not be underestimated. The results were clinically relevant.

The ABBH noted that the Panel noted the conclusion of the study 'Within this observational study of clinical practice, a cohort of patients receiving risedronate had lower rates of hip and nonvertebral fractures during their first year of therapy than a cohort of patients receiving alendronate. These results do not appear to be explained by baseline differences in fracture risk between cohorts. In addition, the observed rates of fracture were consistent with the fracture rates in clinical trials. Thus it appears patients receiving risedronate were better protected from hip and nonvertebral fractures during the first year of therapy than patients receiving alendronate'.

The ABBH submitted that it had addressed the main points in relation to the conclusion of the study, ie the potential bias due to use of 8% alendronate patients on 35mg/week dose and the clinical significance of the data. The ABBH considered that it included all relevant data in the leavepiece, where details and methods of the statistical analysis were clearly presented, including details of the sensitivity analysis which showed that inclusion of the 8% of patients taking alendronate 35mg/weekly did not influence the overall results of the REAL study. Therefore, the overall results presented in the paper were fairly reflected in the leavepiece.

COMMENTS FROM THE COMPLAINANT

The complainant stated that his intention in complaining was to highlight inappropriate and frankly misrepresentative marketing activities perpetrated by the ABBH. Every health professional currently operating within the NHS was subject to tremendous cost containment pressure. Accordingly, promotional campaigns that could result in mis-allocation of overstretched budgets to acquire non-competitively priced products or devices were simply unacceptable and must be curtailed.

The complainant alleged that the key issue was that evidence-based conclusions could only be derived from the outcomes of appropriately designed, randomised controlled clinical studies of adequate duration undertaken in a study population that was representative of those patients likely to be treated in clinical practice once the medicine had been granted

marketing approval. Observational studies inherently lacked the requisite scientific rigour to provide definitive conclusions of relative efficacy of pharmacological agents. It was neither the gift nor capability of pharmaceutical company marketeers to usurp this globally ratified hierarchical approach that had become central to rational clinical decision making and allocation of health resources.

The complainant noted that the companies stated that this complaint was based upon speculation and future NICE guidance, and furthermore, that the analysis was trying to compare apples with pears. The current NICE Technology Appraisal (TA87) did indeed place alendronate and risedronate on an equal footing. The pharmacoeconomic analyses that informed the current NICE Technology Appraisal were based upon acquisition costs of £23.12 for alendronate (4 weekly tablets) and £20.30 for risedronate (4 weekly tablets). It was not speculation to state that the current price of generic alendronate had reduced by 72% to £6.46 for 4 weeks' supply; during the same time frame the price of risedronate had reduced by 7% from £21.83 to £20.30 for 4 weeks' supply. That was a fact; and was naturally the particular fact that had informed the imminent revision of the current NICE Technology Appraisal which would likely place alendronate as the first line agent and indicate that risedronate did not represent a rational use of NHS resources. Expressed another way, in respect of local drug budgets, for every patient treated with risedronate, three patients could be treated with alendronate.

The complainant noted that the ABBH had referred to Cummings *et al* to challenge the validity of deriving conclusions on the relative efficacy of two products based upon surrogate endpoints. Whilst the conclusions of that particular paper could be challenged by findings of other investigators (Hochberg *et al* 2002), the complainant concurred that evidence-based conclusions could not be based on studies that failed to compare the relevant clinical outcome ie fracture in this case. However, the complainant disagreed that such fracture end-point studies were infeasible. Given that 310,000 fragility fracture patients presented to UK hospitals every year, the vast majority of which were drug naïve, the UK alone would provide more than enough patients to recruit to the 30,000 patient study required to prove whether Actonel had any advantage over a generic product that was one third of the price. Globally, there were millions of fragility fracture patients presenting to hospitals every year, the vast majority of whom were currently not treated. The lack of feasibility of such study was not attributable to clinical challenges or lack of patient presentation, rather an unwillingness of pharmaceutical complanies to invest in the, albeit, substantial costs to underwrite such a study.

The complainant alleged that on the issue of generalisability of this data to the UK population, the UK and US populations had a number of clinically relevant distinctions in respect of osteoporosis that might challenge the wisdom of application of these findings to the UK. Indeed, the title of a paper in the British Journal of Radiology provided some insight on this matter 'Prevalence of osteoporotic bone mineral density at the hip in Britain differs substantially from the US over 50 years of age; implications for clinical densitometry' (Holt *et al* 2002). Accordingly, notwithstanding the methodological issues with the REAL study, precisely how REAL were these results derived from US patients when applied to ladies in Inverness, Bolton or Plymouth?

The complainant noted that 'Evidence-based medicine has come a long way: the second decade will be as exciting as the first' was the title of a BMJ paper in 2004 from the McMaster University advocates of evidence-based medicine (Guyatt *et al* 2004); and within the UK NHS evidence-based decision making had indeed progressed substantially. Perhaps in this regard the ABBH should listen to its 'clients' a little more closely. Specious and misrepresentative claims such as 'Protect more patients from hip fractures with Actonel compared to alendronate' that were based upon the findings of observational studies were the stuff of the last century and were best left there.

Evidence-based medicine was founded in Britain; the complainant would not stand by and see its principles flaunted at the expense of patients and the taxpayer. The Appeal Board should uphold this complaint and bring the most severe sanctions at its disposal to bear upon those that would subvert scant resources to line corporate coffers.

In response to a request for the provision of Holt *et al* and Hochberg *et al* the complainant made further comment. In regard to Hochberg *et al* the complainant noted he cited it to illustrate the point that two divergent schools of thought existed on this particular matter. Half a dozen publications could be quoted by the adversarial academic groups, however, this paper with associated references illustrated the opposed view to Cummings *et al* cited by the ABBH. The complainant hoped that this served to inform the Appeal Board that interpretation of the bone mineral density response data was somewhat equivocal, as one would imagine in respect of reliance upon a surrogate end-point.

APPEAL BOARD RULING

The Appeal Board noted that the REAL study was a retrospective observation of bisphosphonate patients which compared the annual incidence of fracture with either once-weekly 35mg Actonel (n=12,215) or once-weekly alendronate (n=21,615). Women for inclusion were aged 65 and over with any use of once-a-week dosing of Actonel or alendronate after July 2002 (when once-weekly versions of both therapies became available). The Appeal Board noted that in the REAL study 8% of the alendronate patients received only 35mg weekly compared to 70mg weekly which was the licensed dose in the UK for the treatment of postmenopausal osteoporosis. The REAL study authors had performed a sensitivity analysis whereby the 1,768 patients who received the 35mg alendronate dose were removed from the study population and the data was reanalysed. The ABBH submitted that the result was

consistent with the primary analysis and remained statistically significant. The sensitivity analysis was included in the leavepiece. Page 2 of the leavepiece compared the incidence of hip fracture during therapy at 6 and 12 months. The percentage of women with a hip fracture on alendronate was 0.29% and 0.58% at 6 and 12 months respectively. The percentage of women with a hip fracture on Actonel was 0.17% and 0.37% at 6 and 12 months respectively; an absolute difference of 0.12% (p=0.02) and 0.21% (p=0.01) respectively. The relative reductions for patients on Actonel were 46% and 43% at 6 and 12 months respectively. The leavepiece presented that data in a bar chart which noted the absolute percentages of women with a hip fracture together with prominent downward arrows showing the relative differences of 46% and 43% at 3 and 6 months respectively. Below the bar chart was the claim 'Actonel reduces the incidence of hip fracture compared to alendronate as early as 6 months in real life'.

The REAL study concluded that, 'within this observational study of clinical practice, a cohort of patients receiving risedronate had lower rates of hip and nonvertebral fractures during their first year of therapy than a cohort of patients receiving alendronate. These results do not appear to be explained by baseline differences in fracture risk between cohorts. In addition, the observed rates of fracture were consistent with the fracture rates in clinical trials. Thus it appears, patients receiving risedronate are better protected from hip and nonvertebral fractures during their first year of therapy than patients receiving alendronate'.

The Appeal Board considered that the leavepiece was not inconsistent with the study authors' comments about the differences between Actonel and alendronate. NHS resources were not referred to. Although the absolute difference was small, a statistically significant difference between the two products had been identified in favour of Actonel. The Appeal Board noted the complainant's comments about scientific rigour and observational studies. The Appeal Board noted the companies' submission that such studies provided a measure of effectiveness across a range of patients and health practices. The Appeal Board noted that observational studies did not measure efficacy. They might nonetheless be used to complement clinical decisions. The Appeal Board also noted the company representatives' submission that the products were suitable subjects for an observational study as their licensed indications were similar and the baseline characteristics of the two study cohorts were similar.

Taking all the factors into account the Appeal Board did not consider that the leavepiece was misleading and thus ruled no breach of Clauses 7.2 and 7.4. The appeal was successful.

Complaint received	**28 March 2007**
Case completed	**14 June 2007**

CASE AUTH/1986/4/07

ASTRAZENECA v GLAXOSMITHKLINE

Symbicort and Seretide cost comparisons

AstraZeneca complained about cost comparisons made by GlaxoSmithKline between AstraZeneca's Symbicort (budesonide/formoterol) and GlaxoSmithKline's Seretide (salmeterol/fluticasone propionate). The items at issue were a one page leavepiece and a slide from a presentation.

The leavepiece was headed 'Cost comparison for combination therapies in asthma at beclometasone equivalent daily doses' followed by 'Seretide (salmeterol/ fluticasone propionate) can be up to £35.08 cheaper for 30 days treatment at a stable dose than Symbicort (budesonide/formoterol) combination'. This was followed by a chart comparing various combinations and doses. The comparisons were grouped according to low dose steroid use (400mcg beclometasone equivalent daily dose), medium dose steroid use (800 - 1,000mcg beclometasone equivalent daily dose), and high dose steroid use (up to 2,000mcg beclometasone equivalent daily dose). The cost per 30 days' treatment at sustained dosing was given and the final column of the chart was headed 'Cost difference with Seretide per 30 day treatment'.

Five of the comparisons showed that there were savings using Seretide compared to sustained treatment with Symbicort, ranging from 86 pence to £35.08. Seretide was £12.19 more expensive than Symbicort in one of the low dose steroid use comparisons.

AstraZeneca alleged that the cost comparison shown in the leavepiece was misleading. In AstraZeneca's view the purpose of the leavepiece was to portray Symbicort as a significantly more expensive option than Seretide. This was not correct when one considered the overall price comparability across the range of their doses and when used similarly. The misleading purpose of the leavepiece was clear from the heading 'Seretide (salmeterol/fluticasone propionate) can be up to £35.08 cheaper for 30 days treatment at a stable dose than Symbicort (budesonide/formoterol) combination'. Although the potential cost difference referred to was the comparison of 30 days of Symbicort 400/12, two puffs bd vs Seretide 500 Accuhaler, one puff bd, this was an unfair comparison on which to base such a broad statement.

Symbicort 400/12, two puffs bd was not a normally recommended dose of Symbicort. The Symbicort 400/12 summary of product characteristics (SPC) stated that the recommended dose, was one puff bd. Although some adults might require up to two puffs bd. Thus very few prescriptions were for Symbicort 400/12, two puffs bd. In the chart the times where Symbicort was shown to be significantly more expensive than Seretide related to the use allowed of two puffs bd. Such comparisons were potentially unfair. Unlike pressurised metered dose inhalers (MDIs) such as Seretide Evohaler, where the unit dose was two puffs, the usual unit dose for dry powder inhalers such as Symbicort Turbohaler and Seretide Accuhaler was one puff. The marketing authorizations for Symbicort, unlike Seretide Accuhaler, allowed flexibility of dosing so the normal dose of one puff bd could be increased to two or even four puffs bd or indeed reduced to one daily. This flexibility allowed short term increases in dosage at times of increased symptoms. The Seretide Accuhaler marketing authorization did not permit similar flexibility as the recommended dose of each product strength was one puff bd, though this might in some cases be reduced to one puff daily. Dosage increases to two or four puffs bd of Symbicort would incur additional cost for the period that the higher dose was used, however, similar dosage increases with Seretide incurred further costs because a new prescription for a higher strength of Seretide would be needed. The cost impact of these important differences was omitted from the chart.

AstraZeneca considered that the statement of a price difference of up to £35.08 and the price comparisons which were based upon dosages of two puffs bd of Symbicort seriously misrepresented the overall price differences in clinical usage and were misleading and exaggerated.

The Panel noted that, according to the SPC, the recommended dose of Symbicort 400/12 was one puff bd and some patients might require up to a maximum of two puffs bd. Both doses appeared on the leavepiece in question.

The Panel noted AstraZeneca's comment that the usual unit dose for dry powder inhalers such as Symbicort Turbohaler was a single puff. However, the SPCs for Symbicort Turbohaler 100/6 and 200/6 gave doses of 1-2 puffs twice daily and stated that some patients might require up to a maximum of 4 puffs twice daily. It noted GlaxoSmithKline's submission that the cost difference in the low dose steroid (400mcg beclometasone equivalent) band related to Symbicort 200/6 one puff bd and Symbicort 400/12 od and that Symbicort 100/6 two puffs bd had been included for completeness.

The Panel noted that Symbicort allowed flexibility of dosing and patients could increase or decrease dosing. Although the leavepiece compared stable dosing there was no mention of flexible dosing with Symbicort which in the Panel's view was relevant even if the costs were clearly based on 30 days' stable dosing.

The Panel considered that the leavepiece was clear that it compared stable doses of Symbicort and Seretide over 30 days. The leavepiece did not imply equivalent control of asthma, it related to beclometasone equivalent daily doses. In that regard the Panel considered that like had been compared with like. However, the Panel considered that the claim that Seretide, '… can be up to £35.08 cheaper for 30 days' was misleading, not a fair comparison and exaggerated the differences between the products; there were instances when Seretide was more expensive than Symbicort. The Panel considered that the claim was not a fair reflection of all the data and was exaggerated. The Panel ruled breaches of the Code.

The slide at issue was headed 'Seretide and Symbicort'. The chart compared the 30 day cost of various presentations of the products at low dose (200mcg/day fluticasone 400mcg/day budesonide), medium dose (500mcg/day fluticasone 800mcg/day budesonide) and high dose (1000mcg/day fluticasone 1600mcg/day budesonide). The slide stated that 'All Seretide options gave 100mcg/day salmeterol'. The depictions of the cost of Symbicort also included the dose of formoterol.

AstraZeneca alleged that the slide was similarly misleading to the leavepiece. It compared the cost of Seretide Accuhaler one puff twice daily with Symbicort dosed at up to eight times daily.

The Panel noted that the dose of Seretide Accuhaler was one inhalation twice daily and Seretide Evohaler was two inhalations twice daily. The Panel considered that information presented in the slide was consistent with the SPC dosing instructions for the products. There was no mention of flexible dosing with Symbicort which in the Panels view was relevant.

The Panel considered that the slide, unlike the leavepiece, did not make it clear that the cost was based on a stable dose of the products. Thus the Panel considered that the slide was misleading and an unfair comparison. Breaches of the Code were ruled.

The Panel noted that the slide was effectively a bar chart presentation of the data shown in the leavepiece. Seretide bars were in purple and Symbicort were in red, with white text along them denoting the dose of formoterol. In the medium steroid dose (500mcg/day fluticasone; 800mcg/day budesonide) band extra Symbicort data had been added to that in the leavepiece ie the use of Symbicort 100/6, 4 puffs twice daily. Although the product could be used in that way, prescribers were much more likely to prescribe Symbicort 200/6 or 400/12 for long-term therapy for reasons of patient compliance and cost. The Panel considered that the addition of this data, and thus a prominent red bar, exaggerated the cost difference between Symbicort and Seretide. Without that bar prescribers would see that for low and medium steroid dose bands, Symbicort and Seretide were similarly priced. A breach of the Code was ruled.

AstraZeneca UK Limited complained about cost comparisons made by GlaxoSmithKline UK Ltd between AstraZeneca's Symbicort (budesonide/formoterol) and GlaxoSmithKline's Seretide (salmeterol/fluticasone propionate). The items at issue were a one page leavepiece (ref SFL/LVP/06/26861/2) and a slide from a presentation (ref SFL/SLK/06/28954/1).

1 Leavepiece SFL/LVP/06/26861/2

The leavepiece was headed 'Cost comparison for combination therapies in asthma at beclometasone equivalent daily doses' followed by 'Seretide (salmeterol/ fluticasone propionate) can be up to £35.08 cheaper for 30 days treatment at a stable dose than Symbicort (budesonide/formoterol) combination'. This was followed by a chart comparing various combinations and doses. The comparisons were grouped according to low dose steroid use (400mcg beclometasone equivalent daily dose), medium dose steroid use (800-1,000mcg beclometasone equivalent daily dose), and high dose steroid use (up to 2,000mcg beclometasone equivalent daily dose). The cost per 30 days' treatment at sustained dosing was given and the final column of the chart was headed 'Cost difference with Seretide per 30 day treatment'.

Five of the comparisons showed that there were savings using Seretide compared to sustained treatment with Symbicort. The savings made ranged from 86 pence to £35.08. Seretide was £12.19 more expensive than Symbicort in one of the low dose steroid use comparisons.

GlaxoSmithKline stated that the leavepiece had been used proactively and reactively by both primary care and secondary care representatives where there was a discussion on cost of Seretide. The leavepiece had also been mailed to health professionals in specific primary care trusts (PCT) regions where there had been pressure to switch to Symbicort from Seretide as a result of the perception that Symbicort was cheaper than Seretide.

COMPLAINT

AstraZeneca alleged that the leavepiece was misleading with respect to the relative cost of treatment with Symbicort compared to Seretide. In AstraZeneca's view the purpose of the leavepiece was to portray Symbicort as a significantly more expensive option than Seretide. This was not correct when one considered the overall price comparability of Symbicort with Seretide across the range of their doses and when used similarly. The misleading purpose of the leavepiece was clear from the heading 'Seretide (salmeterol/fluticasone propionate) can be up to £35.08 cheaper for 30 days treatment at a stable dose than Symbicort (budesonide/formoterol) combination'. Although the potential cost difference referred to was the comparison of 30 days of Symbicort 400/12, two

puffs bd vs Seretide 500 Accuhaler, one puff bd, this was an unfair comparison on which to base such a broad statement of price difference because:

a) Symbicort 400/12, two puffs bd was not a normally recommended dose of Symbicort. The recommended dose of Symbicort 400/12 as stated in its summary of product characteristics (SPC) was one puff bd. For adult asthmatics there was an additional statement that some patients might require up to a maximum of two puffs bd.

b) Consistent with this dosing recommendation only 2.2-3.6% of Symbicort prescriptions were for Symbicort 400/12, two puffs bd. A breakdown of prescribed doses was provided.

c) In the chart the occurrences where Symbicort was shown to be significantly more expensive than Seretide related to dosing regimens of two puffs bd. Such comparisons were potentially unfair. Unlike pressurised metered dose inhalers (MDIs) such as Seretide Evohaler, where the unit dose was two puffs, the usual unit dose for dry powder inhalers such as Symbicort Turbohaler and Seretide Accuhaler was one puff.

   The marketing authorizations for Symbicort, unlike Seretide Accuhaler, allowed flexibility of dosing so the normal dose of one puff bd could be increased to two or even four puffs bd or indeed reduced to one daily. This flexibility could be very useful in clinical practice and was utilised in patients' personal asthma action plans where short term increases in dosage might be recommended at times of increased symptoms. The Seretide Accuhaler marketing authorization did not permit similar flexibility as the recommended dose of each product strength was one puff bd, though this might in some cases be reduced to one puff daily.

   Dosage increases to two or four puffs bd of Symbicort would obviously incur additional cost for the period that the higher dose was maintained, however, similar dosage increases with Seretide incurred further costs because a new prescription for a higher strength of Seretide needed to be issued. The cost impact of these important differences between the products was omitted from the chart.

AstraZeneca considered that the statement of price difference of up to £35.08 and the price comparisons which were based upon dosages of two puffs bd of Symbicort seriously misrepresented the overall price differences between Symbicort and Seretide in clinical usage and were misleading, exaggerated and in breach of Clauses 7.2, 7.3 and 7.10 of the Code.

AstraZeneca stated that it had restricted its comments on the two items to specific aspects of the comparisons as presented. However the company noted that comparisons of this type between products that contained different inhaled steroids were complex because of the lack of consensus on equipotent doses of the different treatments. For example the British Thoracic Society/Scottish Intercollegiate Guidelines Network (BTS/SIGN) asthma guidelines suggested a 2:1 ratio in the equipotent doses of budesonide to fluticasone, but they noted that there might be variations with different delivery devices. Specifically with respect to the Turbohaler they stated 'There is limited evidence from two open studies of less than ideal design that budesonide via the Turbohaler is more clinically effective'. The more recent Global Initiative for Asthma (GINA, 2006) guideline advised a ratio of 8:5 in equipotent doses. The lack of consensus on equipotent doses added further complexity to the understanding of such these data and therefore it was not possible to make accurate direct comparisons between Symbicort and Seretide.

RESPONSE

GlaxoSmithKline noted AstraZeneca's statement that Symbicort 400/12 was not a normally recommended dose of Symbicort but further noted that it was clear from the SPC that two puffs bd was a recommended dose and it was therefore appropriate to include information regarding this dose.

The recommendations for stepwise management of asthma in adults published in the BTS Guideline on the Management of Asthma stated that:

> 'If control remains inadequate on 800mcg daily (adults) of an inhaled steroid plus a long-acting β2-agonist, consider the following interventions:
> - increasing inhaled steroids to 2000mcg/day (adults)…'

In such cases, the most appropriate formulation of Symbicort for delivering this dose would be Symbicort 400/12, two puffs bd.

Given that this dose of Symbicort was recommended in the SPC, and would be the most appropriate formulation for delivering high dose steroid (up to 2000mcg) it was entirely appropriate that this dose was included in the chart.

The IMS prescribing data showed that this dose was used in clinical practice, therefore it was appropriate to tell prescribers that in a stable dosing regimen required to deliver high dose steroid, Symbicort 400/12, two puffs bd was considerably more expensive [£76] than the equivalent beclometasone dose of Seretide, both via an Evohaler [£62.29] or in particular via an alternative dry powder device, the Accuhaler [£40.92].

GlaxoSmithKline stated that the actual frequency of prescribing of the doses referred to in the chart was irrelevant unless a claim of population or median dose was being made. Since no such claim was being made it was appropriate for GlaxoSmithKline to include this information in order to give a complete picture of the cost differences apparent throughout the range of doses and devices available with Seretide and Symbicort for use with all asthma patients receiving low, medium and high doses of steroid medication. This allowed prescribers to use this simple and factual

information based on doses used in clinical practice.

GlaxoSmithKline noted that AstraZeneca had claimed that in both the low dose and high dose bands, the occurrences where Symbicort was shown to be significantly more expensive than Seretide related to dosing regimens of two puffs bd. AstraZeneca claimed that such comparison was potentially unfair as unlike pressurised MDIs such as Seretide Evohaler where the unit dose was two puffs, the usual unit dose for dry powder inhalers such as Symbicort Turbohaler was one puff.

GlaxoSmithKline stated that unfortunately AstraZeneca's statements were factually incorrect on a number of counts:

Firstly, with regard to the low dose steroid (400mcg beclometasone equivalent) band, whilst a dosage regimen of two puffs bd had been included for Symbicort 100/6, the cost difference which was highlighted against the Seretide 50 Evohaler of a saving of at least 86 pence was a comparison of the cost of this device (£18.14) with the cost of either the Symbicort 200/6, one puff bd or Symbicort 400/12, one puff od (both £19), not the cost of Symbicort 100/6, two puffs bd (£33). Furthermore, the cost comparison of Seretide 100 Accuhaler with Symbicort, which highlighted that Seretide might be up to £12.19 more expensive, was a comparison with Symbicort 200/6, one puff bd and Symbicort 400/12, one puff od. It was interesting to note that if the comparison had been made with the two puffs Symbicort option which AstraZeneca had claimed had been done, this would actually have shown that Seretide 100 Accuhaler was £1.81 cheaper than Symbicort 100/6, two puffs.

Secondly, with regard to the high dose steroid (2000mcg beclometasone equivalent) band, it was impossible for GlaxoSmithKine to use anything but Symbicort 400/12, two puffs bd as the comparator. This dosage regimen of Symbicort 400/12 was included in the SPC, as a licensed dose, it was therefore an altogether appropriate dosage regimen for the delivery of a high dose steroid, required in some patients. Since Symbicort 400/12 Turbohaler was the highest dose presentation, there was no formulation of Symbicort that would deliver 2000mcg in a single puff dosing regimen. Consequently it was impossible for clinicians to use any Symbicort formulation for the delivery of 2000mcg in a single puff regimen, and as a result it was entirely logical for GlaxoSmithKline to include the two puffs dosing regimen in the table for the delivery of high dose steroid as this was how it would be delivered in practice.

Sections 4.2 of the Symbicort 100/6 and 200/6 SPCs gave the recommended doses as follows: 'Adults (18 years and older): 1-2 inhalations twice daily. Some patients may require up to a maximum of 4 inhalations twice daily' and 'Adolescents (12-17 years): 1-2 inhalations twice daily.'

It was clear therefore that the recommended doses of Symbicort were either one or two puffs twice daily, and the SPC made no recommendations or suggestions that one dosing regimen had any preference over another. AstraZeneca's suggestion that the usual unit dose for dry powder inhalers such as Symbicort Turbohaler was one puff was not supported by the SPC.

AstraZeneca also highlighted that the marketing authorizations for Symbicort and Seretide were different, and that the SPC for Symbicort allowed flexibility of dosing, with short term dose increases at times of increased symptoms, which was not permitted with Seretide. The purpose of the leavepiece was to compare the price of two competitor medicines based on the dose equivalents of beclometasone. As such the clinician could plainly see the dose equivalency. The suggestion that flexible use of Symbicort when control was lost altered the comparative acquisition cost of Seretide was not relevant. To include such data would require a comparative claim of the relative frequency of exacerbations from a head-to-head study to make such a comparison clinically relevant. This was not GlaxoSmithKline's intention and it made no claim in the leavepiece in that regard. As previously stated the intention of the leavepiece was a simple statement of the acquisition cost of two competitor products at relevant comparator doses. No statement of relative efficacy or frequency of exacerbations and thus dose escalation was made.

For the above reasons it was not relevant to compare costs when a flexible treatment approach was advocated without reference to clinical trial data. GlaxoSmithKline had compared the costs of treatment on the basis of a monthly stable treatment regimen which was factual and not misleading.

It was very useful for clinicians and prescribing advisors who often compared treatment options on the basis of a standard 30 days' treatment cost. Furthermore, whilst the use of Symbicort in a flexible dosing approach was an option, the SPC also recommended a stable dosing regimen reinforcing the fact that this information was consistent with the Symbicort SPC and clinical use.

Therefore it was entirely appropriate for GlaxoSmithKline to compare the costs of a stable dosing regimen of Seretide and Symbicort in order to guide treatment decisions. So as to limit the use of these cost comparisons to only this situation GlaxoSmithKline had made it quite clear in the leavepiece, both in the headline statement and the table, that the cost comparisons were for a stable dosing regimen:

- the headline statement clearly stated that Seretide could be up to £35.08 cheaper for 30 days treatment at a stable dose than Symbicort;
- the column heading in the table indicated cost/30 days treatment at sustained dosing.

In summary, GlaxoSmithKline did not agree that the leavepiece had been designed to deliberately mislead and that it seriously misrepresented the overall price differences. Symbicort was available in a range of formulations which were licensed to give a range of steroid doses by using either one or two puffs, and up

to four puffs, twice daily or even once daily. GlaxoSmithKline had been entirely transparent with the cost comparisons by including the full range of Symbicort Turbohaler devices, and the full range of dosing regimens, which were available to enable the administration of low, medium or high dose steroids; GlaxoSmithKline had clearly grouped the products according to these patient populations. Furthermore, GlaxoSmithKline had clearly stated where Seretide was both cheaper *and* more expensive than Symbicort, so in this regard the comparison was balanced, presented all the relevant information, and made no exaggerated claims. The headline clearly stated that Seretide *could* be cheaper than Symbicort, but did not make the claim that Seretide was *always* cheaper than Symbicort, and consequently this claim was not exaggerated or misleading. Furthermore the heading was balanced by the fact that all the relevant information about the cost of the products across the entire dose range was contained in a clear and obvious manner in the chart directly below it, in the same font and typeface.

PANEL RULING

The Panel noted that, according to the SPC, the recommended dose of Symbicort 400/12 was one puff bd and some patients might require up to a maximum of two puffs bd. Both doses appeared on the leavepiece in question.

The Panel noted AstraZeneca's comment that the usual unit dose for dry powder inhalers such as Symbicort Turbohaler was a single puff. However, the SPCs for Symbicort Turbohaler 100/6 and 200/6 gave doses of 1-2 puffs twice daily and stated that some patients might require up to a maximum of 4 puffs twice daily. It noted GlaxoSmithKline's submission that the cost difference in the low dose steroid (400mcg beclometasone equivalent) band related to Symbicort 200/6 one puff bd and Symbicort 400/12 od and that Symbicort 100/6 two puffs bd had been included for completeness.

The Panel noted that Symbicort allowed flexibility of dosing and patients could increase or decrease dosing. Although the leavepiece compared stable dosing there was no mention of flexible dosing with Symbicort which in the Panel's view was relevant even if the costs were clearly based on 30 day's stable dosing. With regard to AstraZeneca's comments about the lack of consensus on equipotent doses, the Panel noted that the Seretide SPCs stated that 100mcg of fluticasone propionate was approximately equivalent to 200mcg of beclomethasone dipropionate (CFC containing) or budesonide.

The Panel considered that the leavepiece was clear that it compared stable doses of Symbicort and Seretide over 30 days. The leavepiece did not imply equivalent control of asthma, it related to beclometasone equivalent daily doses. In that regard the Panel considered that like had been compared with like. However, the Panel considered that the claim that Seretide, '… can be up to £35.08 cheaper for 30 days' was misleading, not a fair comparison and exaggerated the differences between the products; there were instances when Seretide was more expensive that Symbicort. The Panel considered that the claim was not a fair reflection of all the data and was exaggerated. The Panel ruled breaches of Clauses 7.2, 7.3 and 7.10.

2 Presentation slide SFL/SLK/06/28954/1

The slide at issue was headed 'Seretide and Symbicort'. The chart compared the 30 day cost of various presentations of the products at low dose (200mcg/day fluticasone 400mcg/day budesonide), medium dose (500mcg/day fluticasone 800mcg/day budesonide) and high dose (1000mcg/day fluticasone 1600mcg/day budesonide). The slide stated that 'All Seretide options gave 100mcg/day salmeterol'. The depictions of the cost of Symbicort also included the dose of formoterol.

COMPLAINT

AstraZeneca stated that the slide emerged recently and since the concerns were very similar to the first item, AstraZeneca considered it appropriate to include it in this complaint even though it had not been discussed specifically with GlaxoSmithKline.

AstraZeneca alleged that the slide was similarly misleading to the leavepiece because:

a) It compared the cost of Seretide Accuhaler one puff twice daily with Symbicort dosed at up to eight times daily. For example: in the 'medium dose' band Seretide 250 one puff bd was compared with the cost of Symbicort 100/6 four puffs bd. Although this dosage of Symbicort was within the terms of the marketing authorization, it was misleading to represent it as a comparator when higher strength Symbicort presentations were available which were more appropriate other than for very short-term use.

b) As described above, increasing the number of puffs of Symbicort as a measure to restore or maintain asthma control at times of symptoms could be clinically useful and would incur additional cost for the period of higher dosing. However the chart ignored the cost of similar measures with Seretide where a new prescription was required.

c) Through additional labelling of the Symbicort bars, the chart showed the different daily doses of formoterol associated with the Symbicort regimens. The purpose of this was not made clear. However, alongside the chart it was stated that 'All Seretide options give 100mcg/day of salmeterol'. Such presentation was open to interpretation that the variable dosage of formoterol had some disadvantage. This was potentially misleading.

AstraZeneca alleged that this chart was misleading in breach of Clauses 7.2, 7.3 and 7.10.

AstraZeneca reiterated its comments from point 1 above that comparisons of this type between products

that contained different inhaled steroids were complex because of the lack of consensus on equipotent doses of the different treatments. For example the BTS/SIGN asthma guidelines suggested a 2:1 ratio in the equipotent doses of budesonide to fluticasone, but they noted that there might be variations with different delivery devices. Specifically with respect to the Turbohaler they stated 'There is limited evidence from two open studies of less than ideal design that budesonide via the Turbohaler is more clinically effective'. The more recent GINA 2006 guideline advised a ratio of 8:5 in equipotent doses. The lack of consensus on equipotent doses added further complexity to the understanding of such these data and therefore it was not possible to make accurate direct comparisons between Symbicort and Seretide

RESPONSE

GlaxoSmithKline stated that it was disappointed to see that this complaint included the slide referred to above as this was not previously subject to intercompany dialogue. Although there was a similarity to the complaint above, new complaints were made in that a different dose comparison was referred to at point a and 'additional labelling' at point c. GlaxoSmithKline had serious misgivings concerning the progression of this element of the complaint because of the lack of intercompany dialogue as required by Paragraph 5.2 of the Constitution and Procedure.

For completeness, AstraZeneca's concerns were addressed below, but GlaxoSmithKline asked that the Authority clarify the appropriateness of accepting this complaint.

Although AstraZeneca acknowledged that dosing Symbicort up to eight times daily was within the SPC, it suggested that it was misleading to include it as a comparator when higher strength formulations were available which were more appropriate. GlaxoSmithKline disagreed with this assertion since it was clear that the higher strength formulations were included in the bar chart. AstraZeneca's complaint also made assumptions regarding the formulations that prescribers would use for the delivery of steroid doses, and that prescribers would eliminate certain presentations from their options despite these options being possible through the licences of the products. GlaxoSmithKline considered that it was more appropriate to provide complete information for prescribers concerning the full range of formulations and devices that were available to deliver required doses of steroid. For example, since Symbicort 100/6 was licensed for use at four puffs bd this option had appropriately been included for the delivery of medium doses steroid (800mcg daily) alongside all other formulations of Symbicort that were licensed to deliver this dose. As this presentation was available to clinicians it was likely that it was used in clinical practice to deliver medium dose steroid and it was appropriate to make prescribers aware of the cost of this treatment option, and likewise any other treatment option.

AstraZeneca stated that comparisons between products that contained different inhaled steroids were complex due to the lack of consensus on equipotent doses of the different treatments. AstraZeneca quoted evidence from the BTS/SIGN asthma guidelines which suggested a 2:1 ratio of equipotent doses of budesonide to fluticasone in addition to the GINA 2006 guideline which advised a ratio of 8:5 as equipotent.

GlaxoSmithKline considered this point somewhat superfluous as, in accordance with the Code, all promotion of a medicine must follow its SPC. The SPC for Seretide (and Flixotide) stated quite clearly that:

'Prescribers should be aware that, in patients with asthma, fluticasone propionate is as effective as other inhaled steroids at approximately half the microgram daily dose. For example, 100mcg of fluticasone propionate is approximately equivalent to 200mcg of beclometasone dipropionate (CFC-containing) or budesonide.'

Consequently, in order to comply with the requirements of the Code, GlaxoSmithKline must consider that fluticasone and fluticasone-containing products were equivalent to double the dose of budesonide and beclometasone. As such the cost comparisons at issue did precisely this, and would be required to do so until such time as the SPCs changed.

The purpose of the slide was not to take account of flexible treatment options in the management of asthma, but to provide information on a commonly used metric - 30 days' treatment cost. The fact that these cost comparison referred to 30 days' treatment at stable dose was highlighted and made clear in the presentation.

AstraZeneca raised concerns regarding additional labelling of the Symbicort bars which showed the dose of formoterol which was delivered with each treatment option, and alleged that the statement alongside the chart which read 'All Seretide options give 100mcg/day salmeterol' was open to interpretation that formoterol had some disadvantage, and could be potentially misleading. However, the statements were provided in order that the cost comparison bar chart was completely transparent in showing that at higher doses of Symbicort the patient received increasing doses of long acting beta agonist (LABA), but that all presentations of Seretide delivered the same dose of LABA. GlaxoSmithKline considered that prescribers would be aware that the characteristics of formoterol and salmeterol were different. As such the intent was to be transparent that if Symbicort flexible dosing was used, patients would be receiving more LABA product with the higher doses of Symbicort, whereas with Seretide there was no increase in dose of LABA. There was absolutely no information shown on the slide or any other part of the presentation that would lead prescribers to believe that variable dosing of formoterol incurred any disadvantage as the doses presented were completely in line with the SPC for Symbicort.

The cost comparison chart had been used in both

primary and secondary care. The presentation had only been used to respond to questions about the costs of Seretide and Symbicort. Representatives were briefed via a teleconference regarding the reactive use of the material, and further guidance on its use was contained within the notes attached to each slide in the presentation.

PANEL RULING

Although it noted GlaxoSmithKline's comments about the lack of intercompany discussion about the slide, the Panel nonetheless considered that most of the allegations about the slide and the leavepiece were very similar. The Panel noted that AstraZeneca had raised additional points in relation to the slide. The Panel noted that Paragraph 5.2 of the Constitution and Procedure stated that complaints from pharmaceutical companies would only be accepted if the Director was satisfied that intercompany dialogue at a senior level had been offered in an attempt to resolve the matter. The Director noted that there had been no intercompany activity about AstraZeneca's comments regarding the information about the different daily doses of formoterol (point 2c above). Thus this aspect was not considered. The Director considered that there had been intercompany dialogue on AstraZeneca's comment about the comparison of one inhalation of Seretide with four inhalations of Symbicort in point 1 above so points 2a and 2b were considered.

The Panel noted that the dose of Seretide Accuhaler was one inhalation twice daily and Seretide Evohaler was two inhalations twice daily.

The Panel considered that information presented in the slide was consistent with the SPC dosing instructions for the products. There was no mention of flexible dosing with Symbicort which in the Panel's view was relevant.

The Panel considered that the slide was different to the leavepiece in that the slide did not make it clear that the cost was based on a stable dose of the products. Thus the Panel considered that the slide was misleading and an unfair comparison. Breaches of Clauses 7.2 and 7.3 were ruled.

The Panel noted that the slide was effectively a bar chart presentation of the data shown in the leavepiece. Seretide bars were in purple and Symbicort were in red, with white text along them denoting the dose of formoterol. In the medium steroid dose (500mcg/day fluticasone; 800mcg/day budesonide) band extra Symbicort data had been added to that in the leavepiece ie the use of Symbicort 100/6, 4 puffs twice daily. Although the product could be used in that way, prescribers were much more likely to prescribe Symbicort 200/6 or 400/12 for long-term therapy for reasons for patient compliance and cost. The Panel considered that the addition of this data, and thus a prominent red bar, exaggerated the cost difference between Symbicort and Seretide. Without that bar prescribers would see that for low and medium steroid dose bands, Symbicort and Seretide were similarly priced. A breach of Clause 7.10 was ruled.

Complaint received 5 April 2007

Case completed 11 June 2007

PRESCRIBING ADVISOR v ASTRAZENECA

Crestor journal advertisement

A prescribing advisor alleged that an advertisement for Crestor (rosuvastatin), issued by AstraZeneca, was misleading. The advertisement featured the claim 'Bill's cholesterol only dropped so far with simvastatin, but Crestor was all he needed to achieve his treatment goals…'. The phrase 'First choice second line' appeared beneath the product logo in the bottom right hand corner.

The complainant believed that the advertisement was misleading because it implied that Crestor had been directly compared with simvastatin, which was not so. The complainant noted that a meta-analysis demonstrated that when adequate doses of simvastatin were prescribed the cholesterol lowering was identical. The complainant further considered that the advertisement implied that simvastatin was an inferior medicine and that such criticism of other products was not permitted under the Code.

The Panel did not consider that the advertisement implied that Crestor had been directly compared with simvastatin. The Panel noted AstraZeneca's submission that the meta analysis to which the complainant referred did not assess the efficacy of specific statins. The Panel considered that the claim 'Bill's cholesterol only dropped so far with simvastatin, but Crestor was all he needed to achieve his treatment goals' in conjunction with the strapline 'First choice second line' referred to the second line, use of Crestor after a patient had not achieved treatment goals on simvastatin. The Panel noted data provided by AstraZeneca in this regard. The Panel ruled no breach of the Code.

Further the Panel did not consider that the advertisement inferred that simvastatin was an inferior medicine as alleged. A reference to first and second line treatment did not in itself imply inferiority of the medicine used first line. No breach of the Code was ruled.

During its consideration of this case the Panel was concerned that the phrase 'First choice second line' implied that Crestor was the first choice for second line use. Such an implication was unacceptable in relation to the requirements of the Code. The Panel requested that the company be advised of its views in this regard.

A prescribing advisor complained about a journal advertisement (ref CRES11768) for Crestor (rosuvastatin), issued by AstraZeneca UK Limited, which had appeared in the March/April edition of Pharmacy in Practice.

The advertisement featured a man reading a newspaper in front of the Sydney Opera House and was headed 'No Worries Mate'. Beneath the heading the advertisement continued: 'Bill's cholesterol only dropped so far with simvastatin, but Crestor was all he needed to achieve his treatment goals. Now he can enjoy his trip down under'. The strapline 'First choice second line' appeared beneath the product logo in the bottom right hand corner of the advertisement.

COMPLAINT

The complainant believed that this advertisement was misleading, in breach of the Code, because:

- It implied that Crestor had been directly compared with simvastatin, when this was not the case. Indeed in a large meta-analysis of trials including over 90,000 patients it was demonstrated that when adequate doses of simvastatin were prescribed the cholesterol lowering was identical.
- It implied that simvastatin was an inferior medicine. The complainant understood that such criticism of other products was not permitted under the Code.

When writing to AstraZeneca, the Authority asked it to respond in relation to Clauses 7.2, 7.3 and 7.4 of the Code.

RESPONSE

AstraZeneca stated that the claim 'Bill's cholesterol only dropped so far with simvastatin, but Crestor was all he needed to achieve his treatment goals' described the typical experience of a dyslipidaemic patient failing to reach target on a first-line statin such as simvastatin, transferring to a more efficacious, second-line statin and then reaching target. This was supported by the strapline 'First choice second line'.

UK data showed that approximately 40% of patients given simvastatin might not reach the current UK total cholesterol target of ⩽5mmol/L. The scenario described in the advertisement would be faced by many prescribers on a regular basis, therefore the message could not be considered misleading.

The complainant referred to a Lancet report of a meta-analysis that was described as providing evidence 'that when adequate doses of simvastatin are prescribed the cholesterol lowering is identical' (Cholesterol Treatment Trialists (CTT) Collaborators Study 2005).

It was difficult to comment on this statement as, not only was the comparator unspecified when the complainant stated that 'cholesterol lowering is identical', but there was no efficacy data for simvastatin reported in the Lancet meta-analysis. Two of the 14 trials (originally reported between 1994 and 2004)

included in the study featured simvastatin as a treatment option. However no assessment of the efficacy of specific statins was provided.

Furthermore, a study designed to investigate the comparative cholesterol-lowering effects of statins across the dose ranges demonstrated that it was not possible for simvastatin, at licensed doses, to lower cholesterol to the same extent as Crestor.

The complainant alleged that the advertisement 'implied that simvastatin was an inferior medicine'.

AstraZeneca did not believe that its reference to simvastatin was anything other than accurate and objective. Health professionals were familiar with the current situation in the management of dyslipidaemia where a moderately potent generic statin was recommended first line with a more potent second line alternative available when patients failed to meet target. This pathway was recommended by many local and regional formularies. An example of this clinical scenario in action was provided by a recent report that demonstrated that 68% of dyslipidaemic patients failing to reach General Medical Services (GMS) and Quality Outcome Framework (QOF) target on simvastatin 40mg achieved it on Crestor 10mg (Kassianos et al 2006).

Similar situations existed in other therapeutic areas. AstraZeneca disagreed that reference to situations where a first line generic option had failed, could be interpreted as a 'criticism' of that treatment option, but was a valid representation of how treatment protocols should work to ensure patients achieved appropriate results.

AstraZeneca did not therefore accept that there had been breaches of Clauses 7.2, 7.3 and 7.4.

PANEL RULING

The Panel did not consider that the advertisement implied that Crestor had been directly compared with simvastatin as alleged. Indeed the Panel noted AstraZeneca's submission that the meta analysis to which the complainant referred did not assess the efficacy of specific statins. The Panel considered that the claim, 'Bill's cholesterol only dropped so far with simvastatin, but Crestor was all he needed to achieve his treatment goals …' in conjunction with the strapline beneath the product logo 'First choice second line' referred to the second line use of Crestor after a patient had not achieved treatment goals on simvastatin. The Panel noted data provided by AstraZeneca in this regard. The Panel ruled no breach of Clauses 7.2, 7.3 and 7.4 on this point.

Further the Panel did not consider that the advertisement inferred that simvastatin was an inferior medicine as alleged. A reference to first and second line treatment of a dyslipidaemic patient did not in itself imply inferiority of the medicine used first line. No breach of Clauses 7.2, 7.3 and 7.4 was ruled.

During its consideration of this case the Panel was concerned that the phrase 'First choice second line' implied that Crestor was the first choice for second line use. Such an implication was unacceptable in relation to the requirements of Clause 7.10 of the Code. The Panel requested that the company be advised of its views in this regard.

Complaint received	**5 April 2007**
Case completed	**26 June 2007**

ANONYMOUS v ASTRAZENECA

Alleged inappropriate hospitality

An anonymous complaint was received about inappropriate hospitality alleged to have been provided by three pharmaceutical companies, one of which was AstraZeneca. The complainant provided a copy of the programme for a meeting of the Midlands Psychiatric Research Group to be held in June 2007.

The complainant alleged that a few psychiatrists under the name of 'West Midland Research Group' had been using pharmaceutical companies for their personal advantages, ambitions and growth. The group organised one meeting a year and called it an international conference. There was no scientific committee, no invitation for research abstracts or poster. The group invited whom it wanted to. Until last year the registration fee was very little, about £15. Delegates were allowed to have free hotel, food and an evening cultural programme. It was inappropriate hospitality at the expense of pharmaceutical companies. Even delegates might not be aware that pharmaceutical companies had given money.

The Panel noted that there were some differences between the programme for the 2007 meeting submitted by AstraZeneca and that provided by the complainant.

The programme provided by AstraZeneca provided a statement that AstraZeneca and other companies were providing educational grants.

In relation to the 2007 meeting AstraZeneca had paid £5,000 towards accommodation costs, delegate rates (including lunch and dinner), printing of abstracts, workshop and other educational material, audiovisual and function room hire and speaker fees.

The Panel considered that according to the programme, the scientific/educational content was not unreasonable for sponsorship by a pharmaceutical company. The meeting appeared to be primarily scientific/educational. The venue was not unreasonable. The programme referred only to 'Dinner' each evening. The Panel noted the allegations about the cultural musical event. There was no mention of this on the programme. It considered that if there was to be such entertainment then it would be inappropriate for a pharmaceutical company to sponsor it. The Panel noted AstraZeneca's submission that MPRG had told it that no entertainment activities were planned during the meeting nor were any referred to in its letter to AstraZeneca.

There was no evidence that AstraZeneca's sponsorship had paid for or subsidised a music programme as alleged in relation to the 2007 meeting. On the information before it the Panel considered that AstraZeneca's sponsorship of the meeting as described was not unacceptable and thus no breach was ruled.

An anonymous complaint was received about inappropriate hospitality alleged to have been provided by three pharmaceutical companies, one of which was AstraZeneca UK Limited. The complainant provided a copy of the programme for a meeting of the Midlands Psychiatric Research Group to be held in June 2007.

COMPLAINT

The complainant stated that a few psychiatrists under the name of 'West Midland Research Group' had been using pharmaceutical companies for their personal advantages, ambitions and personal growth. They had organised a conference and taken money from pharmaceutical companies for it. In fact nobody knew what West Midland Research Group was; no research was conducted or published by this group and there was no research grant or funding available for this group. The group organised one meeting a year and called it an international conference. There was no scientific committee, no invitation for research abstracts or poster. The group invited whom it wanted to. Until last year the registration fee was very little, about £15. Delegates were allowed to have free hotel, food and an evening cultural programme. It was inappropriate hospitality at the expense of pharmaceutical companies. Even delegates might not be aware that pharmaceutical companies had given money.

The few psychiatrists used this money to invite speakers who they wanted to oblige and they were friendly. They paid their fare, speaker fees, and hotel expenses. They used pharmaceutical company money for hospitality of delegates who seemed to be their friends and repeatedly attended their conference. They all enjoyed the evening cultural programme. It was like an annual get-together for them.

The group had taken money from AstraZeneca. One of the organisers maintained the data base of most of the Asian and Arabic psychiatrists. It was a number game. They had numbers to influence pharmaceutical companies and pharmaceutical companies tried to oblige vulnerable psychiatrists who could increase the prescriptions.

The pharmaceutical companies wanted to sell their medicines and it was a good nexus to have mutual benefits. It was worth investigating.

More or less the same delegates attended their other meetings such as the South Asian forum meeting. The

majority of delegates were the same every year. It was indicated that money was paid directly to 'West Midland Research Group' and they used this money as they wanted for cultural programmes, hotel and other expenses.

Delegates were motivated by the free hotel and sense of holiday; until last year they were allowed to bring their family, meeting common friends and enjoying night cultural programme.

Organisers benefited by trying to influence and build up relationship with world prominent psychiatrists who they invited as speakers and then used them for personal growth. They got impressed by seeing a large number of psychiatrists.

The motivating factor for pharmaceutical companies was taking advantage of numbers and trying to sell their medicines.

When writing to AstraZeneca, the Authority asked it to respond in relation to Clauses 2, 9.1 and 19.1 of the Code.

RESPONSE

AstraZeneca noted that the Midlands Psychiatric Research Group (MPRG) was an independent group of NHS doctors that was set up by a psychiatrist (the current Chairman) nine years ago for the purpose of organising medical educational activity in the Midlands region. Some of this activity included the facilitation of small collaborative groups to discuss research. The MPRG was not created by, nor did it depend for its existence on, the industry. The group was no different to many such groups in the NHS nationwide that existed to promote and organise educational activity.

The MPRG was not affiliated to the South Asian Forum referred to by the complainant and was open to non-Asian delegates. The educational agendas did not have any focus on South Asian topics.

Since its inception nine years ago, the MPRG had been organising annual CPD approved educational events running over the course of 2-3 days with wide ranging, topical agendas on psychiatry that had attracted speakers and delegates from around the UK and abroad. Each of these meetings was financially part-sponsored by multiple pharmaceutical companies and by delegate registration fees. They were academically sponsored by the WPA (World Psychiatric Association) and WAPR (World Association for Psychosocial Rehabilitation). The group also regularly organised many smaller hospital educational meetings.

AstraZeneca sponsorship of MPRG

AstraZeneca had provided financial part-sponsorship for each of the large annual meetings held since 2004 with the exact proportion of total funding varying annually. The MPRG organised various other much smaller educational activities around the Midlands but AstraZeneca had not provided funding for any of these. Nor had AstraZeneca funded or supported the MPRG for any other form of activity or materials.

AstraZeneca provided funds for the annual meetings on the basis of information provided by the MPRG in sponsorship applications that it initiated. The applications were all considered under the terms of the AstraZeneca sponsorship policy, as were all requests for financial support from NHS institutions, academic groups and such like for projects that would benefit patients and support the NHS.

In its applications, the MPRG provided details of each of these meetings as required by the AstraZeneca sponsorship policy. These details were scrutinised for Code and Policy compliance and funding provided by direct transfer to the MPRG account with no further involvement from AstraZeneca other than the presence of a promotional stand in the exhibition area of the meetings along with other pharmaceutical companies. AstraZeneca personnel did not attend any other parts of the meetings including the educational sessions, dinners or any social events.

AstraZeneca had never chosen, invited, or sponsored the attendance of, individual delegates to these meetings.

The MPRG initiated, organised and delivered these meetings. It created the agenda, chose the venue, speakers and invited the delegates. Spouses were never invited except as delegates in their own right. AstraZeneca provided part-funding on the basis of information about these meetings provided by the MPRG. AstraZeneca had never had any input into, or approval of, any of the meetings content including the presentations and workshops; it had never chosen, briefed or recommended any of the speakers and had not determined nor used any outputs of any of the meetings. Nor did it have any intention of doing so in the future. AstraZeneca provided funding on the basis that these meetings would be of ultimate benefit to patients and the NHS and had never attached any conditions or requirements for commercial or other benefit to AstraZeneca from these meetings in any way.

Therefore, AstraZeneca believed that final responsibility for these meetings rested with the MPRG.

AstraZeneca provided detailed information about by the MPRG in relation to each of the annual meetings from 2004 to 2007.

1 Meeting on 14 - 16 June 2007

AstraZeneca paid £5,000 towards this meeting which the MPRG estimated would cost £38,000-£40,000. Five other pharmaceutical companies had also provided funding. In response to this complaint, the MPRG had indicated that delegate fees would contribute approximately £6,150 towards the total cost (with around 123 delegates paying a £50 registration fee each).

AstraZeneca approved and provided this funding on the basis of information provided by the MPRG in its letter of application, which was provided.

Below was the information that the MPRG submitted in support of its application (in bold) followed by AstraZeneca comments on the acceptability of that information:

- **The MPRG submitted that this was to be a CPD approved, quality medical educational event that would be of benefit to patients and the NHS.** A high quality medical educational event in topical areas of psychiatry would upskill clinicians and was therefore of clear ultimate benefit to patients and the NHS. From the repute of the stated speakers and fact of academic sponsorship from the WPA and WAPR, this was a very high quality medical educational event.
- **Draft agenda for the meeting setting out timings, subjects and speakers** (provided). This agenda detailed 16 hours high quality, non-promotional education over 3 days (Friday, Saturday, Sunday) and 2 nights. The two overnight stays were justified since delegates were expected from all over the country and because of the length of the educational content. The speakers were of national and international repute and three of them were from other countries (one each from the USA, Italy and India). The quality of this agenda would lead to ultimate benefit to patients and would support the NHS. This draft was sent to delegates upon invitation early in the year and did not acknowledge industry sponsorship because it was created before such support had been finalised. This was the same draft as submitted by the complainant. However, the initial invite/registration letter (provided) sent to delegates along with this draft agenda did refer to industry funding (see second to last bullet below). Also, the final agenda (provided) referred to the receipt of educational grants from AstraZeneca and five other companies.
- **A breakdown of the specific ways in which sponsorship funds would be used and the projected total cost of the meeting (£38-40K).** The MPRG stated that the funds were to be used on accommodation costs, delegate rates (including lunch and dinner), printing of abstracts, workshop and other educational material, audiovisual and function room hire, and speaker fees. All of these were legitimate meetings costs. In response to the complaint, the MPRG had provided AstraZeneca with an accepted delegate list that contained 123 anticipated attendees. With a total meeting cost of up to £40K spread across these 123 delegates, that equated to £325 per delegate which was not an unreasonable amount considering that this included payment for all these meeting related costs including accommodation and subsistence across 3 days. AstraZeneca believed that these costs were modest and at levels that the delegates would adopt when paying for themselves.
- **The venue.** This was a 3 star venue that was not recognised as a luxury or sporting venue and had suitable conference, restaurant and accommodation facilities that were conducive to the primary educational purpose of the meeting. The typical charge for overnight accommodation at this venue was modest and in line with the levels that delegates would adopt when paying for themselves.
- **The nature of the delegates to be invited** (NHS consultants and junior doctors). All delegates were invited by the MPRG. AstraZeneca had not chosen, invited or sponsored the attendance of any individual delegates. The MPRG did not have a formal membership and had told AstraZeneca that meeting invitations (in the form of a draft agenda and invite/registration letter) were posted to attendees of previous meetings. The draft agenda for the meeting was also advertised on hospital notice-boards around the Midlands region and other areas. In response to the complaint, the MPRG had given AstraZeneca a copy of the invitation/registration letter (provided). This letter made clear that spouses and non-medical individuals should not attend. The MPRG had stated to AstraZeneca that spouses and non-medical family members were not invited to (and nor did they attend) any of the meetings from 2004-2007 unless they were delegates in their own right.
- **The existence of academic sponsorship by the internationally recognised World Psychiatric Association (WPA) and the World Association for Psychosocial Rehabilitation (WAPR).** Sponsorship by these associations was an independent validation of the high educational content of these meetings. A copy of the letter to the MPRG, confirming academic sponsorship from the WPA and WAPR, was provided.
- **A written assurance that the contribution of AstraZeneca would be acknowledged on all materials relating to the event.** In response to this complaint, the MPRG had made available the initial invitation/registration letter (provided) that was sent to the delegates. This letter stated '… some pharmaceutical companies are providing some funding ..'. No individual companies were named because at the time that this was sent, such funding had not been confirmed. This letter also made clear that spouses and non-medical individuals should not attend. Also provided was a copy of the final agenda (to be disseminated at the meeting), which clearly stated that educational grants had been received from AstraZeneca and five other companies.
- **A written assurance that the MPRG would comply with the Code in the conduct of the meeting.**

AstraZeneca noted that the MPRG's application for sponsorship did not refer to any social or entertainment events.

Having scrutinised this sponsorship application, AstraZeneca paid £5,000 as part-funding towards the total costs by way of a direct bank transfer into the official MPRG account. At the same time, a letter of agreement was sent to the MPRG (provided) setting out terms & conditions. These terms stated that the funds were being provided only for the use stated by the applicant.

In response to the complaint, the MPRG had also given AstraZeneca the final delegate list (provided). This list contained 123 delegates of whom 81 were from the Midlands, 32 were from other parts of the UK and 10 were from abroad. This emphasised the broad national and international appeal of the agenda and the need for overnight stays because more than a third of these 123 delegates would have to travel for 1.5 hours or more.

The MPRG had stated to AstraZeneca that no entertainment activities were planned during this meeting nor were any such referred to, in its letter of application.

Summary

The MPRG initiated, organised and delivered this meeting. AstraZeneca had contributed a fraction of the total costs, on the basis of information provided in an application initiated by the MPRG. This was an educationally valid, independent meeting that had been sponsored by several pharmaceutical companies. The arrangements had made for accommodation and subsistence were modest, in line with the Code and secondary to the educational purpose of the meeting. AstraZeneca believed that this was a valid sponsorship request. Therefore, AstraZeneca denied a breach of the Code with regard to Clauses 2, 9.1 and 19.1.

Overlap of delegates across meetings

In response to the complaint, the MPRG had told AstraZeneca that delegates were chosen on the basis of their status as clinicians in psychiatry. Delegates to previous meetings were invited to subsequent meetings on the basis that their previous attendance demonstrated an interest in the type of educational agenda that the MPRG created. AstraZeneca believed that this was a valid basis for an invitation. In addition, the agenda was more widely circulated on hospital notice boards and the MPRG had stated that 20-30% of attendees at each meeting had never attended a previous meeting. It was likely that many delegates would re-attend successive meetings as was likely to occur in any valid, annual educational event or congress.

In its letter of application, the MPRG stated that the criterion for invitation was purely the status of the invitee as a clinician and not any personal or other relationship.

Conclusions

AstraZeneca maintained that sponsorship of these educational meetings was entirely valid, Code compliant and led to significant benefits to patients and the NHS through the maintenance and enhancement of the medical skills and knowledge of clinicians. The MPRG was an independent organisation whose applications for sponsorship AstraZeneca had scrutinised for Code compliance and funded in good faith along with several other companies.

PANEL RULING

The Panel noted that there were some differences between the 2007 programme submitted by AstraZeneca and that provided by the complainant. The Panel noted that the 2007 meeting was to start on the evening of 14 June with a lecture and dinner. According to the programme provided by AstraZeneca, the programme for Friday 15 June ran from 9.15am until 4.45pm and the arrangements for Saturday were similar, 9.30am until 5pm. There were small differences in timing in the agenda provided by the complainant.

The programme provided by AstraZeneca stated that AstraZeneca and other companies were providing educational grants.

The Panel noted that the complainant included the programme for the 2007 meeting. No specific allegations had been made about other meetings. AstraZeneca had provided details of its interactions with the West Midlands Research Group in relation to annual meetings from 2004 onwards.

The 2007 meeting was to be held in Coventry. AstraZeneca had paid £5,000 towards accommodation costs, delegate rates (including lunch and dinner), printing of abstracts, workshop and other educational material, audiovisual and function room hire and speaker fees.

The Panel considered that according to the programme, the scientific/educational content was not unreasonable for sponsorship by a pharmaceutical company. The meeting appeared to be primarily scientific/educational. The venue was not unreasonable. The programme referred only to 'Dinner' each evening. The Panel noted the allegations about the cultural musical event. There was no mention of this on the programme. It considered that if there was to be such entertainment then it would be inappropriate for a pharmaceutical company to sponsor it. The Panel noted AstraZeneca's submission that MPRG had told AstraZeneca that no entertainment activities were planned during the meeting nor were any referred to in its letter to AstraZeneca.

There was no evidence that AstraZeneca's sponsorship had paid for or subsidised a music programme as alleged in relation to the 2007 meeting. On the information before it the Panel considered that AstraZeneca's sponsorship of the meeting as described was not unacceptable and did not breach Clause 19.1. The Panel did not consider that there had been breaches of Clauses 2 and 9.1.

Complaint received	**27 April 2007**
Case completed	**21 May 2007**

ANONYMOUS v JANSSEN-CILAG

Alleged inappropriate hospitality

An anonymous complaint was received about inappropriate hospitality alleged to have been provided by three pharmaceutical companies, one of which was Janssen-Cilag.

The complainant alleged that a few psychiatrists under the name of 'West Midland Research Group' had been using pharmaceutical companies for their personal advantages, ambitions and growth. The group organised one meeting a year and called it an international conference. There was no scientific committee, no invitation for research abstracts or poster. The group invited whom it wanted to. Until last year the registration fee was very little, about £15. Delegates were allowed to have free hotel, food and an evening cultural programme. It was inappropriate hospitality at the expense of pharmaceutical companies. Even delegates might not be aware that pharmaceutical companies had given money.

The Panel noted that there were some differences between the programme for the 2007 meeting submitted by Janssen-Cilag and that provided by the complainant.

No specific allegations had been made about other meetings. Janssen-Cilag had provided details of its interactions with the West Midlands Research Group.

In relation to the 2007 meeting, Janssen-Cilag would pay £2,000 sponsorship towards the hire of the venue, audiovisual equipment, speaker expenses plus the cost of one of the speakers. Janssen-Cilag had not sponsored any delegates to attend.

The Panel considered that according to the programme, the scientific/educational content was not unreasonable for sponsorship by a pharmaceutical company. The meeting appeared to be primarily scientific/educational. The programme referred only to 'Dinner' each evening. The Panel noted the allegations about the cultural musical event. There was no mention of this on the programme. It considered that if there was to be such entertainment then it would be inappropriate for a pharmaceutical company to sponsor it.

There was no evidence that Janssen-Cilag's sponsorship had paid for or subsidised a music programme as alleged. On the limited information before it the Panel considered that Janssen-Cilag's sponsorship of the meeting as described was not unacceptable and thus no breach was ruled.

An anonymous complaint was received about inappropriate hospitality alleged to have been provided by three pharmaceutical companies, one of which was Janssen-Cilag Ltd.

COMPLAINT

The complainant stated that a few psychiatrists under the name of 'West Midland Research Group' had been using pharmaceutical companies for their personal advantages, ambitions and growth. They had organised a conference and taken money from pharmaceutical companies for it. In fact nobody knew what West Midland Research Group was as no research was conducted or published by this group and there was no research grant or funding available for this group. The group organised one meeting a year and called it an international conference. There was no scientific committee, no invitation for research abstracts or poster. The group invited whom it wanted to. Until last year the registration fee was very little, about £15. Delegates were allowed to have free hotel, food and an evening cultural programme. It was inappropriate hospitality at the expense of pharmaceutical companies. Even delegates might not be aware that pharmaceutical companies had given money.

The few psychiatrists used this money to invite speakers who they wanted to oblige and they were friendly. They paid their fare, speaker fees, and hotel expenses. They used pharmaceutical company money for hospitality of delegates who seemed to be their friends and repeatedly attended their conference. They all enjoyed the evening cultural programme. It was like an annual get-together for them.

The group had taken money from Janssen-Cilag. One of the organisers maintained the data base of most of the Asian and Arabic psychiatrists. It was a number game. They had numbers to influence pharmaceutical companies and pharmaceutical companies tried to oblige vulnerable psychiatrists who could increase the prescriptions.

The pharmaceutical companies wanted to sell their medicines and it was a good nexus to have mutual benefits. It was worth investigating.

More or less the same delegates attended their other meetings such as south Asian forum meeting. The majority of delegates were the same every year. It was indicated that money was paid directly to 'west midland research group' and they used this money as they wanted for cultural programmes, hotel and other expenses.

Delegates were motivated by the free hotel and sense of holiday; until last year they were allowed to bring their family, meeting common friends and enjoying night cultural programme.

Organisers benefited by trying to influence and build up relationship with world prominent psychiatrists

who they invited as speakers and then used them for personal growth. They got impressed by seeing a large number of psychiatrists.

The motivating factor for pharmaceutical companies was taking advantage of numbers and trying to sell their medicines.

When writing to Janssen-Cilag, the Authority asked it to respond in relation to Clauses 2, 9.1 and 19.1 of the Code.

RESPONSE

Janssen-Cilag denied any breaches of Clauses 2, 9.1 and 19.1 and contended that the meetings referred to were of a high scientific standard, worthy of support, and provided a valuable educational benefit to members of the West Midlands' psychiatry community who attended.

The anonymous complaint was remarkably similar to a previous anonymous complaint about a legitimate educational meeting arranged by the South Asian Forum (Case AUTH/1897/10/06) to which Janssen-Cilag responded and was found not in breach of the Code. Janssen-Cilag believed this complaint to be vexatious toward the West Midlands Research Group (and supportive pharmaceutical companies).

Janssen-Cilag explained that the Midlands Psychiatric Research Group (MPRG) and the West Midlands Research Group were the same entity. The group had evolved over the past few years, and as well as holding small academic sessions, now held annual meetings, the latest of which was the forthcoming meeting in Coventry; known as the Midlands Psychiatric Research Group International Seminar; it was due to be held in June 2007.

The seminar was organised by the MPRG in collaboration with the World Association for Psychosocial Rehabilitation (WAPR) and the Section on Developing Countries of the World Psychiatric Association (WPA) and was of a high scientific standard, indeed the President elect of the WPA, (from Italy), was to be a guest speaker talking on the 'Current Problems of Diagnosis in Psychiatry'. In addition, other eminent and internationally known speakers from the USA and the UK were also due to present at the meeting.

Janssen-Cilag provided a copy of the latest draft of the scientific programme and noted that although meal times ie lunch and dinner were indicated, there was no social agenda of music, dance or cultural programme as alleged by the complainant.

The forthcoming international seminar was open to any health professional practising mental health, mainly, but not exclusively, in the West Midlands. The organisers had advised Janssen-Cilag that it accepted and encouraged registration of all those who wished to participate, notwithstanding that places were limited, and applicants were accepted on a first come, first served basis. Information regarding the meeting was sent to those individuals who had attended previous meetings, and also the meeting details were circulated to other groups of psychiatrists. In addition information on the international seminar was at different educational events in the West Midlands for general information.

In terms of the geographic location of origin of the delegates, in addition to psychiatrists working in the Midlands region, the meeting attracted about 30% of its participants from other parts of the country and also some overseas delegates.

For the forthcoming meeting, Janssen-Cilag would provide £2,000 sponsorship towards the hire of the venue, audiovisual equipment hire, and speaker expenses. In return Janssen-Cilag could erect a promotional stand at the meeting. The venue for the meeting was Coventry.

For this year's international seminar, Janssen-Cilag would also sponsor a speaker, a consultant in psychiatry and research fellow from a UK university. An honorarium of £950 would be paid directly to this speaker by Janssen-Cilag; the title of the lecture would be 'Long Acting Injectable Anti-psychotic Medication'.

In 2006, Janssen-Cilag sponsored that year's international seminar, also held in Coventry, with a £2,000 grant and also sponsored an international speaker from Canada who spoke on 'Schizophrenia: Compliance and Long-term Outcome'

Janssen-Cilag provided further details of the 2006 and 2005 meetings.

Janssen-Cilag had not sponsored any delegates to attend (other than the two speakers already identified for the 2006 and 2007 meetings), nor was Janssen-Cilag organising the meeting directly and was therefore not able to provide precise costs for the venue. Janssen-Cilag suggested however, that a £2,000 contribution towards venue hire and audiovisual support was not excessive within the overall framework of these international seminars.

Janssen-Cilag contended that the MPRG was a bona fide professional organisation; its annual international seminar was of a high standard, with the content pertinent to health professionals practising mental health. Its meetings attracted high calibre international speakers, and also, as delegates, many psychiatrists and other health professionals from predominantly, but not exclusively, the West Midlands. Janssen-Cilag considered that such meetings deserved support and submitted that the manner in which it had supported them did not contravene the Code. Janssen-Cilag therefore denied breaches of Clauses 2, 9.1, or 19.1.

PANEL RULING

The Panel noted that there were some differences between the programme submitted by Janssen-Cilag and that provided by the complainant. The Panel noted

that the 2007 meeting was to start on the evening of 14 June with a lecture and dinner. According to the programme provided by Janssen-Cilag, the programme for Friday 15 June ran from 9.30am until 4.45pm and the arrangements for Saturday were similar, 9.30am until 5pm. There were small differences in timing in the agenda provided by the complainant.

The programme provided by Janssen-Cilag stated that AstraZeneca, Janssen-Cilag, Lilly, Lundbeck, Bristol-Myers Squibb and Wyeth were providing educational grants.

The Panel noted that the complainant included the programme for the 2007 meeting. No specific allegations had been made about other meetings. Janssen-Cilag had provided details of its interactions with the West Midlands Research Group.

The 2007 meeting was to be held in Coventry. Janssen-Cilag would pay £2,000 sponsorship plus the cost of one of the speakers. Janssen-Cilag had not sponsored any delegates to attend. The £2,000 was towards the hire of the venue, audiovisual equipment hire and speaker expenses.

The Panel considered that according to the programme, the scientific/educational content was not unreasonable for sponsorship by a pharmaceutical company. The meeting appeared to be primarily scientific/educational. The programme referred only to 'Dinner' each evening. The Panel noted the allegations about the cultural musical event. There was no mention of this on the programme. It considered that if there was to be such entertainment then it would be inappropriate for a pharmaceutical company to sponsor it.

There was no evidence that Janssen-Cilag's sponsorship had paid for or subsidised a music programme as alleged. On the limited information before it the Panel considered that Janssen-Cilag's sponsorship of the meeting as described was not unacceptable and did not breach Clause 19.1. The Panel did not consider that there had been breaches of Clauses 2 and 9.1.

Complaint received	**27 April 2007**
Case completed	**21 May 2007**

ANONYMOUS v WYETH

Alleged inappropriate hospitality

An anonymous complaint was received about inappropriate hospitality alleged to have been provided by three pharmaceutical companies, one of which was Wyeth. The complainant provided a copy of the programme for a meeting of the Midlands Psychiatric Research Group to be held in June 2007.

The complainant alleged that a few psychiatrists under the name of 'West Midland Research Group' had been using pharmaceutical companies for their personal advantages, ambitions and growth. The group organised one meeting a year and called it an international conference. There was no scientific committee, no invitation for research abstracts or poster. The group invited whom it wanted to. Until last year the registration fee was very little, about £15. Delegates were allowed to have free hotel, food and an evening cultural programme. It was inappropriate hospitality at the expense of pharmaceutical companies. Even delegates might not be aware that pharmaceutical companies had given money.

The Panel noted that there were some differences between the programme for the 2007 meeting submitted by Wyeth and that provided by the complainant.

The programme provided by Wyeth gave no details about which companies were providing educational grants.

Wyeth had not decided whether it was going to sponsor the 2007 meeting or not. If it were to sponsor the meeting it would be limited to the scientific meeting only and not the sponsorship of delegates. Wyeth would not provide sponsorship for the social programme or for family members.

The Panel considered that according to the programme, the scientific/educational content was not unreasonable for sponsorship by a pharmaceutical company. The meeting appeared to be primarily scientific/educational. The programme referred only to 'Dinner' each evening. The Panel noted the allegations about the cultural musical event. There was no mention of this on the programme. It considered that if there was to be such entertainment then it would be inappropriate for a pharmaceutical company to sponsor it.

The Panel considered that as Wyeth had not agreed to sponsor the 2007 meeting there could be no breach of the Code and ruled accordingly.

An anonymous complaint was received about inappropriate hospitality alleged to have been provided by three pharmaceutical companies, one of which was Wyeth Pharmaceuticals.

COMPLAINT

The complainant stated that a few psychiatrists under the name of 'West Midland Research Group' had been using pharmaceutical companies for their personal advantages, ambitions and growth. They had organised a conference and taken money from pharmaceutical companies for it. In fact nobody knew what West Midland Research Group was; no research was conducted or published by this group and there was no research grant or funding available for this group. The group organised one meeting a year and called it an international conference. There was no scientific committee, no invitation for research abstracts or poster. The group invited whom it wanted to. Until last year the registration fee was very little, about £15. Delegates were allowed to have free hotel, food and an evening cultural programme. It was inappropriate hospitality at the expense of pharmaceutical companies. Even delegates might not be aware that pharmaceutical companies had given money.

The few psychiatrists used this money to invite speakers who they wanted to oblige and they were friendly. They paid their fare, speaker fees, and hotel expenses. They used pharmaceutical company money for hospitality of delegates who seemed to be their friends and repeatedly attended their conference. They all enjoyed the evening cultural programme. It was like an annual get-together for them.

The group had taken money from Wyeth this time. One of the organisers maintained the data base of most of the Asian and Arabic psychiatrists. It was a number game. They had numbers to influence pharmaceutical companies and pharmaceutical companies tried to oblige vulnerable psychiatrists who could increase the prescriptions.

The pharmaceutical companies wanted to sell their medicines and it was a good nexus to have mutual benefits. It was worth investigating.

More or less the same delegates attended their other meetings such as the South Asian Forum meeting. The majority of delegates were the same every year. It was indicated that money was paid directly to 'West Midland Research Group' and they used this money as they wanted for cultural programmes, hotel and other expenses.

Delegates were motivated by the free hotel and sense of holiday; until last year they were allowed to bring their family, meeting common friends and enjoying a night cultural programme.

Organisers benefited by trying to influence and build up relationship with world prominent psychiatrists

who they invited as speakers and then used them for personal growth. They got impressed by seeing a large number of psychiatrists.

The motivating factor for pharmaceutical companies was taking advantage of numbers and trying to sell their medicines.

When writing to Wyeth, the Authority asked it to respond in relation to Clauses 2, 9.1 and 19.1.

RESPONSE

Wyeth stated that it was not aware of the existence of the West Midlands Research Group. The Midland Psychiatric Research Group ran an annual scientific meeting aimed mainly at Asian psychiatrists at which eminent speakers were invited from all over the world. Wyeth's outlined its interactions with this group in 2005 and 2006 and noted that it was currently reviewing a request to provide sponsorship for the group's 2007 annual meeting to be held in Coventry. Any such sponsorship would be limited to part sponsorship of the scientific meeting only and again it was not considering the sponsorship of delegates. At this stage Wyeth did not have copies of the invitations and therefore did not know if family members were also invited to any part of the event. Wyeth did not know what the whole cost of the meeting would be. The draft agenda was provided. At this stage Wyeth did not have comprehensive details of the arrangements of any social programme and it would not provide any sponsorship for these. Wyeth did not know how the delegates were invited, but it believed that they came from throughout the UK, and it was clear that the speakers were invited internationally.

As a part of Wyeth's review of this sponsorship request it had noted a statement from a website which identified the ethical guidelines of the Midland Psychiatric Research Group.

'COVENTRY (UK): Midland Psychiatric Research Group followed the ethical guidelines while organizing its annual conference which was funded by the pharmaceutical companies. To begin with all the participants were informed that:

1. *Latest ethical guidelines will be followed. It clearly states that "academic meetings will only be attended by medical professionals and spouses or non-medical guests will not be allowed to participate in the academic and social functions organized during this meeting." It was strictly enforced.*
2. *All the invited speakers declared before their presentations the research grants, honorarium or any other consultation fees etc., which they have received in the past along with the name of the companies.*
3. *No representative of the pharmaceutical companies who had sponsored any function or had extended any financial assistance to the organizers was invited to the official conference banquet.*
4. *The musical programme arranged at the Banquet was funded by the organizers from the Registration Fee and not by any pharmaceutical company.'*

From the above and for the following reasons Wyeth denied breaches of Clauses 2, 9.1 and 19.1.

Clause 19.1 referred to 'Meetings and Hospitality'. Wyeth believed that the facilities and hospitality provided at these meetings complied with the requirements of Clause 19.1:

- Prior to sponsoring the meeting in 2006, Wyeth reviewed a draft agenda: this showed that the meetings had a clear scientific content and were continuing professional development (CPD) approved. Wyeth noted that these meetings were organised in collaboration with the World Psychiatric Association and the World Association for Psychosocial Rehabilitation.
- The amount of sponsorship was appropriate. For the 2006 meeting when Wyeth provided £6,000 of sponsorship there were over 100 delegates ie £60 per delegate which seemed reasonable as this would only cover part of the accommodation costs. The delegates had to pay a £40 registration fee themselves.
- The venues were appropriate and conducive to the main purpose of the meetings.
- The level of subsistence in 2006 was modest and secondary to the nature of the meeting.
- On the registration form the following was printed *'As this meeting is funded by pharmaceutical companies, we are obliged to follow the recent guidelines that clearly say that academic meetings will only be attended by medical professionals, and spouses or non medical guests will not be allowed to participate in the academic or social functions organised during this meeting'*. Given that delegates had to pay a £40 registration fee and the organisers' clear awareness of Code issues, Wyeth did not consider that its financial contribution paid for or subsidised any social element of the agenda.

As Wyeth believed that there had been no breach of Clause 19.1, this led it to believe that neither Clause 2 nor Clause 9.1 had been breached.

PANEL RULING

The Panel noted that there were some differences between the programme for the 2007 meeting submitted by Wyeth and that provided by the complainant. The Panel noted that the 2007 meeting was to start on the evening of 14 June with a lecture and dinner. According to the programme provided by Wyeth, the programme for Friday 15 June ran from 9.15am until 4.45pm and the arrangements for Saturday were similar, 9.30am until 5pm. There were small differences in timing in the agenda provided by the complainant.

The programme provided by Wyeth gave no details about which companies were providing educational grants.

The Panel noted that the complainant included the programme for the 2007 meeting. No specific allegations had been made about other meetings. Wyeth had provided details of its interactions with the West Midlands Research Group since 2005.

The 2007 meeting was to be held in Coventry. Wyeth had not decided that it was going to sponsor the meeting. If it were to sponsor the meeting it would be limited to the scientific meeting only and not the sponsorship of delegates. Wyeth would not provide sponsorship for the social programme or for family members.

The Panel considered that according to the programme, the scientific/educational content was not unreasonable for sponsorship by a pharmaceutical company. The meeting appeared to be primarily scientific/educational. The programme referred only to 'Dinner' each evening. The Panel noted the allegations about the cultural musical event. There was no mention of this on the programme. It considered that if there was to be such entertainment then it would be inappropriate for a pharmaceutical company to sponsor it.

The Panel considered that as Wyeth had not agreed to sponsor the 2007 meeting there could be no breach of Clauses 2, 9.1 and 19.1 and ruled accordingly.

Complaint received **27 April 2007**

Case completed **21 May 2007**

ROCHE v GLAXOSMITHKLINE

Promotion of Tykerb

Roche complained about the promotion of Tykerb (lapatinib) by GlaxoSmithKline. Roche noted that a pre-licence advertisement for lapatinib ('Coming soon … Tykerb') was published in the January 2007 issue of 'The Oncologist', including its UK circulation. GlaxoSmithKline claimed that this was an 'inadvertent error' and attributed to its US colleagues placing the advertisement without its knowledge in the UK. Nevertheless, the impact was made.

The Panel noted that supplementary information to the Code stated that advertisements published in professional journals came within the scope of the Code if they were produced in the UK and/or intended for a UK audience. International journals that were produced in English in the UK were subject to the Code even if only a small proportion of their circulation was to a UK audience.

The Oncologist was published by AlphaMed Press, Carolina, USA, and AlphaMed Europe based in Northern Ireland. The Panel noted GlaxoSmithKline's submission that when commissioning the advertisement, the US company was unaware of any non US print runs for The Oncologist and did not specify any particular run for the advertisement. Further the journal had no separate European run. GlaxoSmithKline thus submitted that the issue of the journal in question was obtained in the US. The Panel noted that had the advertisement appeared in a separate run of the journal that had been produced in the UK or had otherwise been intended for a UK audience it would have come within the scope of the Code. However, on the basis of GlaxoSmithKline's submission the Panel decided that the run of The Oncologist at issue did not satisfy the criteria and thus the matter was outside the scope of the Code. No breach was ruled.

Roche's ongoing media monitoring had shown high levels of Tykerb/lapatinib coverage. Roche had had correspondence with GlaxoSmithKline on this matter, specifically relating to an article in the Sunday Express on 17 September in which a GlaxoSmithKline source was quoted as saying that the medicine would achieve better results than Herceptin. Although Roche received assurances from GlaxoSmithKline that this had not arisen from GlaxoSmithKline briefings, it was clearly attributed to GlaxoSmithKline. Tykerb was unlicensed in the UK and no head-to-head comparative data existed against Herceptin. Should this statement have come via a GlaxoSmithKline supported agency, GlaxoSmithKline was still responsible.

Evidence of an engineered campaign of pre-marketing was supported by the consistency of wording of claims that were appearing in the media, including regular comparisons with Herceptin. More specifically, there had been several mentions that lapatinib might be 'better than Herceptin', that lapatinib might be effective in 'Herceptin resistant' patients, that lapatinib might be effective in brain metastases, and that lapatinib might have less cardiotoxicity than Herceptin. There was no evidence to support the above claims and whilst Roche accepted that there might be an element of misunderstanding amongst the media, the consistency with which such messages had been conveyed in the media strongly suggested that there must be some origin for these unfounded claims. It seemed a totally improbable coincidence that this could originate from a source other than GlaxoSmithKline. Totally unfounded statements over safety were of particular concern and should be viewed as a breach of Clause 2.

The Panel noted that the article in question in the Sunday Express referred to the superiority of lapatinib over Herceptin. The article stated that 'GlaxoSmithKline claims the drug will achieve better results than Herceptin, a rival treatment …'. Complaints about articles in the media were judged on the information provided by the company to the journalist. The Panel noted GlaxoSmithKline's submission that neither it nor its agency had spoken to the journalist in question. GlaxoSmithKline had however issued a corporate press release about the Tykerb US filing and thereafter answered a question from a different journalist at the Sunday Express about when the filing was due to take place. GlaxoSmithKline had surmised that this second journalist had relayed this information to the author of the article and that it was possible that the Sunday Express article may have been prompted by the embargoed press release.

The press release was headed 'GlaxoSmithKline seeks US approval for Tykerb (lapatinib ditosylate) for the treatment of advanced breast cancer'. The date of issue was Monday, 18 September. The press release described the product's proposed US licensed indication – in combination with Xeloda for the treatment of advanced or metastatic HER2 (ErbB2) positive breast cancer in women who had received prior therapy, including Herceptin. The compound had been granted fast track status by the FDA in this patient population. The press release made it clear that Tykerb was an investigational medicine and had not been approved for marketing by any regulatory body. The trial on which the application was based, was described and referenced to Data on file, King of Prussia. It was noted that an interim analysis showed that relevant women in whom the disease progressed following treatment with Herceptin and other cancer therapies when transferred either to Tykerb and

Xeloda or Xeloda alone, the combination of Tykerb and Xeloda nearly doubled median time to progression (36.7 weeks [8.5 months] in the combination arm vs 19.1 weeks [4.4 months] versus Xeloda alone, p= 0.00008). The press release also stated that in March 2006 an independent data monitoring committee recommended that enrolment ceased based on the early success of the trial. The study met its primary endpoint of time to disease progression and exceeded the predetermined stopping criteria. Enrolment stopped in April 2006. The press release supplied by GlaxoSmithKline did not mention an embargo.

The Panel did not consider that the press release supplied to the Sunday Express implied that Tykerb would achieve better results than Herceptin, nor that head-to-head comparative data existed as alleged. References to Herceptin were within the context of the proposed licensed indication in the US which was clearly stated in the press release. No breach of the Code ruled.

In relation to the allegation about a premarketing campaign involving comparative claims with Herceptin the Panel noted GlaxoSmithKline's submission that any conversations with journalists had been restricted to messages in the approved press releases. The evidential burden was on Roche to establish, on the balance of probabilities that GlaxoSmithKline had supplied material to the media which was misleading or otherwise in breach of the Code as alleged. The Panel noted the series of published articles provided by Roche and a summary of the coverage. Roche cited that Tykerb might be 'better than Herceptin', 'effective in Herceptin resistant patients', 'effective in brain metastases' and 'have less cardiotoxicity than Herceptin'. Nonetheless, the Panel also noted that none of the press releases issued by GlaxoSmithKline or its corporate office featured the comparative claims referred to by Roche.

GlaxoSmithKline had provided copies of press releases dated from May 2006 to December 2006. Two were clearly marked for medical press only, one was a London Stock Exchange announcement. Eight discussed phase III data, one noted its imminent publication. The licensing status was made clear. The Panel was concerned that the intended audience was not always clear on the face of the press release. The Panel was also concerned that the heading to a press release dated 28 December described the phase III data as 'Landmark' data and referred to it changing the 'treatment paradigm'. Other press releases described the phase III trial more modestly as 'positive new data'. However, on the evidence before it the Panel did not consider that the press materials overall amounted to promotion of a medicine prior to the grant of marketing authorization or were otherwise in breach of the Code as alleged. No breach of the Code was ruled.

Roche Products Limited complained about the promotion of Tykerb (lapatinib) by GlaxoSmithKline UK Ltd.

1 Tykerb pre-licence advertisement

COMPLAINT

Roche noted that an advertisement for lapatinib ('Coming soon … Tykerb') was published in the January 2007 issue of 'The Oncologist', including its UK circulation. GlaxoSmithKline claimed that this was an 'inadvertent error' and attributed it to its US colleagues placing the advertisement without its knowledge in the UK. Roche provided GlaxoSmithKline's written response. Nevertheless, the impact was made. Roche alleged that the advertisement breached Clauses 3.1, 9.1 and 9.2 of the Code.

RESPONSE

GlaxoSmithKline submitted that the advertisement in question was placed in the January 2007 issue of 'The Oncologist', an international journal, by GlaxoSmithKline personnel in the US operating company without GlaxoSmithKline UK's prior knowledge or consent. Once this became known to GlaxoSmithKline UK, it contacted US colleagues who promptly withdrew the advertisement and were now fully aware of the importance of regulations relating to information and advertisements in journals with distribution outside the USA.

Nevertheless, 'teaser' advertising was permitted under US Food and Drugs Administration (FDA) regulations and since the journal in question was produced outside of the UK and was not primarily intended for a UK audience (UK readership of The Oncologist was approximately 10% of total circulation), GlaxoSmithKline did not believe that this complaint should fall under the scope of the ABPI Code. GlaxoSmithKline therefore denied breaches of Clauses 3.1, 9.1 and 9.2 of the Code.

In response to a request for further information, GlaxoSmithKline stated that the Oncologist was published monthly by AlphaMed Press, North Carolina USA and AlphaMed Europe Limited, Northern Ireland.

At the time of commissioning the Tykerb piece, GlaxoSmithKline's US colleagues were unaware of any non-US print runs for The Oncologist which was a US-based journal with no separate European print run and had minimal (under 200 copies) international circulation; as a result they did not specify any particular run for the advertisement.

It was therefore most likely that the issue of the journal with the advertisement under discussion was obtained in the US; in which case US regulations applied confirming GlaxoSmithKline UK's position of not having breached the Code.

PANEL RULING

The Panel noted the supplementary information to

Clause 1.1 of the Code, Journals with an International Distribution stated that advertisements published in professional journals came within the scope of the Code if they were produced in the UK and/or intended for a UK audience. International journals that were produced in English in the UK were subject to the Code even if only a small proportion of their circulation was to a UK audience.

The Panel noted that The Oncologist was published by AlphaMed Press, Carolina, USA, and AlphaMed Europe based in Northern Ireland. The Panel noted GlaxoSmithKline's submission that when commissioning the advertisement, the US company was unaware of any non US print runs for The Oncologist and did not specify any particular run for the advertisement. Further the journal had no separate European run. GlaxoSmithKline thus submitted that the issue of the journal in question was obtained in the US. The Panel noted that had the advertisement appeared in a separate run of the journal that had been produced in the UK or had otherwise been intended for a UK audience it would have come within the scope of the Code. However, on the basis of GlaxoSmithKline's submission the Panel decided that the run of The Oncologist at issue did not satisfy the criteria set out in Clause 1.1 and thus the matter was outside the scope of the Code. No breach of Clauses 3.1, 9.1 and 9.2 was accordingly ruled.

2 Tykerb media coverage

COMPLAINT

Roche's ongoing media monitoring had shown high levels of Tykerb/lapatinib coverage. Roche had had correspondence with GlaxoSmithKline on this matter, specifically relating to an article in the Sunday Express on 17 September 2006 in which a GlaxoSmithKline source was quoted as saying that the medicine would achieve better results than Herceptin. Although Roche received assurances from GlaxoSmithKline that this had not arisen from GlaxoSmithKline briefings, it was clearly attributed to GlaxoSmithKline. Hence, Roche alleged breaches of Clauses 3.1, 7.2 and 8.1. Tykerb was unlicensed in the UK and no head-to-head comparative data existed against Herceptin. Should this statement have come via a GlaxoSmithKline supported agency, GlaxoSmithKline was still responsible under Clause 20.6.

Evidence of an engineered campaign of pre-marketing was supported by the consistency of wording of claims that were appearing in the media, including regular comparisons with Herceptin. More specifically, there had been several mentions that lapatinib might be 'better than Herceptin', that lapatinib might be effective in 'Herceptin resistant' patients, that lapatinib might be effective in brain metastases, and that lapatinib might have less cardiotoxicity than Herceptin. There was no evidence to support the above claims and whilst Roche accepted that there might be an element of misunderstanding amongst the media, the consistency with which such messages had been conveyed in the media strongly suggested that there must be some origin for these unfounded claims. It seemed a totally improbable coincidence that this could originate from a source other than GlaxoSmithKline (or an agency working for it) via a written or verbal briefing. Totally unfounded statements over safety were of particular concern and should be viewed as a breach of Clause 2.

RESPONSE

GlaxoSmithKline confirmed that no one at GlaxoSmithKline UK (or other parts of the organisation) or from its PR agency had spoken to the Sunday Express journalist in question. The journalist was not GlaxoSmithKline's usual contact and was not known to it. GlaxoSmithKline could only hypothesise on what might have happened. It was possible that the article might have been prompted by an embargoed press release issued by GlaxoSmithKline corporate media in relation to lapatinib's US filing around the same time. The article did refer to a GlaxoSmithKline spokeswoman in relation to a comment on the US and EU filings for lapatinib, but it believed this arose because a separate journalist from the Sunday Express had contacted GlaxoSmithKline's corporate media team to ask when the filings were due to take place. It was possible that this journalist relayed that information to the author of the article.

The reference to GlaxoSmithKline claiming superiority over Herceptin was not in quotes, nor attributed to a GlaxoSmithKline spokesperson, but was paraphrased. GlaxoSmithKline could only assume that the journalist made her own interpretation of the content of the press release, either in relation to the anticipated licence indication for lapatinib (ie for patients who had previously received Herceptin) and/or in relation to the findings of the pivotal registration trial, as reflecting superiority to Herceptin. The relevant paragraphs from the press release were as follows:

> '…..approval to market Tykerb (lapatinib ditsoylate), in combination with Xeloda (capecitabine), for the treatment of advanced or metastatic HER2 (ErbB2) positive breast cancer in women who have received prior therapy, including Herceptin (trastuzumab).'
>
> 'A planned interim analysis of the Phase III international, multicenter, open-label trial randomized 324 women who had advanced or metastatic breast cancer with documented HER2 overexpression and whose disease progressed following treatment with herceptin and other cancer therapies, to TYKERB and Xeloda or Xeloda alone. In this pivotal trial, the combination of Tykerb and Xeloda versus Xeloda alone nearly doubled median time to progression (36.7 weeks [8.5 months] in the combination arm versus 19.1 weeks [4.4 months] with Xeloda alone, p=0.00008).'

As could be seen, the press release accurately represented the design of the study and the results and clearly did not make a superiority claim against Herceptin. GlaxoSmithKline had been unable to find

any other references to such a claim and could confirm that it had undertaken no media briefings to journalists where such a claim could have been made. GlaxoSmithKline could only conclude that the statement must represent the journalist's own interpretation, either of this press release or of other press coverage, or of data she might have seen at, or reported from, scientific congresses.

GlaxoSmithKline strongly refuted the allegation of an engineered pre-marketing campaign for lapatinib.

GlaxoSmithKline UK activities

GlaxoSmithKline UK's media activities had solely consisted of issuing press releases to the medical press around significant milestones for lapatinib - the presentation of significant new data at a scientific congress (ESMO 2006), and the EU filing. GlaxoSmithKline UK had not organised or undertaken any press briefings with the medical press or health correspondents on the UK national press. As was standard practice upon issuing a press release, journalists had been followed up by phone to check they had received the press release. All such conversations were restricted to only the approved messages in the press releases.

GlaxoSmithKline corporate media activities

GlaxoSmithKline's corporate media team had also issued corporate press releases on key data and on the US and EU filings to the investment community and health correspondents on the national press. Both GlaxoSmithKline's corporate office and its PR agency had confirmed that any conversations with journalists were restricted to the messages in the approved press releases.

The press coverage in relation to lapatinib, alleged by Roche to be part of a campaign, was most likely to have been generated by legitimate corporate activities related to the investment community. This was reinforced by details provided by Roche predominantly featuring coverage generated in the business press.

None of GlaxoSmithKline's press releases (either developed by GlaxoSmithKline UK or by the corporate media team) had contained any of the claims that Roche alleged. No claims had been made relating to superiority of lapatinib over Herceptin, lapatinib having less cardiotoxicity than Herceptin, lapatinib being effective in 'Herceptin resistant' patients or lapatinib being effective in brain metastases.

With reference to the allegation regarding lapatinib in brain metastases, it was important to be aware that brain metastases were an increasing clinical problem in patients with HER2-positive (HER2+) breast cancer, and were associated with significant morbidity, mortality and impaired quality of life. There were very few treatment options available and the management of breast cancer with brain metastases was an elusive clinical challenge. The statements that had appeared regarding brain metastases in press releases sent by GlaxoSmithKline corporate media accurately represented the preliminary nature of the evidence and plans for future studies with lapatinib in this area. GlaxoSmithKline believed this to be a legitimate provision of information given the level of interest in finding new treatments in this area of significant unmet medical need.

GlaxoSmithKline was aware that the area of cancer (particularly breast cancer) was one that had developed a high media profile, and as such, it had provided factual releases to ensure that correct and balanced information was available to investment, medical and health journalists who might write stories relating to these events. The considerable media interest in this area was reflected by the fact that press articles had appeared intermittently and not necessarily around the time when GlaxoSmithKline had issued press releases. Many of the articles might have come out of the release of landmark data per se, rather than a GlaxoSmithKline press release around such data.

In summary, GlaxoSmithKline strongly denied the alleged breaches of the Code. It believed that the information on lapatinib disseminated in these GlaxoSmithKline press releases constituted a legitimate activity to provide information to journalists writing for the medical press and the investment community in an area of high media interest, particularly given the novel nature of lapatinib and the current high unmet need for patients with HER2-positive (HER2+) advanced/metastatic breast cancer who had progressed on Herceptin - the target first indication for lapatinib. The content of all such press releases were an accurate, balanced, fair and objective reflection of the available evidence for lapatinib. GlaxoSmithKline refuted having made any inappropriate statements regarding the safety of lapatinib, and particularly, regarding the comparative safety of lapatinib and Herceptin. There was no evidence that any of the claims cited by Roche had originated from concerted campaign by GlaxoSmithKline, either directly, or from one of its agencies.

GlaxoSmithKline therefore refuted any alleged breach of Clauses 2, 3.1, 7.2, 8.1 and 20.6.

PANEL RULING

The Panel noted that the article in question in the Sunday Express referred to the superiority of lapatinib over Herceptin. The article stated that 'GlaxoSmithKline claims the drug will achieve better results than Herceptin, a rival treatment …'. The Panel noted that complaints about articles in the media were judged on the information provided by the company to the journalist. The Panel noted GlaxoSmithKline's submission that neither it nor its agency had spoken to the journalist in question. GlaxoSmithKline had however issued a corporate press release about the Tykerb US filing and thereafter answered a question from a different journalist at the Sunday Express about when the filing was due to take place. GlaxoSmithKline had surmised that this second journalist had relayed this information to the author of the article and that it was possible that the Sunday

Express article may have been prompted by the embargoed press release.

The Panel noted that the press release was headed 'GlaxoSmithKline seeks US approval for Tykerb (lapatinib ditosylate) for the treatment of advanced breast cancer'. The date of issue was Monday, 18 September. The press release described the product's proposed US licensed indication – in combination with Xeloda for the treatment of advanced or metastatic HER2 (ErbB2) positive breast cancer in women who had received prior therapy, including Herceptin. The compound had been granted fast track status by the FDA in this patient population. The press release made it clear that Tykerb was an investigational medicine and had not been approved for marketing by any regulatory body. The phase III open label trial on which the application was based, was described and referenced to Data on file, King of Prussia. It was noted that an interim analysis showed that relevant women in whom the disease progressed following treatment with Herceptin and other cancer therapies when transferred either to Tykerb and Xeloda or Xeloda alone, the combination of Tykerb and Xeloda nearly doubled median time to progression (36.7 weeks [8.5 months] in the combination arm vs 19.1 weeks [4.4 months] versus Xeloda alone, p= 0.00008). The press release also stated that in March 2006 an independent data monitoring committee recommended that enrolment ceased based on the early success of the trial. The study met its primary endpoint of time to disease progression and exceeded the predetermined stopping criteria. Enrolment stopped in April 2006. The press release supplied by GlaxoSmithKline did not mention an embargo.

The Panel did not consider that the press release supplied to the Sunday Express implied that Tykerb would achieve better results than Herceptin, nor that head-to-head comparative data existed as alleged. References to Herceptin were within the context of the proposed licensed indication in the US which was clearly stated in the press release. No breach of Clauses 3.1, 7.2 and 8.1 was ruled on this point.

In relation to the allegation about a premarketing campaign involving comparative claims with Herceptin, the Panel noted GlaxoSmithKline's submission that any conversations with journalists had been restricted to messages in the approved press releases. The Panel noted that the evidential burden was on Roche to establish, on the balance of probabilities, that GlaxoSmithKline had supplied material to the media which was misleading or otherwise in breach of the Code as alleged. The Panel noted the series of published articles provided by Roche and a summary of the coverage. Roche cited that Tykerb might be 'better than Herceptin', 'effective in Herceptin resistant patients', 'effective in brain metastases' and 'have less cardiotoxicity than Herceptin'. Nonetheless, the Panel also noted that none of the press releases issued by GlaxoSmithKline or its corporate office featured the comparative claims referred to by Roche.

The Panel noted that GlaxoSmithKline had provided copies of press releases dated from May 2006 to December 2006. Two were clearly marked for medical press only, one was a London Stock Exchange announcement. Eight discussed phase III data, one noted its imminent publication. The licensing status was made clear. The Panel was concerned that the intended audience was not always clear on the face of the press release. The Panel was also concerned that the heading to a press release dated 28 December described the phase III data as 'Landmark' data and referred to it changing the 'treatment paradigm'. Other press releases described the phase III trial more modestly as 'positive new data'. However, on the evidence before it the Panel did not consider that the press materials overall amounted to promotion of a medicine prior to the grant of marketing authorization or were otherwise in breach of the Code as alleged. No breach of Clauses 3.1, 7.2 and 8.1 was ruled. Given its ruling there could be no breach of Clause 2.

The Panel noted that Roche had referred to Clause 20.6 which read ' Companies are responsible for information about their products which is issued by their public relations agencies'. The Panel considered that Clause 20.6 was a simple statement of fact which could not be infringed.

Complaint received 27 April 2007

Case completed 10 July 2007

ANONYMOUS GENERAL PRACTITIONER v MERCK SHARP & DOHME

Invitation to a meeting

An anonymous complaint was received from a general practitioner about an invitation to a meeting issued by Merck Sharp & Dohme.

The complainant stated that the invitation was one of the most unprofessional invitations he had seen. It took a while to try to figure out where it came from.

The Panel noted that the invitation stated 'Dear …' immediately followed by 'Merck Sharp & Dohme cordially invites you to attend a medical meeting entitled: …'. Details of the meeting followed. The letter was signed by two representatives. The company name followed each representative's job title. The bottom of the letter stated 'Meeting sponsored by Merck Sharp & Dohme Limited'.

The Panel noted that although the invitation did not appear to have been printed on headed paper, it was clear that it was from Merck Sharp & Dohme. The arrangements for the meeting were also clear. The Panel did not consider that the invitation was unprofessional as alleged and no breach of the Code was ruled.

An anonymous complaint was received from a general practitioner about an invitation to a meeting issued by Merck Sharp & Dohme Limited

COMPLAINT

The complainant stated that the invitation issued by two Merck Sharp & Dohme representatives, was one of the most unprofessional invitations he had seen. It took a while to try to figure out where it came from, and if the representatives whose names were on it were really senior and executive representatives, suggesting a length of time and training with the company, they should know better.

The complainant had recently received a copy of the Guidance on the Code for Health Professionals. This did not cover the use of invitations, but other invitations the complainant had received seemed to have had a much more professional look about them and at least the company name was displayed so you knew where it was from. The complainant was sure that Merck Sharp & Dohme had a better procedure for invitations and queried if this was a representative training issue.

The Authority asked Merck Sharp & Dohme to respond in relation to the requirements of Clause 15.2 of the Code.

RESPONSE

Merck Sharp & Dohme was sorry that the complainant felt the invitation was unclear, it was based on a template which met all of the requirements of the Code. Merck Sharp & Dohme's involvement was clear in both the first line, and the last line. The subject matter, agenda and logistical arrangements were clear, as were the limitations such as inability to accommodate spouses.

Merck Sharp & Dohme therefore submitted that high standards had been maintained by its representatives, and that no breach had occurred.

Merck Sharp & Dohme stated that both representatives had passed the ABPI representatives' examination.

PANEL RULING

The Panel noted that the copy of the invitation provided by the complainant stated 'Dear …' immediately followed by 'Merck Sharp & Dohme cordially invites you to attend a medical meeting entitled: …'. Details of the meeting followed. The letter was signed by two representatives. The company name followed each representative's job title. The bottom of the letter stated 'Meeting sponsored by Merck Sharp & Dohme Limited'.

The Panel noted that although the invitation did not appear to have been printed on headed paper, it was clear that it was an invitation from Merck Sharp & Dohme. The arrangements for the meeting were also clear. The Panel did not consider that the invitation was unprofessional as suggested by the complainant. The Panel ruled no breach of Clause 15.2.

Complaint received	18 May 2007
Case completed	18 June 2007

ALLERGAN v PFIZER

Arrangements for meetings

Allergan complained about the arrangements for two meetings, sponsored by Pfizer Inc, which took place during the annual meeting of the American Academy of Ophthalmology (AAO) in Las Vegas, 9 to 11 November 2006. Allergan's concerns related to the hospitality provided to UK delegates, especially the venues for the two meetings.

Allergan did not believe that a symposium and associated hospitality at a wax museum was an appropriate venue for an educational meeting; it appeared to have been chosen for its entertainment value, rather than being conducive to the main purpose of the meeting. Pfizer had stated that its only involvement with this meeting was by provision of an unrestricted educational grant.

The second was a meeting 'From Theory to Therapy (treatment of AMD)' with associated hospitality at a nightclub. Allergan did not believe that a nightclub was an appropriate or conducive venue for scientific/medical education. The venue was clearly used for its voyeuristic entertainment facilities and was unsuitable for hosting a scientific/medical meeting or the associated hospitality. Pfizer had again stated that its involvement was limited to providing an unrestricted educational grant, although it appeared to acknowledge that an 'evening social event' was arranged. Allergan also believed that Pfizer's failure to appreciate the inappropriate nature of this venue showed a disregard for maintaining high standards, taste and suitability.

The Panel noted that the meetings at issue had been organised by an infirmary and a subsidiary of a publishing company. The role of Pfizer Limited's parent company, Pfizer Inc, had been limited to the provision of an unrestricted education grant.

It was an established principle under the Code that UK companies were responsible for the acts or omissions of their overseas affiliates that came within the scope of the Code. Pfizer Limited was thus responsible for any acts or omissions of Pfizer Inc that came within the scope of the Code.

The Panel noted that in relation to international meetings held in the US the hospitality provided directly to UK delegates by the sponsoring company (accommodation, travel and subsistence etc) had to comply with the ABPI Code. Any material at meetings directed solely at members of the UK health professions also had to comply with the ABPI Code. It appeared that the meetings had been arranged independently and at arms length from Pfizer Inc. The Panel noted that the meetings were not directed to a UK audience; in addition neither Pfizer Limited nor Pfizer Inc had invited UK delegates to attend the meetings.

In the circumstances Pfizer Limited was not responsible for the meetings and the Panel accordingly ruled no breach of the Code.

Allergan Limited complained about the arrangements for two meetings, sponsored by Pfizer Inc, the American parent of Pfizer Limited, which took place during the annual meeting of the American Academy of Ophthalmology (AAO) in Las Vegas, 9 to 11 November 2006.

COMPLAINT

Allergan's concerns related to the hospitality provided to UK delegates, especially the venues for two meetings which were described below and in the AAO programme which was issued to all attendees.

1 A symposium entitled 'Evaluating Risk, Judging Progression' with associated hospitality at a Wax Museum' sponsored by Pfizer Inc.

Allergan did not believe that a waxwork museum was an appropriate venue for an educational meeting or that it constituted appropriate associated hospitality. The venue appeared to have been chosen for its entertainment value, rather than being conducive to the main purpose of the meeting. Pfizer had stated that its only involvement with this meeting was by provision of an unrestricted educational grant. However, the pharmaceutical industry had a responsibility to ensure appropriate hospitality was provided for health professionals invited to scientific meetings and associated symposia when it is funding the event. The front cover of the February 2007 Code of Practice Review stated:

'… before sponsoring attendance at such meetings UK companies must ensure that all of the arrangements for the health professionals to attend comply with the Code'.

Allergan alleged that the use of such a venue for a meeting involving UK delegates breached Clause 19.1.

2 A meeting 'From Theory to Therapy (treatment of AMD)' with associated hospitality at a nightclub, part sponsored by Pfizer Inc.

Allergan stated that it did not believe that a nightclub was an appropriate or conducive venue for scientific/medical education. Allergan attached two internet reviews of the nightclub for reference. The venue was clearly used for its voyeuristic entertainment facilities and was totally unsuitable for

hosting a scientific/medical meeting or the associated hospitality. Pfizer had again stated that its involvement was limited to providing an unrestricted educational grant, although its response appeared to acknowledge that it was aware that an 'evening social event' at this venue was arranged. Not only was such hospitality involving UK delegates in breach of Clause 19.1, Allergan also believed that Pfizer's failure to appreciate the inappropriate nature of this venue showed a disregard for maintaining high standards, taste and suitability, and was therefore in breach of Clause 9.1.

RESPONSE

Pfizer submitted that neither symposium was organised by Pfizer Inc. The two meetings constituted an accredited continuing medical education activity, organised and developed independently by an infirmary and a subsidiary of a publishing company. Pfizer Inc's involvement was solely the provision of an unrestricted educational grant, which was clearly indicated in the agreement between Pfizer Inc and the infirmary which stated that the funds were to be used appropriately to support the educational programme only.

Pfizer Inc acted entirely properly in this regard since, in order to comply with applicable US regulations, sponsors of such accredited programmes were not permitted to have any involvement in the content, programme or the venue chosen for such events.

UK delegates were not invited to attend either symposium by Pfizer Limited or Pfizer Inc.

Furthermore, the agenda for the symposium 'Evaluating Risk, Judging Progression' clearly stated that it was held in the hotel. Pfizer understood that the post-meeting reception was secondary to the meeting and was held in a part of the wax museum which was closed to the general public. Similarly, the agenda for the meeting 'Theory to Therapy (treatment of AMD) stated that it was held in the hotel. Pfizer understood that the post-meeting reception was secondary to the meeting and that the nightclub was closed to the general public.

For the above reasons, Pfizer considered that with regard to both meetings there had been no breach of Clauses 9.1 or 19.1. Pfizer Inc's conduct was in accordance with US regulations for sponsoring third party accredited meetings. No UK delegates were invited to the meetings.

PANEL RULING

The Panel noted that the meetings at issue took place during the American Academy of Ophthalmology Annual meeting in Las Vegas, November 2006. Neither of the meetings had been organised by Pfizer Limited or its American parent, Pfizer Inc. The meetings had been organised by an infirmary and a subsidiary of a publishing company. The role of Pfizer Limited's parent company, Pfizer Inc, had been limited to the provision of an unrestricted education grant.

The Panel noted that it was an established principle under the Code that UK companies were responsible for the acts or omissions of their overseas affiliates that came within the scope of the Code. Pfizer Limited was thus responsible for any acts or omissions of Pfizer Inc that came within the scope of the Code.

The Panel noted that in relation to international meetings held in the US the hospitality provided directly to UK delegates by the sponsoring company (accommodation, travel and subsistence etc) had to comply with the ABPI Code. Any material at meetings directed solely at members of the UK health professions also had to comply with the ABPI Code. It appeared that the meetings had been arranged independently and at arms length from Pfizer Inc. The Panel noted that the meetings were not directed to a UK audience; in addition neither Pfizer Limited nor Pfizer Inc had invited UK delegates to attend the meetings.

In the circumstances Pfizer Limited was not responsible for the meetings and the Panel accordingly ruled no breach of Clause 19.1 in relation to each. The Panel also ruled no breach of Clause 9.1.

Complaint received 29 May 2007

Case completed 10 July 2007

GENERAL PRACTITIONER v PFIZER

Celebrex journal advertisement

A general practitioner complained that a journal advertisement for Celebrex (celecoxib) issued by Pfizer exaggerated the efficacy of Celebrex (celecoxib) in that the claim 'I need a treatment that will relieve my pain' in close association with efficacy claims for Celebrex invited the suggestion of a guaranteed 100% pain relief for all patients. The efficacy data for Celebrex did not support this suggestion.

The Panel noted from the Celebrex summary of product characteristics (SPC) that it was indicated, inter alia, for symptomatic relief in the treatment of osteoarthritis (OA), rheumatoid arthritis (RA).

The Panel considered that the claim 'I need a treatment that will relieve my pain' was an aspiration. The claim was immediately followed by a claim that in OA and RA Celebrex was a valuable treatment option. The Panel did not consider that the audience would be misled into thinking Celebrex guaranteed 100% pain relief for all patients. The Panel did not consider the claim misleading, exaggerated or incapable of substantiation as alleged. No breach of the Code was ruled.

A general practitioner complained about an advertisement (COX459h) for Celebrex (celecoxib) issued by Pfizer Limited and published in Geriatric Medicine, May 2007.

COMPLAINT

The complainant wondered whether the claim 'I need a treatment that will relieve my pain' in close association with efficacy claims for Celebrex invited the suggestion of a guaranteed 100% pain relief for all patients with respect to this medicine and could be regarded as somewhat of an exaggeration regarding the efficacy of Celebrex. The efficacy data for Celebrex did not support this suggestion.

The Authority asked Pfizer to respond in relation to the requirements of Clauses 7.2, 7.4 and 7.10 of the Code.

RESPONSE

Pfizer did not consider the advertisement was in breach. As stated in the summary of product characteristics (SPC), Celebrex was licensed for 'Symptomatic relief in the treatment of osteoarthritis [OA], rheumatoid arthritis [RA] and ankylosing spondylitis'. Symptomatic relief, to 'relieve pain' was a specific aspect of the marketing authorization.

The word 'relieve' was defined as 'alleviate or remove (pain, distress or difficulty)', and 'alleviate' was to 'make (pain or difficulty) less severe'. The use of the word relieve therefore encompassed the full range of responses, from making pain less severe (by any amount) to complete relief. Therefore even a medicine that would relieve pain would not guarantee 100% pain reduction by any means.

In addition, the statement 'I need a treatment that will relieve my pain' was a patient aspiration. A patient who required treatment for their pain was unlikely to be seeking a treatment that 'might reduce my pain' or that 'will partially reduce my pain'. This was followed by the statement 'In OA and RA, Celebrex was a valuable treatment option', highlighting that Celebrex was a treatment that deserved to be given consideration in appropriate patients, but certainly did not guarantee 100% efficacy.

The advertisement was further balanced by the inclusion of a statement detailing where to find information on the Medicines and Healthcare products Regulatory Agency (MHRA) website regarding the cardiovascular safety of Cox-2 inhibitors (including Celebrex).

With regard to Clauses 7.2, 7.4 and 7.10, Pfizer submitted that the overall impression and content of the advertisement gave a fair and balanced interpretation of the data for Celebrex, was fully substantiated, and did not exaggerate the properties of the medicine. Patients needed treatments that would 'relieve their pain' in OA and RA, and in line with this aspiration, Celebrex was a valuable treatment option.

PANEL RULING

The Panel noted from the Celebrex SPC that it was indicated for symptomatic relief in the treatment of OA, RA and ankylosing spondylitis.

The Panel considered that the claim 'I need a treatment that will relieve my pain' was an aspiration. The claim was immediately followed by a claim that in OA and RA Celebrex was a valuable treatment option. The Panel did not consider that the audience would be misled into thinking Celebrex guaranteed 100% pain relief for all patients. The Panel did not consider the claim misleading, exaggerated or incapable of substantiation as alleged. No breach of Clauses 7.2, 7.4 and 7.10 was ruled.

Complaint received	**29 May 2007**
Case completed	**6 July 2007**

CODE OF PRACTICE REVIEW – AUGUST 2007

Cases in which a breach of the Code was ruled are indexed in **bold type.**

1925/12/06	**Novartis v ApoPharma**	**Breach of undertaking**	**Breaches Clauses 2, 7.2, 9.1 and 22**	**Appeal by respondent**	**Page 3**
1941/1/07	**AstraZeneca v Altana Pharma**	**Promotion of Protium**	**Three breaches Clause 7.2 Two breaches Clause 7.3 Two breaches Clause 7.4**	**Appeal by respondent**	**Page 7**
1950/1/07	**Former Employee v AstraZeneca**	**Promotion of Casodex 150**	**Breach Clause 7.2 and 15.9**	**Appeal by complainant**	**Page 17**
1951/2/07 to 1955/2/07	**Media/Director v AstraZeneca**	**Insert on statins in The Pharmaceutical Journal**	**Case AUTH/1951/2/07- Breach Clause 2 Three breaches Clause 7.2 Breaches Clauses 7.4, 9.1 and 10.1** **Case AUTH/1952/2/07- Breach Clause 2 Two breaches Clause 7.2 Breaches Clauses 7.4, 9.1 and 10.1** **Case AUTH/1953/2/07- Breaches Clauses 2 and 4.1 Three breaches Clause 7.2 Breaches Clauses 7.10, 9.1 and 10.1** **Case AUTH/1954/2/07 and Case AUTH/1955/2/07- Breaches Clauses 4.1, 9.1 and 10.1**	**Appeal by respondent**	**Page 27**
1960/2/07	**Consultant in Anaesthesia and Pain Management v Grünenthal**	**Versatis journal advertisement**	**Breaches Clauses 3.2**	**Appeal by respondent**	**Page 45**
1962/2/07	Primary Care Trust Pharmaceutical Adviser v AstraZeneca	Report presented at a meeting	No breach	No appeal	Page 49
1968/2/07 and 1969/2/07	**Anonymous v Genus and ProStrakan**	**Tabphyn MR journal advertisement**	**Breach Clause 7.2**	**No appeal**	**Page 52**
1974/3/07	**Anonymous employees v Merck Sharp & Dohme**	**Provision of a service and representative call rates**	**Breach Clause 15.9**	**Appeal by complainants**	**Page 54**
1976/3/07	General Practitioner/ Director v Sanofi-Aventis	Accomplia journal advertisement	No breach	No appeal	Page 64
1978/3/07	**Primary Care Trust Assistant Director of Medicines Management v Takeda**	**Amias mailing undertaking**	**Breaches Clauses 7.2 and 10.1**	**No appeal**	**Page 69**
1981/3/07	**Consultant in Respiratory Medicine v Alk-Abelló**	**Unsolicited emails**	**Breaches Clauses 9.9 and 12.2**	**No appeal**	**Page 71**
1984/4/07 and 1985/4/07	Anonymous Consultant Physician v Sanofi-Aventis and Procter & Gamble	Actonel leavepiece	No breach	Appeal by respondents	Page 74

1986/4/07	**AstraZeneca v GlaxoSmithKline**	**Symbicort and Seretide cost comparisons**	**Two breaches Clause 7.2 Two breaches Clause 7.3 Two breaches Clause 7.10**	**No appeal**	**Page 81**
1987/4/07	Prescribing Advisor v AstraZeneca	Crestor journal advertisement	No breach	No appeal	Page 88
1993/4/07	Anonymous v AstraZeneca	Alleged inappropriate hospitality	No breach	No appeal	Page 90
1994/4/07	Anonymous v Janssen-Cilag	Alleged inappropriate hospitality	No breach	No appeal	Page 94
1995/4/07	Anonymous v Wyeth	Alleged inappropriate hospitality	No breach	No appeal	Page 97
1996/4/07	Roche v GlaxoSmithKline	Promotion of Tykerb	No breach	No appeal	Page 100
1998/5/07	Anonymous General Practitioner v Merck Sharp & Dohme	Invitation to a meeting	No breach	No appeal	Page 105
1999/5/07	Allergan v Pfizer	Arrangements for meetings	No breach	No appeal	Page 106
2005/5/07	General Practitioner v Pfizer	Celebrex journal advertisement	No breach	No appeal	Page 108

PRESCRIPTION MEDICINES
CODE OF PRACTICE AUTHORITY

The Prescription Medicines Code of Practice Authority was established by The Association of the British Pharmaceutical Industry (ABPI) in 1993 to operate the Code of Practice for the Pharmaceutical Industry at arm's length from the ABPI itself. Compliance with the Code is obligatory for ABPI member companies and, in addition, about sixty non member companies have voluntarily agreed to comply with the Code and to accept the jurisdiction of the Authority.

The Code covers the advertising of medicines to health professionals and administrative staff and also covers information about prescription only medicines made available to the public.

It covers:

- journal and direct mail advertising
- the activities of representatives, including detail aids and other printed material used by representatives
- the supply of samples
- the provision of inducements to prescribe, supply, administer, recommend, buy or sell medicines by the gift, offer or promise of any benefit or bonus, whether in money or in kind
- the provision of hospitality
- the sponsorship of promotional meetings
- the sponsorship of scientific and other meetings, including payment of travelling and accommodation expenses
- all other sales promotion in whatever form, such as participation in exhibitions, the use of audio-cassettes, films, records, tapes, video recordings, electronic media, interactive data systems, the Internet and the like
- the provision of information to the public either directly or indirectly, including by means of the Internet
- relationships with patient organisations.

Complaints submitted under the Code are considered by the Code of Practice Panel which consists of the three members of the Code of Practice Authority acting with the assistance of independent expert advisers where appropriate. Both complainants and respondents may appeal to the Code of Practice Appeal Board against rulings made by the Panel. The Code of Practice Appeal Board is chaired by an independent legally qualified Chairman, Mr William Harbage QC, and includes independent members from outside the industry.

In each case where a breach of the Code is ruled, the company concerned must give an undertaking that the practice in question has ceased forthwith and that all possible steps have been taken to avoid a similar breach in the future. An undertaking must be accompanied by details of the action taken to implement the ruling. Additional sanctions are imposed in serious cases.

Complaints about the promotion of medicines, or the provision of information to the public, should be sent to the Director of the Prescription Medicines Code of Practice Authority, 12 Whitehall, London SW1A 2DY
(telephone 020 7930 9677
facsimile 020 7930 4554)
By email to: complaints@pmcpa.org.uk.